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Electrical stimulation of the gastrointestinal tract has been touted as a possible therapy for intestinal motor dysfunction since 1963 when Bilgutay et al. reported the use of transluminal electrical stimulation at the tip of a nasogastric tube to induce peristalsis and shorten the time period of post-laparotomy ileus [1]. They found that stimulation of the stomach with electrical pulse bursts resulted in increased gastric emptying demonstrated by fluoroscopy, but no quantitative measurements were obtained. However, subsequent randomized controlled studies failed to show any benefit of gastric stimulation on decreasing the duration of postoperative ileus [2–4]. In the late 1960s and 1970s, the myoelectrical activity of the gastrointestinal tract was elucidated along with its relationship to gut contractility [5–7]. Out of this initial research, several clinical applications of gastrointestinal electrical stimulation have arisen. These include gastric stimulation for treatment of gastroparesis and sacral nerve stimulation for treatment of urinary disorders and fecal incontinence. All the initial studies and subsequent FDA trials were limited to adult patients. However, over the past 10 years, a few pediatric surgeons interested in pediatric neurogastroenterology have been performing gastric stimulation for gastroparesis and sacral nerve stimulation for fecal and urinary incontinence with excellent results (see below).

46.1 Gastroparesis and Gastric Electrical Stimulation

There are very few pharmacologic agents currently available for the treatment of gastroparesis, and their efficacy in the treatment of severe motility disorders is questionable. At the same time, classic surgical approaches such as pyloroplasty, total gastrectomy, and placement of gastrojejunal and

jejunosomy feeding tubes rarely provide significant, long-term symptom relief in patients with severe gastroparesis. Gastroparesis and severe dyspepsia are associated with poor quality of life, are often refractory to dietary and pharmacological interventions, and are associated with higher medical costs [8, 9].

Gastric electrical stimulation (GES) for the treatment of gastroparesis gained FDA approval with a Humanitarian Device Exemption (<4000 cases diagnosed/year in the United States) in 2000. The Enterra™ therapy system (Medtronic Inc., Minneapolis, MN) requires individual hospital Institutional Review Board approval and should only be implanted after all available medical therapies for gastroparesis have failed. Since 2000 the Enterra™ system has been implanted in more than 10,000 adults worldwide for gastroparesis. Implantation in pediatric patients is more recent with probably <250 children having undergone GES therapy to date [10–12].

GES is a low-energy, high-frequency system that stimulates the nerves that innervate the gastric antral muscle. Several studies have demonstrated that GES improves nausea and vomiting, but the exact mechanisms remain unproven [13–15]. Proposed mechanisms include modulation of enteric or afferent neural activity that influences symptom perception, acceleration of gastric emptying, enhanced vagal activity, alterations in CNS control mechanisms of nausea and vomiting, and enhanced gastric accommodation [14].

Symptomatic improvement is not correlated with improvement in gastric emptying or changes in electrogastrography (EGG) [16]. Patients with drug refractory nausea but baseline normal gastric emptying as well as patients with baseline delayed gastric emptying that does not improve after GES therapy may still experience symptomatic relief [16].

46.1.1 Temporary Gastric Stimulation

Although not part of the FDA-approved protocol, in many patients, temporary GES is used to predict a patient's response to GES [17]. The temporary GES electrode used is

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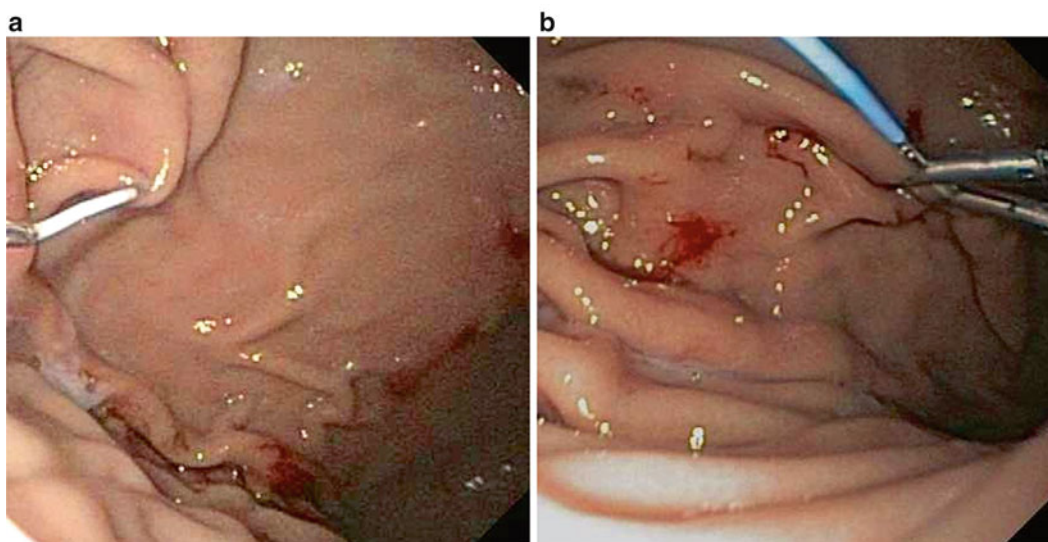


Fig. 46.1 Endoscopic pictures of temporary GES placement. The lead is screwed clockwise into the gastric mucosa (a). Clips are placed endoscopically to anchor the lead to the mucosa between the gastric body and antrum (b)

a temporary cardiac pacing lead (model 6414-100 or 6414-200, Medtronic Inc., Minneapolis, MN) which is placed through an existing gastrostomy site or passed through the side port of a gastroscope and brought out through the nose or mouth. The lead is screwed clockwise into the gastric mucosa at the junction of the body and antrum of the stomach (Fig. 46.1a). Endoscopic clips are then applied to hold the lead in place (Fig. 46.1b). The lead is connected to an external GES battery that is placed into a telemetry pouch. The pulse generator is interrogated (desired impedance 400–1500 Ω) and initially programmed at relatively high settings (voltage, 5 V; pulse width, 330 μ s; frequency, 28 Hz; time on 1.0 s; and time off 4.0 s). This allows the patient response to temporary GES to be determined within 2–3 days. In general the lead can stay in place for about 7 days before eventual dislodgement. The temporary lead is easily removed by rotating counterclockwise with gentle traction.

46.1.2 Permanent Gastric Stimulation

The electrodes for the permanent Enterra™ system can be placed laparoscopically or by open laparotomy if necessary due to previous surgeries or if a gastrostomy is present. Two electrodes 1 cm apart and in parallel alignment are placed intramural along the greater curvature of the stomach at the junction of the antrum and body of the stomach (Fig. 46.2a). The electrodes are placed under endoscopic visualization to ensure that the leads are not intraluminal. The electrodes are then secured to the gastric wall (Fig. 46.2b). The two leads are connected to the GES pulse generator (Fig. 46.2c), and the generator is placed into a subcutaneous pocket

(Fig. 46.2d). The pulse generator is interrogated (desired impedance 400–800 Ω) and initially programmed (voltage, 5 V; pulse width, 330 μ s; frequency, 14 Hz; time on, 1.0 s; and time off, 4.0 s). Postoperatively, the parameters can be adjusted if the patient does not achieve satisfactory relief of symptoms. However, there is no standard algorithm for modifying the settings. We have had greater success with symptom relief by increasing the pulse width and frequency initially. Adjustments are performed every few weeks to months as needed.

46.1.3 Outcomes

Several studies demonstrate that GES provides long-term relief in adults with gastroparesis. In McCallum's study, there was overall improvement in gastroparesis symptoms and nutritional status and decreased medication usage 56 months after placement of the Enterra™ system [18]. In an earlier study, Lin et al. reported the 1-year postoperative status of 63 adults with gastroparesis who were treated with the Enterra™ system [16]. All symptoms including abdominal pain, bloating/distention, nausea, vomiting, and early satiety were significantly improved. Interestingly, 4-h gastric emptying was not significantly improved. This confirms the observation that symptomatic improvement does not correlate with improvement in gastric emptying.

The first series of pediatric patients with chronic nausea and vomiting successfully treated with GES was reported by Islam et al. [10]. All patients improved initially with temporary gastric stimulation and went on to have implantation of the permanent Enterra™ system [10]. One patient had

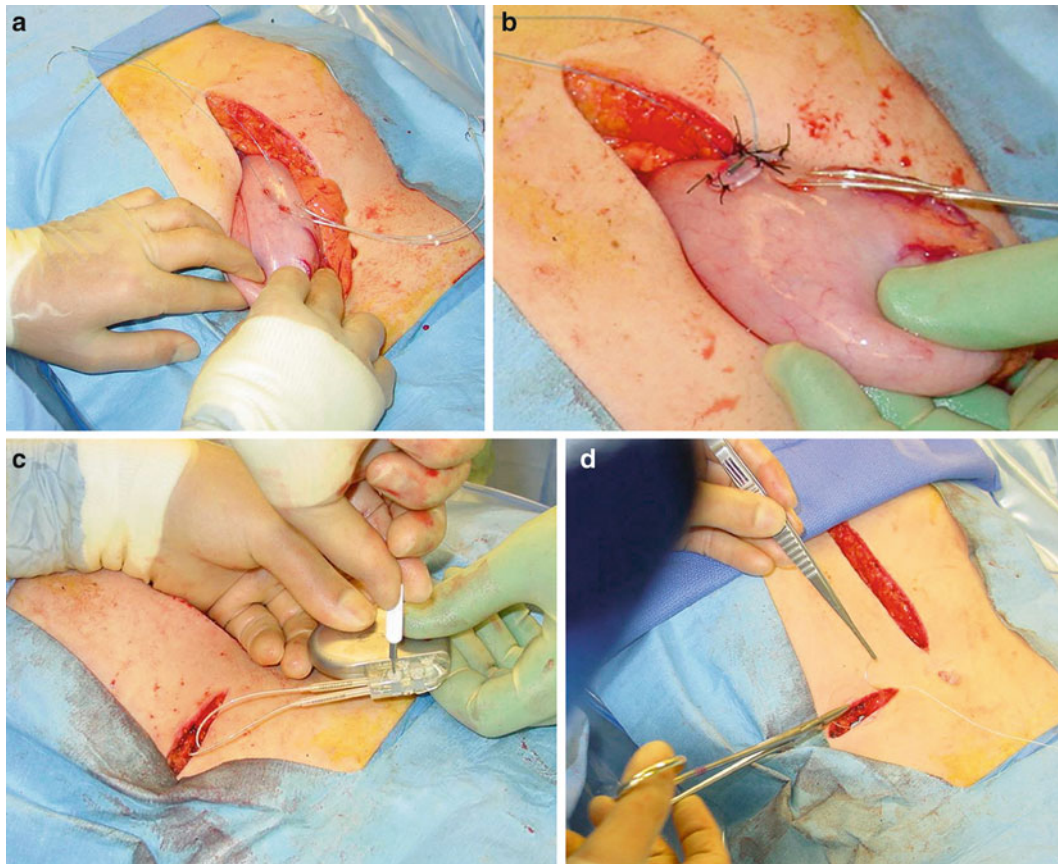


Fig. 46.2 Surgical placement of a GES via laparotomy. Gastric stimulator leads placed parallel to each other in the gastric wall along the greater curvature (a). The leads are sutured to the gastric wall (b). The

leads are attached to the pulse generator (c). The pulse generator is sutured into the superficial pocket (d)

recurrence of symptoms and one patient required removal of the system. In 2013 we reported our results after placement of the Enterra™ system in our first 16 pediatric patients with chronic nausea and vomiting and functional dyspepsia [11]. After placement of the permanent Enterra™ system, there was significant improvement in severity and frequency of all symptoms. Lu et al. then reported our 2-year follow-up of 24 patients who received GES for functional dyspepsia [12]. There were significant improvements in multiple areas of the PedsQL with 65% reporting that their health was much improved after placement of the Enterra™ system. Five patients experienced minor complications, but none required removal of the GES system. These initial pediatric series demonstrate excellent results in a difficult group of heterogeneous pediatric patients. In general, pediatric patients with a permanent Enterra™ system are more challenging than adults due to their very active lifestyle that subjects the stimulator leads and battery to potential damage. The effect of significant growth during puberty on the GES system is unknown, as long-term follow-up of pediatric patients with the Enterra™ system has not yet been reported.

There are a few published reports citing the use of GES therapy for treatment of intractable vomiting in patients with chronic intestinal pseudo-obstruction (CIP) [19]. Most likely this is due to the known effect of the Enterra™ system on the stomach with no effect on the small bowel. We have successfully treated several children with CIP-related nausea and vomiting and high-output gastrostomy drainage with the Enterra™ system (unpublished). The GES therapy has allowed the gastrostomy to remain closed and even allowed patients to eat small amounts of food by mouth.

46.2 Sacral Nerve Stimulation

Sacral nerve stimulation is a low-energy, high-frequency system that directly stimulates the third sacral nerve roots. For the urinary system, the effect of sacral nerve stimulation is believed to be somatic afferent inhibition of sensory processing in the spinal cord [20]. For fecal incontinence, sacral nerve stimulation of the pelvic floor via the pelvic plexus and pudendal nerve is thought to excite the autonomic and

somatic nervous systems and cause both direct and reflex-mediated responses to the fecal incontinence mechanism as well as cause changes in cortico-anal excitability [21]. Several studies have documented that sacral nerve stimulation increases anal sphincter resting and squeeze pressure and increases colonic peristalsis with induction of pan-colonic propagating waves [22, 23].

In 2012 the FDA approved sacral nerve stimulation as a treatment for fecal incontinence. A study by Tjandra et al. demonstrated that sacral nerve neuromodulation significantly improved the outcome in 60 adult patients with severe fecal incontinence compared with a control group undergoing optimal medical therapy [24]. A prospective multicenter study of 120 adults with fecal incontinence showed significant therapeutic success with 83% of patients achieving therapeutic success at 12 months and 85% success at 24 months [25]. Sacral neuromodulation is also cost-effective for urge urinary and/or fecal incontinence [26].

Bowel and bladder dysfunction (BBD) encompasses symptoms of gastrointestinal and urinary dysfunction including chronic constipation, urinary retention, and fecal and urinary incontinence [27]. Adult patients with BBD have been successfully treated with sacral nerve stimulation for more than a decade [24]. However, only in the last 5 years have published reports of pediatric patients with both GI and urinary dysfunction documented impressive results [28–30]. Pediatric patients with BBD represent a complex group of patients that will require long-term follow-up to demonstrate ongoing symptomatic improvement. Since BBD symptoms are difficult to quantify, validated quality of life measures and symptom improvement scoring are essential to determine the clinical utility of sacral nerve stimulation [31–33].

46.2.1 Implantation

The patient is placed in the prone position on the OR table. The sacroiliac joints are identified by fluoroscopy and a line is drawn between them. Starting 2 cm superior and lateral to the midpoint of the line, the access needle is passed through the skin into the third sacral foramen using fluoroscopic guidance to confirm correct positioning. The InterStim™ sacral nerve stimulator system (Medtronic Inc., Minneapolis, MN) stimulator lead is inserted into the third sacral foramen using the Seldinger technique (Fig. 46.3). Placement is confirmed with fluoroscopy and stimulator testing which demonstrates a “bellows effect” of the perineum with dorsiflexion of the toes with stimulation of all four electrodes. The lead is attached to a test stimulator for up to 3 weeks to determine the patient’s response to sacral nerve stimulation. If the test is successful, then the test stimulator is removed, and the lead is attached to a permanent sacral nerve stimulator (SNS) pulse generator/battery that is placed into a subcutaneous pocket over the buttock.

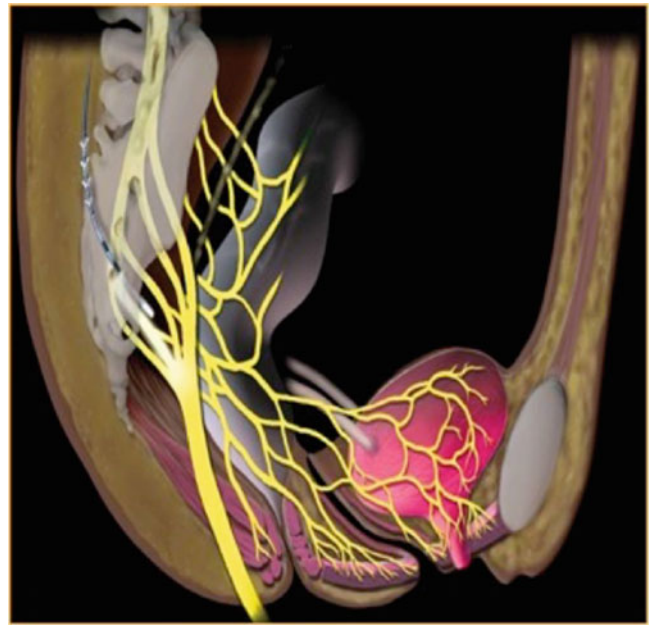


Fig. 46.3 Depiction of sacral nerve stimulator lead in correct position adjacent to L3 nerve root. Reprinted with the permission of Medtronic, Inc. © 2014

46.2.2 Outcomes

In 2014 Dwyer et al. reported on their series of 105 children with BBD. With a median follow-up of 2.72 years, 94% of patients had improvement of at least one symptom and only 11% had at least one symptom worsen [30]. Fifty-six percent of patients required reoperation, mainly for device malfunction, and 35% of patients underwent explantation, mainly for complete symptom resolution. Recently, we reported our results with the first 29 patients with BBD treated with a SNS with a median follow-up of 17.7 months [34]. Fifty-five percent of patients with a pre-SNS cecostomy no longer required an antegrade bowel regimen as they now had voluntary bowel movements, and 91% of patients no longer require anticholinergic medications for bladder overactivity after sacral nerve stimulation.

As is true with the Enterra™ gastric stimulator system, pediatric patients with a permanent InterStim™ system are more challenging than adults due to their very active lifestyle that subjects the stimulator lead and battery to potential damage. The effect of significant growth during puberty on the SNS system is unknown, as long-term follow-up of pediatric patients with the InterStim™ system has not yet been reported.

46.3 Esophageal Stimulation

Gastroesophageal reflux (GER) caused by transient relaxation of the lower esophageal sphincter commonly occurs in otherwise healthy infants, children, and adults.

Gastroesophageal reflux disease (GERD) is far less common than GER, but the prevalence of GERD in all age groups appears to be increasing [35]. Pediatric patients at high risk for GERD include children with neurologic impairment, esophageal atresia, and some genetic disorders [36, 37]. A fundoplication in these patients is concerning since they are also predisposed to poor esophageal motility, often with swallowing dysfunction. Furthermore, there is a higher risk of gagging and wrap disruption than with otherwise normal patients [38, 39]. For these reasons an alternative to pediatric fundoplication is extremely desirable, especially in these at-risk pediatric subgroups. Over the past 5 years, several adult series utilizing esophageal stimulation rather than fundoplication for GERD have been reported.

The initial studies of electrical stimulation of the lower esophageal sphincter (LES) were performed using a canine model of surgically induced esophagogastric junction incompetence [40–42]. In both acute and chronic models, electrical stimulation of the LES increased resting LES pressure. Human subjects with GERD treated with short-term electrical stimulation of the LES via endoscopically placed temporary electrodes demonstrated similar results with no effect on physiologic LES relaxation [43, 44].

The LES stimulation system (EndoStim BV, the Hague, Netherlands) is an implantable electrical stimulator that delivers long-term electrical stimulation to the LES. The EndoStim™ system is composed of three components: a bipolar electrical stimulator lead, an implantable pulse generator (IPG), and an external programmer. The EndoStim™ system is placed laparoscopically. The two electrodes are implanted within the LES muscle parallel and 1 cm apart (Fig. 46.4a).

The electrodes are secured and the lead is attached to the IPG that is placed in a subcutaneous pocket (Fig 46.4b).

Open-label adult human trials are ongoing in Europe, Asia, and South America [45–47]. These studies demonstrated a sustained improvement in GERD outcomes with electrical stimulation therapy of the LES [47]. Patients report sustained improvement in GERD-HRQL, elimination of the need for daily GERD medications, and improvement in esophageal acid exposure [47]. Regurgitation and nocturnal symptoms often remain despite maximal medical therapy and are the major causes of patient dissatisfaction. These two symptoms are tremendously improved with EndoStim™ therapy [47]. A US adult clinical trial has recently been approved by the FDA and should be initiated in 2016. The author is aware that several children with severe GERD outside the United States have been treated with EndoStim™ therapy and pediatric trials outside the United States are in the planning stages.

46.4 Conclusion

While some clinical applications for electrical stimulation of the gastrointestinal tract have been elucidated, much work in the field remains. More controlled trials, especially pediatric ones, are necessary for gastric stimulation, sacral nerve stimulation, and electrical stimulation of the LES. The mechanisms of action for these devices need to be better defined and updated device components and software are necessary. Electrical stimulation of the gastrointestinal tract continues to have great potential for many GI disorders.

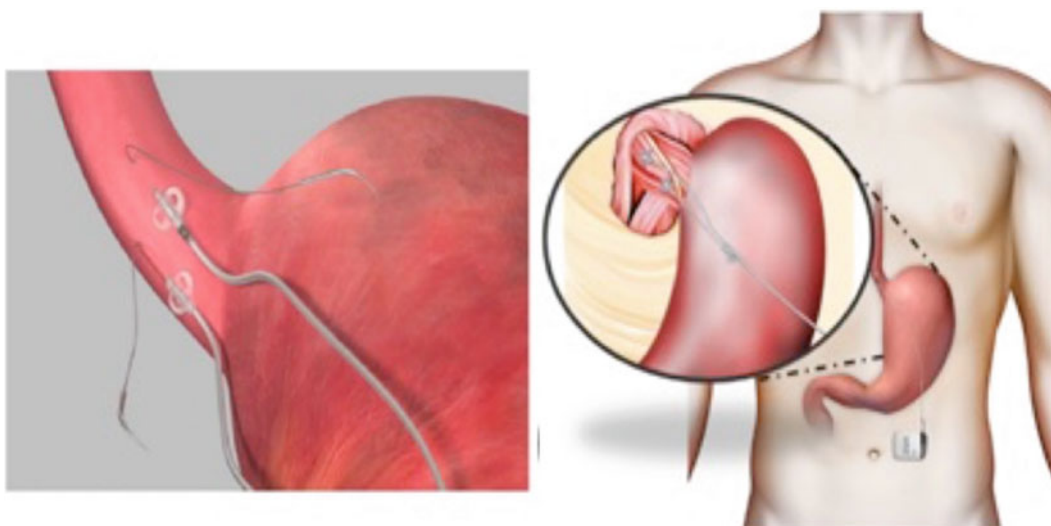


Fig. 46.4 Depiction of lead placement for electrical stimulation of the LES (a) and complete system with battery in subcutaneous pocket of the abdominal wall (b). Reprinted with the permission of Medtronic, Inc. © 2014

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