Gastric Electrical Stimulation: Who Are the Best Candidates? What Are the Results?

by Farid Namin, Zhiyue Lin, Irene Sarosiek, and Richard W. McCallum

Nausea and vomiting are common problems among patients who suffer from gastroparesis. These symptoms arise from gastric neuromuscular dysfunction including poor gastric emptying due to different types of gastric pathophysiology. Diabetic gastropathy is the most common type, followed by idiopathic and then the post gastric surgery (vagotomy) group. Gastric electrical stimulation (GES) is a treatment modality for gastroparetics who are resistant to standard medical therapy. In this subgroup of patients which is approximately 30% of patients referred to our medical center, implantation of the GES device has significantly reduced their symptoms and days of hospitalization, and has also improved quality-of-life indices as well as HgbA1c in the diabetic subgroup. In this review article we describe the theories behind the electrical parameters being utilized for GES, discuss patient selection and the profile of patients who seem to benefit the most, describe the complications, and update on putative mechanisms of action for the device. We hope that this article increases the understanding of gastric electrical stimulation as a major advance in the treatment of gastroparesis where standard medical therapy has not been effective.
Gastric Electrical Stimulation

A SPECIAL ARTICLE

INTRODUCTION

Gastroparesis is a chronic condition of impaired gastric motility resulting in delayed gastric emptying in the absence of mechanical obstruction, e.g. gastric outlet obstruction. Early satiety, post-prandial fullness, bloating, epigastric distention and pain, nausea, vomiting, anorexia, dehydration and weight loss are hallmarks of this condition. Gastroparesis may be due to abnormal myoelectrical activity or neuromuscular dysfunction. Patients with a history of diabetes mellitus, scleroderma and post-vagotomy are the classic subgroups of patients with this entity. In addition, there is a population who suffers from this disorder where there is no obvious etiology, hence termed idiopathic. This assumes that all other organic abnormalities have been investigated. Many risk factors of this subgroup are thought to be related to a viral/bacterial infection with neural and/or myoelectric changes resulting from the infection impairing these structures in the wall of the stomach (1,2).

Demonstrating delayed gastric emptying through a radionuclide solid food test meal is a necessary requirement. Once the gastroparesis is identified, medical therapy can be started. The approach to medical therapy may differ among physicians but relies on the use of a combination of prokinetic and antiemetic agents along with dietary modifications (3,4). The volume, osmolarity, consistency, fat and fiber content of the diet, all contribute to the rate of gastric emptying. Hyperglycemia (glucose >160 mg %) has also been
shown to exacerbate symptoms of gastroparesis. Therefore, nutritional consults benefit these patients by diet modification to low-fat, low-fiber small volume and frequent meals, use of more liquid meals, and liquid calorie supplements.

In our Center, we follow the treatment protocol, as summarized in Figure 1, where we maximize the combined use of nutritional interventions, antiemetics, and prokinetics. Side-effects of these latter medications are closely monitored. Extrapyramidal, Parkinsonism-like side-effects and depression have occurred with long-term treatment with Metoclopramide. The recent article indicating that erythromycin prolongs cardiac depolarization and is associated with torsades de pointes and possible sudden death (5) will further curtail the already limited medical therapy menu. If the patient fails medical therapy or needs consideration for enteral/parenteral feeding, he is a candidate for gastric electrical stimulation (GES) (Figure 1).

WHAT IS GaSTRIC ELECTRICAL STIMULATION?

Both the low energy/high frequency (neurostimulation) parameters and high energy/low frequency (gastric pacing) parameters have benefited the symptoms of gastroparesis (6). Improvements in gastric emptying as well as symptoms have only been achieved by pacing the stomach at its intrinsic slow wave frequency (7).

Using an external device, the authors were able to “pace” the stomach by entraining the rhythm at a rate 10% faster than the intrinsic slow waves by utilizing a high energy, long pulse (300 ms) to induce electromechanical coupling and initiation of smooth muscle contractions (7).

Neurostimulation, on the other hand, utilizes high frequency and low energy (330 µs) stimulation (short pulse) and is thought to control nausea and vomiting through activation of central control mechanisms in the brain stem or by relaxing the proximal body of the stomach. Gastric electrical stimulation using this method is an FDA approved device (called Enterra™) under Humanitarian Device Exemption™ (HDE) application which restricts the sale to <4,000 devices per year, and requires informed consent and a protocol passed by the Institutional Review Board (IRB) from the medical center.

Enterra therapy requires pre-authorization of the surgery, which can be a very challenging process while dealing with insurance companies. Medicare covers this therapy, but there is a great variability in different parts of US in regards to other insurance carriers. Frequent calls and extensive correspondence can take place before an initial denial can be overturned.

WHAT DOES GES CONSIST OF?

The implantable GES system consists of three components: a pulse generator, called the neurostimulator...
Gastric Electrical Stimulation

A SPECIAL ARTICLE

Figure 3. Placement of electrodes and pulse generator at laparotomy.

(Medtronic Enterra Therapy Model 3116); two intramuscular leads (Medtronic Model 4351); and an external (N'Vision clinician programmer Medtronic Model 8840) (Figure 2). The pulse-generator is a battery powered device and contains an electronic circuit that controls when the stimulation pulse should be delivered to the stomach and how strong the pulse should be. The two leads carry the electrical energy from the device to the stomach muscle. They are 35 cm in length with a 1 cm long electrode on the end of the wire. An external programmer is used to activate the settings of the pulse generator to a structured range. There are situations where those parameters can be adjusted to fit a patient’s individual needs, e.g. increasing voltage if resistance or impedance increases, or increasing current if patient is not sustaining an overall improvement of symptoms. This technique of interrogation involves placing the head of the programmer on the skin over the implant site, and in seconds the investigator can identify the strength and timing of the stimulation pulse and continue the program or alter it.

HOW IS THE GES IMPLANTED?

The device is placed surgically either by laparoscopy or laparotomy through an upper midline incision (8-10). Two permanent electrodes are placed on the greater curvature of the stomach, at 9.5 and 10.5 cm proximal to the pylorus (Figure 3). The electrodes are secured into the muscularis propria layer of the stomach. Intra-operative gastroscopy is performed to ensure that there is no penetration of the electrodes into the lumen. The other ends of the electrodes are connected to the pulse generator, which is then placed in a subcutaneous pocket above the abdominal wall fascia to the right of the umbilicus. The pocket is generously irrigated with an antibiotic-containing solution and the patient receives intravenous antibiotics, both before and for two days post-surgery. The load impedance is tested using the programmer to verify electrical integrity of the implant system, both with an open and closed neurostimulator pocket. The pulse generator is initially programmed to standardized parameters: pulse width, 330 µs (microseconds); (current) amplitude, 5 mA; rate, 14 Hz; cycle ON: 0.1 seconds; cycle OFF: 5.0 seconds and usually activated in the operating room or within 48 hours after surgery. At various intervals of follow-up after the implant, the device can then be interrogated. We typically see the following ranges: impedance or resistance between 200 to 800 ohms, voltage (amplitude) between 1.0 and 4.0 volts. During follow-up, if the impedance becomes more than 1000 ohms, this usually means that there is a problem, e.g., dislodgement of electrode from the gastric wall. An abdominal X-ray to compare electrode locations to the initial post-surgery baseline will be needed if the impedance exceeds 1000 ohms or vomiting returns following a fall, injury, or worsening symptoms after a period of good control.

EARLY CLINICAL DEVELOPMENT

The trial that led to the approval by the FDA device committee in April 1998 was the Worldwide Anti-Vomiting Electrical Stimulation Study (WAVES) (8). It was conducted at 11 centers in the U.S., Canada, and Europe in compliance with all applicable regulations in each respective country. This is the only double-blind study published thus far. The patients who were selected had to have more than 7 episodes of vomiting per week, delayed gastric emptying with more than 60% retention at 2 hours and more than 10% at 4 hours on the basis of (continued on page 30)
standardized scintigraphic method for solid meals (low fat egg meal); the duration of symptoms of at least 1 year, weight loss >10% of BMI, many hospitalizations, and finally refractoriness or intolerance to at least 2 out of 3 classes of prokinetic and antiemetic drugs. Thirty-three patients with chronic gastroparesis (17 diabetic and 16 idiopathic) participated in that trial.

After implantation, patients were randomized in a double-blind crossover design to stimulation ON or OFF for one-month periods. The blind was then broken, and all patients were programmed to stimulation ON and evaluated at 6 and 12 months. Based on self-reported vomiting frequency during the one month ON versus one month OFF period, it was shown that high-frequency/low energy gastric electrical stimulation significantly decreased vomiting frequency. Also over the next 10 months this significant reduction was sustained along with improvement in other gastroparesis symptoms, and quality-of-life. These data led to approval of this therapy in March 2000 by the device committee of the FDA.

WHO ARE THE BEST CANDIDATES?

The patient selection criteria currently adopted at our center have evolved since the FDA approval in 2000. One change is that post-surgery gastroparesis is now included if certain parameters are met. Patients with 50% or more of their stomach still present after partial gastrectomy, or who have undergone a vagal nerve injury (typically during a fundoplication surgery for gastroesophageal reflux) are now candidates. Another modification is that vomiting is not a major prerequisite, chronic daily nausea can qualify a patient as well. Also diabetic patients who are post-renal or pancreas transplants are accepted. Gastric retention criteria are now the following: >50% at 2 hours and equal to or >6% at 4 hours. Symptom severity, quality-of-life, level of function at work and in the family setting are some of the important subjective measures that play a role in patient selection criteria. Other objective measures include weight loss, requirements for nutritional support, TPN and/or gastro-jejunal tubes (j-tube), the number of ER visits and hospitalizations. Patients are excluded if they are: pregnant, suffering from chemical dependency, rumination syndrome, eating disorder, cyclic vomiting syndrome, paraneoplastic syndrome, undergoing peritoneal dialysis, or have a limited life-span based on diagnosis of cancer.

The evaluation process requires a team approach which includes the input of GI motility research personnel, endocrinology, dietitians, surgery, psychology, pain management teams, Medtronsics representatives, insurance companies, and hospital administration.

The goals of GES include a significant improvement in nausea, vomiting within 3-6 months of device placement and elimination of other nutritional support, e.g., j-tube feeding and TPN. Clinically relevant symptom change has been defined as greater than 50% improvement after GES. Published data indicates that approximately 70% of patients achieve this response (8,10). Most of the remaining 25% to 30% feel that some improvement has been achieved. However, a subgroup experienced minimal improvement in symptoms or the number of days hospitalized. This subgroup which is approximately 5% of all implanted patients in our series are candidates for a total gastrectomy to overcome vomiting and reduce or prevent hospitalizations.

We have learned that there may be predictors for clinical outcome. Negative indicators include: the pre-operative dose level and continuing requirement for narcotics; the relationship of abdominal pain as a preceding event that may induce vomiting, a history of poorly controlled migraine headaches, and timing of the menstrual cycle in worsening symptoms. We have recently completed a study showing that marked gastric slow wave dysrhythmias as measured by the electro-gastrogram can be a marker for loss of the interstitial cells of Cajal. These are the cells that initiate the gastric signal, integrate it with the myenteric plexus and provide the blue print for gastric motor function (11,12). Positive indicators, on the other hand, include: a homogeneous group of patients with known pathophysiology like diabetes mellitus. The diabetic population manifesting gastroparesis as a long-term complication of their illness comprise the majority of the GES recipients among centers world-wide. The second largest group is the idiopathic group which is more heterogeneous in etiology; often have a significant abdominal pain component that can require narcotics and have a less uniform or predictable response to Enterra therapy.
WHAT ARE SOME COMPLICATIONS?

There are approximately a total of 1000 patients implanted with the GES world-wide. Thirty-seven or 3.7% of the devices have been removed due to complications which include:

1. Infection at the pulse generator pocket site.
2. Pain due to the contact of the leads with the abdominal wall, typically through adhesions.
3. Detachment of the electrodes from the gastric wall.
4. Migration of the pulse generator out of its pocket.

In our center, we have observed a variety of these complications. In one case we detected electrode displacement by an X-ray after we noted impedance levels in the programmer exceeded 1000 ohms. This patient had a preceding accident which we assume contributed to this detachment. In another case, the patient complained of worsening symptoms and the abdominal X-ray revealed a tangling of wires around the pulse generator. This resulted in detachment of electrodes from the stomach wall and hence dysfunction of the device (Figure 4).

Skin penetration of the pulse generator in a thin patient after physical activity has also occurred. Recently, after a patient complained of worsening symptoms upper GI endoscopy was performed and we detected perforation of the electrodes through the gastric mucosa (Figure 5).

HOW DOES GES WORK?

The following are the theories about how the device works (10–16):

1. Activation of the central mechanisms for nausea and vomiting control based on brain P.E.T. imaging and related to afferent nerves being stimulated by the constant high frequency current in the stomach wall.

(continued on page 35)
2. Enhanced relaxation of the fundus of the stomach by this current thus providing better accommodation after eating a meal and decreased sensitivity to distention.

3. Augmentation of the amplitude of the gastric slow wave after eating.

4. Increase in cholinergic function and decreased sympathetic function based on analysis of autonomic testing.

5. A small improvement in gastric emptying.

WHAT IS THE CURRENT GES DATA?

Until now, several animal and human studies using either low energy/high frequency or high energy/low frequency stimulation techniques supported the hypothesis that gastric electrical stimulation improves the symptoms of gastroparesis and accelerates gastric emptying (6–8,13,17,18).

In animal models, it was shown that gastric electrical pacing with high energy, low frequency parameters improved gastric emptying in dogs with gastroparesis induced by vagotomy and glucagon (19). Researchers then successfully applied these concepts to the human stomach (7) and these results opened up a new avenue for refractory gastroparesis patients. However the Enterra device now in clinical use works with high frequency and low energy does not “pace” the stomach as the animal model does and is thought to work through the mechanisms already outlined above.

We will now summarize the pertinent literature for clinical efficacy of this device. In one study involving 36 gastroparesis patients with either diabetic or idiopathic etiology who did not respond to medical therapy, high frequency/low energy gastric electrical stimulation significantly decreased vomiting severity and frequency and other gastrointestinal symptoms, while also improving the quality-of-life at 6 and 12 months follow-up (18) measured with QOL SF-36 questionnaire.

In another report of 55 gastroparetic patients, also refractory to medical therapy, who received gastric electrical stimulation for 1 year, the total symptom scores and physical and mental composite scores of quality-of-life improved significantly (13). Reduction in the days of hospitalization also significantly declined to 29% of the baseline within 1 year follow-up.

The largest single center experience is by our group at Kansas University Medical Center, where 160 implants have been performed since 1998. The demographics in our center are as follows: The majority of
Gastric Electrical Stimulation

A SPECIAL ARTICLE

the subjects are female (80%) with the mean age of 37 and range of 21–66 year old. Caucasians comprise 93% of the studied subjects with the main etiologies of gastroparesis being diabetes (62%), follow by idiopathic (20%) and post-surgical (13%). Five percent of our GES recipients had functional vomiting with normal gastric emptying and they received the device due to severity of their nausea and vomiting.

We will now review the data from our Center in those patient subsets. In one study of 48 adult diabetic patients with refractory gastroparesis the GES implanted system resulted in significant improvement of upper GI symptoms, health-related quality-of-life, nutritional status, glucose control and days of hospitalization (Table 1) (20). We would like to highlight that the follow-up of HgbA1c in the diabetics showed a decrease by 1.4 after 1 year and 2.1 beyond 3 years follow-up. This is clinically meaningful since a recent cohort study of 10,232 diabetics and non-diabetics has demonstrated that an increase of 1% point in HgbA1c is associated with a 20 to 30% increase in mortality and cardiovascular complications (21). In addition the control of vomiting allows those patients to be candidates for renal and/or pancreas transplantation because they can now be relied on to absorb immune suppressive medications needed in the post-transplant period.

It is recognized that a small sub-group of patients (10%) who have undergone vagotomy during upper-gastrointestinal surgery, develop post-surgical gastroparesis. In a report of 16 patients with post-surgical gastroparesis who failed standard medical therapy, the severity and frequency of upper GI symptoms were significantly improved. (22). Although the gastric emptying was not significantly changed, the upper GI symptoms were better by six months and sustained at 12 months. Therefore, long-term GES can significantly improve upper GI symptoms, quality-of-life and the nutritional status and hospitalization requirement of patients with post-surgical gastroparesis (22) despite the fact that vagal nerve damage is present.

There are data on symptoms and adverse events beyond 3 years of Enterra therapy use (23,24). This demonstrates that improvements achieved at 1 year post-implant can be sustained beyond 3 years in all areas mentioned previously. In one study 29 patients (16 diabetics, 9 idiopathics, and 4 post-surgical) followed beyond 3 years indicated that their total symptoms score improvement was 70% (24). Overall >75% of patients had more than 50% improvement and the remaining group averaged 13%. This is consistent with the previous report that up to 25% of patients implanted have a limited (<25%) clinical response (18,20,23).

There has been no consistent demonstration of a significant acceleration in gastric emptying of a solid meal. We have noted that 20% of diabetics have normalized their gastric emptying at 1 year, with varying rates of normalization in our “idiopathics” population over time. Since many “idiopathics” are thought to result from post-infection damage to the vagus nerve or the myenteric plexus, then recovery from this neural damage is expected over time (e.g., 6 months to up to 5 years). Hence, the normalization in gastric emptying cannot be attributed to the device but to the expected slow recovery from neural injury.

Because the majority of patients will have minimal to no improvement in gastric emptying, they must be maintained on prokinetic therapy post-implant. This is also why the symptoms of bloating, fullness, post-prandial satiety and discomfort are less improved. Nausea and vomiting are the symptoms that are most consistently and dramatically reduced by GES. Abdominal pain is an unpredictable outcome and not the goal or focus for being considered for an Enterra device.

In addition, time to response after surgery needs to be appreciated. One to three months is the usual time that is necessary before attempting to judge response. Recovery from surgery, post-operative pain medication and glucose control all play a role in the response time. During this period all pre-operative antiemetics and prokinetic should be continued. Later on, some tapering or stopping of the medications does occur.

FUTURE DIRECTIONS

As previously mentioned, not all recipients of the GES device may have an expected clinical response and continue to be a challenge. Therefore, it is imperative to explore this technology further. One goal is multi-point electrical stimulation which will synchronize stimula-

(continued on page 38)
Gastric Electrical Stimulation

A SPECIAL ARTICLE

(continued from page 36)

tion by arranging electrodes at 2 to 4 sites extending proximally to distally in the stomach and have flexibility in programming to different energies and frequencies. The goal is to achieve acceleration of gastric emptying as well as symptom reduction. Perhaps the high energy would be reserved for pre- and post-prandial periods and low energy for fasting and at night in order to preserve battery power. Electrical stimulation is also being investigated for problems beyond gastroparesis such as in the small bowel for intestinal pseudo-obstruction and in the colon for constipation.

CONCLUSIONS

The era of the “gut” electrical stimulation has begun and promises to produce more exciting results. Dr. Keith Kelly, the renowned Mayo clinic surgeon regarded by many as the “Father of the clinical application of gastric pacing” can be justly proud that his early observations and contributions have spawned such great interest in electrophysiology of the gut, as well as growth in the evolving role for therapeutic tar-

References

1. Soykan I, Sivri B, Sarosiek I, Kiernan B, McCallum R. Demogra-