

Gastric Electrical Stimulation for Medically Refractory Gastroparesis

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Background & Aims: This study investigated the efficacy of gastric electrical stimulation for the treatment of symptomatic gastroparesis unresponsive to standard medical therapy. **Methods:** Thirty-three patients with chronic gastroparesis (17 diabetic and 16 idiopathic) received continuous high-frequency/low-energy gastric electrical stimulation via electrodes in the muscle wall of the antrum connected to a neurostimulator in an abdominal wall pocket. After implantation, patients were randomized in a double-blind crossover design to stimulation ON or OFF for 1-month periods. The blind was then broken, and all patients were programmed to stimulation ON and evaluated at 6 and 12 months. Outcome measures were vomiting frequency, preference for ON or OFF, upper gastrointestinal tract symptoms, quality of life, gastric emptying, and adverse events. **Results:** In the double-blind portion of the study, self-reported vomiting frequency was significantly reduced in the ON vs. OFF period ($P < 0.05$) and this symptomatic improvement was consistent with the significant patient preference ($P < 0.05$) for the ON vs. OFF period determined before breaking the blind. In the unblinded portion of the study, vomiting frequency decreased significantly ($P < 0.05$) at 6 and 12 months. Scores for symptom severity and quality of life significantly improved ($P < 0.05$) at 6 and 12 months, whereas gastric emptying was only modestly accelerated. Five patients had their gastric electrical stimulation system explanted or revised because of infection or other complications. **Conclusions:** High-frequency/low-energy gastric electrical stimulation significantly decreased vomiting frequency and gastrointestinal symptoms and improved quality of life in patients with severe gastroparesis.

Gastroparesis, a disorder of gastric motility, is defined as delayed emptying of a solid meal with accompanying symptoms of nausea, vomiting, abdominal pain, early satiety, fullness, bloating, anorexia, and weight loss. It is attributed to abnormal gastric myoelectrical activity (e.g., abnormal slow-wave frequency, low slow-wave amplitude, and slow-wave uncoupling) or ab-

normal gastric motility (e.g., gastric hypomotility and uncoordinated gastric or duodenal contractions). Although a number of conditions can lead to gastroparesis, 2 common etiologies are diabetes mellitus and prior gastric surgery involving vagotomy. When there is no recognized predisposing factor, gastroparesis may be classified as idiopathic, although a number of these patients are suspected of having previous gastrointestinal (GI) tract viral infections.¹

Medical management involves prokinetic therapy combined with antiemetic agents, nutritional support (e.g., oral caloric supplementation, enteral tube feeding with a jejunostomy, or total parenteral nutrition), and pain management. Prokinetic agents stimulate gastric motility and coordinate gastric-duodenal motor activity. They include metoclopramide, erythromycin, cisapride, and domperidone. However, in the United States, only metoclopramide and erythromycin are commercially available, and both have side effects that make them intolerable for more than 40% of patients.² Partial or complete gastrectomy is regarded as a last resort because of the associated mortality and morbidity.³

Several animal and human studies using either low-energy/high-frequency or high-energy/low-frequency stimulation techniques support the hypothesis that gastric electrical stimulation (GES) improves the symptoms of gastroparesis and accelerates gastric emptying.⁴⁻⁹ McCallum et al.⁵ showed improvement in gastric emptying and symptoms in patients with gastroparesis by using a high-energy/low-frequency external stimulation device with temporary electrodes to pace the stomach at the

Abbreviations used in this paper: GES, gastric electrical stimulation; GI, gastrointestinal; HQOL, health-related quality of life; MCS, mental composite score; PCS, physical composite score; TSS, total symptom score.

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0016-5085/03/\$30.00
doi:10.1016/S0016-5085(03)00878-3

intrinsic slow-wave frequency. The very wide pulse width (300 ms) used in that study resulted in entrainment of the gastric rhythm and induced gastric contractions. In contrast, Familoni et al.⁶ reported increased gastric contractility in canines with a low-energy/high-frequency device that delivered a stimulus pulse at 4 times the intrinsic slow-wave frequency. In a subsequent report, Familoni et al.⁷ reported improvement in symptoms and liquid gastric emptying in a diabetic patient with severe gastroparesis by using an external stimulation unit and temporary cardiac pacing leads with stimulation parameters (amplitude, 2 mA; pulse width, 300 μ s; frequency, 12 cycles per minute) derived from the earlier animal study. A large single-center study⁸ and a multicenter feasibility evaluation⁹ using a commercially available implantable neurostimulator showed significant improvement in symptoms and nutritional status in patients with refractory gastroparesis. The low-energy/high-frequency parameters used in these studies (amplitude, 5 mA; pulse width, 330 μ s; frequency, 14 Hz; cycle ON time, 0.1 seconds; cycle OFF time, 5.0 seconds) resulted in 2 charge-balanced pulses delivered every 5 seconds and were subsequently adopted in this current study. However, these parameters do not entrain the gastric slow wave or induce gastric contractions.¹⁰

The goals of our study were to: (1) investigate the short-term effect of low-energy/high-frequency GES on symptom reduction in a randomized, double-blind, crossover trial; (2) assess the effectiveness of GES on symptoms, gastric retention, and health-related quality of life (HQOL) over a 12-month period; and (3) evaluate adverse events.

Materials and Methods

The Worldwide Antivomiting Electrical Stimulation Study, was conducted at 11 centers in the United States, Canada, and Europe in compliance with all applicable regulations of each country. Approval was obtained from the institutional review board or ethical committee of each center, and patients gave their written, informed consent before entering the trial.

Patients

Study entry criteria included (1) more than 7 episodes of vomiting per week; (2) delayed gastric emptying (>60% retention at 2 hours and >10% at 4 hours, on the basis of a standardized scintigraphic method for solid meals¹¹); (3) symptoms consistent with gastroparesis for longer than 12 months; and (4) refractoriness or intolerance to 2 of 3 classes of prokinetic drugs (cholinergic agonists, motilin receptor agonists, and dopamine receptor antagonists) and 2 of 3 classes of antiemetics (antihistamines, serotonin receptor antagonists, and dopamine receptor antagonists). Patients with documented intestinal pseudo-obstruction, prior gastric surgery,

vagotomy, organ transplantation, seizures, primary swallowing disorders, chemical dependency, pregnancy, or psychogenic vomiting and those who were medically unstable or at high surgical risk were excluded.

Surgical and Stimulation Techniques

The implanted GES system consisted of 2 intramuscular electrodes (model no. 4300; Medtronic, Minneapolis, MN) connected to an implanted neurostimulator (model no. 7425; Medtronic). The pair of electrodes was inserted by laparotomy (US centers, 27 cases) or laparoscopy (Canadian and European centers, 6 cases) into the muscularis propria of the greater curvature, 10 cm from the pylorus and separated by approximately 1 cm. The neurostimulator was positioned subcutaneously in the abdominal wall, typically in the right mid-quadrant (Figure 1), and was programmed to standardized parameters (frequency, 14 Hz; intensity, 5 mA; pulse width, 330 μ s; cycle ON, 0.1 seconds; cycle OFF, 5.0 seconds) by using a Medtronic model no. 7432 programmer and model no. 7457 control software. The mean duration of surgery was 1.6 hours. Postoperative management included parenteral analgesia as required, sliding scale insulin administration in the diabetic patients, and continuation of jejunostomy feedings or conversion of parenteral nutrition to jejunostomy tube feedings.

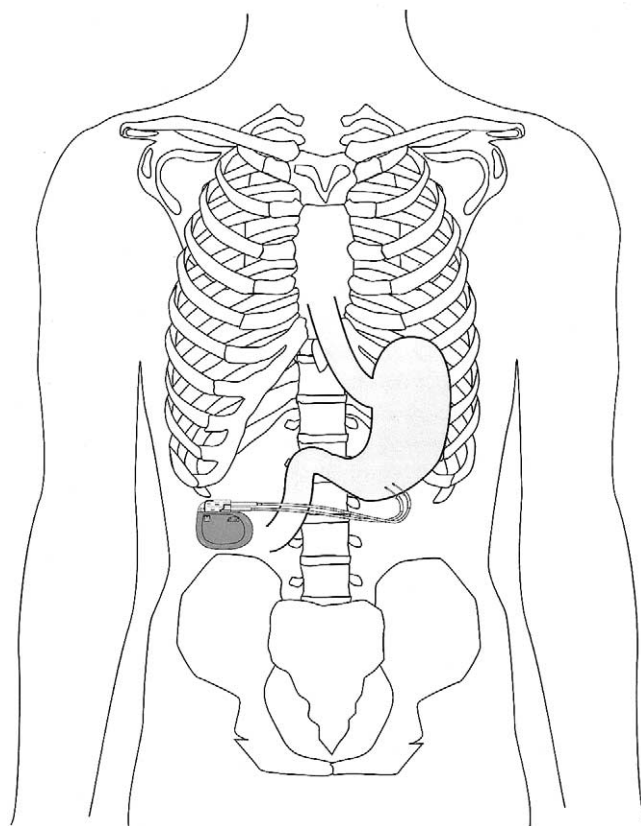


Figure 1. Gastric electrical stimulation (GES) system and its location. The GES unit comprised a pair of leads secured in the muscularis propria along the greater curvature, 10 cm proximal to the pylorus, 1 cm apart, and connected to an implantable battery-powered neurostimulator positioned subcutaneously in the abdominal wall.

Study Design

The 12-month study was conducted in 2 phases. Phase I, a 2-month randomized, placebo-controlled, double-blind, crossover trial, was followed immediately by phase II, a 10-month open-label period. Patients were instructed to continue their current antiemetic or prokinetic therapy during the 12-month study.

For phase I, patients were randomized to stimulation either ON or OFF. Each etiology was randomized separately by using a random number table. Each patient's neurostimulator was programmed to ON or OFF after the patient recovered from surgery (5.6 ± 3.3 days [mean \pm SD]). At the end of the first month, the neurostimulator was programmed to the opposite mode (OFF or ON), and monitoring continued for a second month. The patient, physician, and study coordinator were blinded to stimulation status during phase I, and a person not involved in the patient's care performed all programming and interrogation of the gastric stimulator. Earlier work^{8,9} indicated that patients felt no sensation from the neurostimulator when it was ON. At the end of the second month, while still blinded, patients were asked for their preference (month 1 or month 2) as a global measure of quality of life in phase I. For phase II, all patients' stimulators were programmed to ON with the patients' knowledge.

Monitored Parameters

Patients were evaluated at baseline and 4 follow-up visits (1, 2, 6, and 12 months). Baseline was defined as the 4-week period before surgery. To monitor vomiting frequency, patients recorded daily vomiting episodes in either 2-week (idiopathic patients) or 4-week (diabetic patients) diaries before baseline and at each follow-up visit. The diary period was longer for the diabetic patients, because their symptoms fluctuate more. We also assessed the subjective severity of upper GI tract symptoms (vomiting, nausea, early satiety, bloating, postprandial fullness, and epigastric pain) at baseline and each follow-up visit by using a 5-point symptom interview questionnaire in which symptoms were rated by the study coordinator as 0, absent; 1, mild (not influencing the usual activities); 2, moderate (diverting from, but not requiring modifications of, usual activities); 3, severe (influencing usual activities severely enough to require modifications); and 4, extremely severe (requiring bed rest). The sum of the severity ratings of the 6 symptoms was used as an overall total symptom score (TSS). Gastric retention was quantified after a solid meal at baseline and at the 6- and 12-month follow-up visits by using a standardized scintigraphy method and a low-fat test meal.¹¹ This method was developed specifically for this study to standardize the measurement of solid food emptying over 4 hours. Patients were asked to discontinue prokinetic medication 2 to 3 days before the test.

HQOL was assessed at baseline and the 1-, 2-, 6-, and 12-month follow-up visits by using the previously validated SF-36 Health Status Survey (Acute) questionnaire.¹² Two summary scores, the Physical Composite Score (PCS) and the Mental Composite Score (MCS), in addition to 8 subscores,

were derived from the SF-36. PCS and MCS are norm-based measures in which the mean \pm SD for the general US population is 50 ± 10 .¹³

Adverse events, including hospitalizations, were identified throughout the follow-up period. The route of supplemental nutrition and glycosylated hemoglobin in diabetic patients was also monitored.

Statistical Analysis

The primary outcome measure in phase I was the difference in vomiting frequency with stimulation OFF compared with ON. The mean weekly vomiting frequency was determined for each patient diary, and these data were then further assessed by the Wilcoxon signed rank test. The results are reported as median and interquartile range and are considered significant for $P < 0.05$. A secondary outcome, the patient's preference for stimulation ON or OFF, was analyzed by using the Mainland-Gart test and was considered significant for $P < 0.05$.¹⁴

For phase II, the primary outcome measures were the changes between baseline and the 6- and 12-month follow-up visits for weekly vomiting frequency, symptom severity, gastric emptying, and HQOL. The Wilcoxon signed rank test was used for paired comparisons of weekly vomiting frequency and gastric emptying. Results are reported as median and interquartile range and are considered significant for $P < 0.05$. Symptom severity subscores, TSS, and SF-36 scores were analyzed with paired t tests and are reported as mean \pm SE. Results for TSS were considered significant for $P < 0.05$. Symptom severity and the SF-36 subscores were adjusted for multiple comparisons and were considered significant for $P < 0.005$, whereas the SF-36 summary scores (PCS and MCS) were considered significant for $P < 0.025$. All patients who received implants were included in the analysis of adverse events. Correlation analyses between vomiting frequency and gastric emptying test results used Pearson's correlation coefficient.

The initial study plan provided for an enrollment of 40 diabetic and 40 idiopathic patients. Because of slow recruitment, the sponsor stopped the study after enrollment of 33 patients. These 33 patients were randomized to phase I, continued to phase II, and form the basis of this report. All results are reported for the combined patient group and for each subgroup separately.

Patient Flow

Sixty-three patients were screened for the study. Of these, 5 vomited before completing the gastric emptying test, 20 did not meet the gastric emptying requirements, 1 had a history of seizures, 3 were unstable or at high surgical risk, and 1 did not meet the etiology requirement. Thus, 33 patients were enrolled and completed phase I. Phase I data were analyzed on an intent-to-treat basis. The 33 patients continued into phase II, and between the second and sixth month, 1 patient left the study because of lead perforation of the stomach, 2 were lost to follow-up, and 1 was too ill to complete the 6-month follow-up visit. Of the 29 patients who were eligible

Table 1. Patient Demographics and Baseline Measures

Variable	All Patients	Diabetic Patients	Idiopathic Patients
n	33	17	16
Sex (male/female)	9/24	9/8	0/16
Age, yr, mean (range)	38.9 (19–65)	38.1 (22.0–65.1)	41.1 (19.1–60.4)
BMI, kg/m ² (mean ± SD)	23.8 ± 5.2	24.7 ± 4.7	22.9 ± 5.7
Duration of symptoms, yr, mean (range)	6.3 (1–28)	6.3 (1–28)	6.2 (1–24)
GET, % retention (interquartile range)			
2 h	78 (67–84)	80 (69–88)	76.5 (64–79)
4 h	34 (26–57)	46 (28–68)	28 (25–38)
Patients on supplemental nutrition			
Enteral feeding tube	5	3	2
Total parenteral nutrition	9	2	7

BMI, body mass index; GET, gastric emptying test.

for the 6-month follow-up data analysis, diary data were unavailable for 2, and gastric emptying data were incomplete for 3 (1 patient refused, and 2 patients vomited after the test meal). In addition, 5 of the 29 patients did not complete the 12-month follow-up visit: 1 was pregnant, 2 had infection at the implant site, 1 died of cardiopulmonary arrest, and 1 was lost to follow-up. Thus, 24 patients participated in the 12-month follow-up. In these 24 patients, 2- and 4-hour gastric emptying data were not reported for 4 (1 had illness unrelated to gastroparesis or the therapy, 1 refused the test, 2 completed their tests more than 2 months later than scheduled, and 1 had unavailable 4-hour gastric emptying data because of vomiting during the test). Phase II data were analyzed on a treatment-received basis.

Results

Baseline Demographics

Thirty-three patients from 11 centers (17 diabetic [9 male and 8 female] and 16 female idiopathic patients) from 19 to 65 years old were enrolled. The number of patients enrolled at each center varied from 1 to 13. These patients were highly symptomatic, with a median weekly vomiting frequency of 17.3 episodes per week and with mean vomiting and nausea severity scores of 3.3 and 3.5, respectively; had delayed gastric emptying at 2 and 4 hours; and met all entry criteria. Most were receiving antiemetic (n = 25) or prokinetic (n = 28) therapy, and 14 required some form of enteral or paren-

teral feeding. Vomiting and other symptoms suggestive of gastroparesis were present for a mean of 6.2 years. See Table 1 for patient demographics.

Phase I

All patients completed phase I, and none crossed from ON to OFF or from OFF to ON prematurely. Table 2 summarizes the phase I results. There was a significant treatment effect for the combined patient group, with a 50% decrease in median vomiting frequency between stimulation OFF and ON ($P < 0.05$). The diabetic and idiopathic subgroups also experienced a decreased vomiting frequency between stimulation OFF and ON (53% and 7% decrease in median vomiting frequency, respectively), but these changes did not reach statistical significance ($P = 0.16$ for both groups). For the combined group, all symptom severity scores, TSS, 5 of 8 SF-36 subscores, and the 2 composite summary scores trended toward improvement in the ON vs. OFF period, although these changes did not reach statistical significance.

Before breaking the blind at the end of phase I, 21 patients (10 diabetic and 11 idiopathic) expressed preference for the stimulation ON, whereas 7 (4 diabetic and 3 idiopathic) preferred stimulation OFF, and 5 (3 diabetic and 2 idiopathic) had no preference. Preference for stimulation ON was statistically significant for the combined

Table 2. Phase I Results

Variable	All Patients		Diabetic Patients		Idiopathic Patients	
	OFF	ON	OFF	ON	OFF	ON
WVF	13.5 (5.5–25.4)	6.8 (3.9–16.5) ^a	12.8 (5.5–24.2)	6.0 (3.0–14.8)	13.8 (5.4–27.8)	12.8 (4.0–20.3)
TSS	13.9 ± 1.1	12.5 ± 1.0	13.2 ± 1.7	11.3 ± 1.5	14.8 ± 1.3	13.8 ± 1.4
Patient preference	7	21 ^a	4	10	3	11 ^a

NOTE. Weekly vomiting frequency (WVF; episodes/week) is reported as median and interquartile range. Total symptom score (TSS) is reported as mean ± SE. Patient preference is the number of patients who preferred ON or OFF before the blind was broken in phase I; 3 diabetic and 2 idiopathic patients expressed no preference.

^a $P < 0.05$

group ($P < 0.05$) and the idiopathic subgroup ($P < 0.05$), but not for the diabetic subgroup ($P = 0.08$).

Phase II Results

All patients had their stimulators turned ON at the beginning of phase II, and all remained ON through the 6- and 12-month follow-up visits. No patient's stimulator was turned OFF during phase II. Phase II results are summarized in Table 3. Vomiting frequency at the 6- and 12-month follow-up visits significantly decreased when compared with baseline ($P < 0.05$). More specifically, at 6 months, the median vomiting frequency decreased 85%, 81%, and 88% for the combined, diabetic, and idiopathic patient groups, respectively. At 12 months, vomiting frequency decreased 72%, 63%, and 83% for the combined, diabetic, and idiopathic patient groups, respectively. When stimulation OFF (phase I) was compared with the 12-month follow-up visit (phase II), vomiting frequency decreased 64% for the combined group ($P < 0.01$), 62% for the diabetic group ($P =$

0.054), and 67% for the idiopathic group ($P = 0.057$). See also Figure 2.

Further analysis showed that, when compared with baseline, the median vomiting frequency at 12 months decreased by $>50\%$ in 70% of diabetic patients and 77% of idiopathic patients, and it decreased by $>80\%$ for 50% of the patients in both groups. Only 13% of patients overall had a decrease in vomiting frequency $<25\%$.

TSS was significantly improved ($P < 0.05$) at 6 and 12 months compared with baseline for the combined group and for both etiologies. For the combined group, 4 of 6 symptom subscores were significantly improved at 6 months, and 3 of 6 symptom severity scores were significantly improved at 12 months ($P < 0.005$). Vomiting and nausea severity subscores were significantly improved in the diabetic subgroup at 6 and 12 months, whereas the vomiting severity and epigastric pain were significantly improved in the idiopathic subgroup at 6

Table 3. Phase II Results

Variable	Baseline			All Patients		Diabetic		Idiopathic	
	All Patients	Diabetic	Idiopathic	6 Mo	12 Mo	6 Mo	12 Mo	6 Mo	12 Mo
WVF and symptom severity (n)	33	17	16	27	24	13	11	14	13
WVF	17.3 (11.8–45.7)	13.4 (8.8–55.6)	26.8 (13.0–38.4)	2.6 (0.6–12.0) ^a	4.8 (0.1–7.6) ^a	2.6 (0.9–12.5) ^a	4.9 (0.1–7.4) ^a	3.0 (0.2–13.8) ^a	4.5 (2.5–7.0) ^a
Vomiting	3.3 ± 0.1	3.4 ± 0.1	3.3 ± 0.2	2.0 ± 0.3 ^b	2.0 ± 0.3 ^b	1.9 ± 0.4 ^b	1.8 ± 0.5 ^b	2.0 ± 0.4 ^b	2.2 ± 0.5
Nausea	3.5 ± 0.1	3.4 ± 0.1	3.5 ± 0.2	2.4 ± 0.2 ^b	2.4 ± 0.3 ^b	2.3 ± 0.4 ^b	2.3 ± 0.3 ^b	2.5 ± 0.3	2.5 ± 0.5
Early satiety	2.5 ± 0.2	2.4 ± 0.3	2.7 ± 0.3	1.9 ± 0.3	1.7 ± 0.3 ^b	2.0 ± 0.4	1.4 ± 0.4	1.9 ± 0.4	1.9 ± 0.4
Bloating	2.3 ± 0.2	2.5 ± 0.4	2.1 ± 0.3	1.5 ± 0.2 ^b	1.5 ± 0.3	1.4 ± 0.3	1.3 ± 0.4	1.6 ± 0.3	1.5 ± 0.3
Postprandial fullness	2.6 ± 0.2	2.7 ± 0.3	2.6 ± 0.4	1.6 ± 0.3	1.5 ± 0.3	1.5 ± 0.4	1.2 ± 0.4	1.7 ± 0.4	1.8 ± 0.4
Epigastric Pain	2.6 ± 0.3	2.4 ± 0.4	2.8 ± 0.3	1.5 ± 0.3 ^b	1.9 ± 0.4	1.5 ± 0.3	1.0 ± 0.4	1.5 ± 0.4 ^b	2.6 ± 0.5
TSS	16.8 ± 0.9	16.8 ± 1.2	16.9 ± 1.3	11.1 ± 1.3 ^a	11.4 ± 1.3 ^a	10.7 ± 1.7 ^a	9.2 ± 1.5 ^a	11.6 ± 1.9 ^a	13.2 ± 2.0 ^a
SF-36 parameters (n)	33	17	16	29	24	15	11	14	13
Physical functioning	33.6 ± 3.7	34.4 ± 5.3	32.8 ± 5.1	51.2 ± 5.0 ^b	49.9 ± 5.5 ^b	48.3 ± 5.4 ^b	56.8 ± 7.4	54.3 ± 8.8 ^b	43.9 ± 7.9
Role physical	7.6 ± 3.6	11.8 ± 6.8	3.1 ± 2.1	30.5 ± 7.1 ^b	33.3 ± 8.6 ^b	20.6 ± 7.8 ^b	43.2 ± 13.1	41.1 ± 11.6 ^b	25.0 ± 11.3
Bodily pain	26.8 ± 4.1	31.6 ± 6.3	21.6 ± 5.3	50.0 ± 4.9 ^b	42.0 ± 5.4 ^b	52.3 ± 7.7 ^b	52.4 ± 8.4	47.4 ± 6.2 ^b	33.3 ± 6.2 ^b
General health	21.0 ± 2.4	17.9 ± 2.9	24.3 ± 3.8	36.6 ± 4.5 ^b	38.6 ± 4.2 ^b	29.3 ± 5.6	39.2 ± 4.7 ^b	44.4 ± 6.7	38.0 ± 6.8
Vitality	21.4 ± 3.4	17.7 ± 3.4	25.4 ± 6.0	37.6 ± 4.1 ^b	40.6 ± 4.3 ^b	33.7 ± 3.9	45.9 ± 3.1 ^b	41.8 ± 7.4	36.2 ± 7.4
Social functioning	26.9 ± 4.1	28.7 ± 6.0	25.0 ± 5.8	55.2 ± 6.1 ^b	53.6 ± 6.6 ^b	53.3 ± 8.2 ^b	61.4 ± 7.4 ^b	57.1 ± 9.2 ^b	47.1 ± 10.4
Role emotional	31.3 ± 7.0	43.8 ± 10.4	18.8 ± 8.6	56.3 ± 8.5	52.8 ± 8.7	48.9 ± 12.1	57.6 ± 12.8	64.3 ± 11.8	48.7 ± 12.3
Mental health	50.7 ± 3.9	50.6 ± 6.4	50.8 ± 4.7	62.0 ± 4.4	66.8 ± 4.1 ^b	59.6 ± 6.5	72.7 ± 5.5	64.6 ± 6.0	61.8 ± 5.8
PCS	25.8 ± 1.5	26.1 ± 2.3	25.4 ± 1.9	33.5 ± 2.0 ^c	32.4 ± 2.2 ^c	32.0 ± 2.0 ^c	35.2 ± 2.9 ^c	35.1 ± 3.5 ^c	30.0 ± 3.2
MCS	36.1 ± 2.2	37.3 ± 3.5	34.9 ± 2.8	43.7 ± 2.4 ^c	45.1 ± 2.1 ^c	42.0 ± 3.5	47.3 ± 2.2	45.5 ± 3.4	43.3 ± 3.4
GET (n)	33	17	16	26	20	11	9	15	11
GET (2 h)	78 (67–84)	80 (69–88)	76.5 (64–79)	65 (53–80) ^a	56 (45–74) ^a	67 (50–79)	46 (29–61)	62 (54–80)	59 (52–77)
GET (4 h)	34 (26–57)	46 (28–68)	28.0 (25–38)	27 (14–54)	22 (11–37) ^a	44 (21–67)	16 (1–30) ^a	20 (11–46)	23 (17–49)

NOTE. Weekly vomiting frequency (WVF; episodes/week) and gastric emptying results (GET; % retention) are reported as median and interquartile range. All other outcomes are reported as mean ± SE.

^a $P < 0.05$; ^b $P < 0.005$; ^c $P < 0.025$.

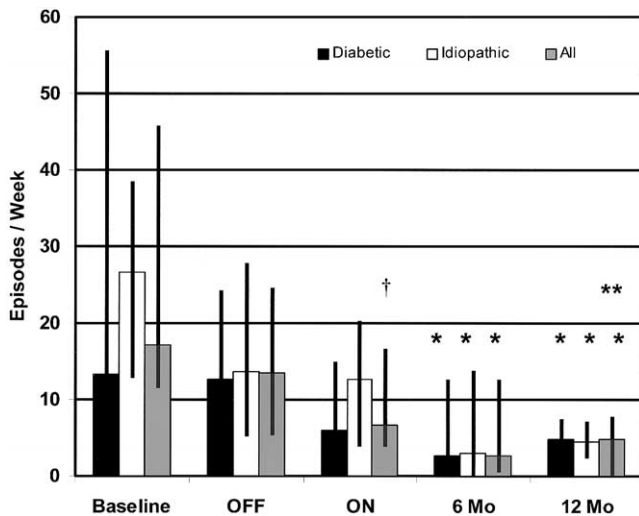


Figure 2. Weekly vomiting frequency (median and interquartile range). The bar graph illustrates the changes in weekly vomiting frequency as recorded in patient diaries at baseline, during the ON and OFF periods of the double-blind phase, and at 6 and 12 months during the open-label phase. Diabetic: baseline, $n = 17$; ON, $n = 17$; OFF, $n = 17$; 6 months, $n = 13$; 12 months, $n = 11$. Idiopathic: baseline, $n = 16$; ON, $n = 16$; OFF, $n = 16$; 6 months, $n = 14$; 12 months, $n = 13$. ($\dagger P < 0.05$, ON vs. OFF; $* P < 0.05$ vs. baseline; $** P < 0.05$ vs. OFF).

months ($P < 0.005$). Enteral or parenteral nutritional support was necessary for 14 patients at baseline and 7 patients at 12 months.

At baseline, mean PCS scores (24.2 and 24.6 for the diabetic and idiopathic subgroups, respectively) were significantly below the US norm (50 ± 10 ; $P < 0.0001$). Likewise, mean MCS scores (13.5 and 15.1 for the diabetic and idiopathic subgroups, respectively), were significantly below the US norm (50 ± 10 ; $P < 0.0001$).¹² Mean PCS scores were significantly improved for all 3 groups (diabetic, idiopathic, and combined) when 6-month data were compared with baseline ($P < 0.025$) and were significantly improved in the diabetic and combined groups when 12-month data were compared with baseline ($P < 0.025$). Mean MCS scores were significantly improved for the combined group when both 6- and 12-month data were compared with baseline ($P < 0.025$). Refer to Table 3 for details about subscore improvement.

Gastric emptying results at baseline, 6 months, and 12 months are shown in Table 3. Baseline 2-hour gastric retention of an isotope-labeled meal was 78% for the combined group, and this decreased significantly ($P < 0.05$) to 65% at 6 months and 56% at 12 months. The changes in 2-hour gastric emptying were not significant for the diabetic and idiopathic groups separately. Baseline 4-hour gastric retention of an isotope-labeled meal was 34% for the combined group, and this decreased significantly ($P < 0.05$) to 22% at 12 months. Four-hour

gastric retention for the diabetic group declined significantly from a baseline of 46% to 16% at 12 months ($P < 0.05$). At 12 months, 6 of 9 diabetic patients and 6 of 11 idiopathic patients had 2- or 4-hour gastric retention that was within the reference range established for this study ($< 60\%$ at 2 hours and $< 10\%$ at 4 hours).

There was no correlation between baseline vomiting frequency and gastric emptying at 2 or 4 hours ($r = 0.03$ and $r = 0.02$, respectively). Additionally, there was no correlation between changes in vomiting frequency and changes in 2- or 4-hour gastric emptying between baseline and 6 months ($r = -0.18$ and $r = -0.22$) or between baseline and 12 months ($r = -0.04$ and $r = 0.10$).

Several device-related adverse events required surgical intervention. Infection of the neurostimulator pocket occurred in 2 idiopathic patients (6%) and necessitated surgical removal of the device. The system was removed in an idiopathic patient because of pain related to lead perforation of the stomach and in a diabetic patient in whom the pulse generator eroded through the skin. Discomfort from migration of the pulse generator necessitated surgical intervention to reposition and reanchor the pulse generator in another idiopathic patient.

Discussion

The results of phase I, the double-blind study period, showed a consistently positive outcome for the combined group (significantly decreased vomiting frequency and preference for stimulation ON). The results of phase I were less compelling when each patient subgroup was examined separately (i.e., there was no significant difference in vomiting frequency in either the diabetic or idiopathic subgroup and no significant difference in ON/OFF preference in the diabetic subgroup). Several factors may explain these findings. A larger number of enrolled patients would have caused more robust statistics. Second, the duration of phase I may not have been sufficiently long enough for improvements in symptoms or GI function to occur in all patients. More recent data indicate that 2 to 3 months may be required before sustained improvement from GES is observed.⁸ Third, ileus, a common postoperative side effect,¹⁵ may be exacerbated or prolonged in patients with gastroparesis. Fourth, prolonged postoperative use of pain medication may have interfered with gut motility during phase I. Finally, during phase I, the diabetic patients were still equilibrating in regard to glucose control after the stress of surgery and the subsequent return to more substantial oral and/or enteral intake than before or during the surgery period. For these reasons, we recommend that future protocols include a postoperative recovery time of

1 to 3 months before randomization and that electrical stimulation in placebo-controlled studies be extended to at least 3 months.

During phase II, the statistically significant decrease in vomiting frequency and TSS reflected a striking clinical turnaround for our patients. These results are consistent with earlier studies of GES in gastroparesis. For example, 9 diabetic, idiopathic, and postsurgical patients receiving an external high-energy/low-frequency neurostimulator for up to 90 days experienced a significant improvement in symptoms.⁵ In another report, vomiting and nausea decreased significantly, and the decrease was sustained over 12 months.⁸ Finally, an open-label trial of GES in a heterogeneous group of 26 diabetic, idiopathic, and postsurgical patients that used an implanted neurostimulator (programmed to the same parameters as in this study) over 3 to 6 months indicated significant symptom reduction.⁹

Based on our experience managing patients with severe symptoms from gastroparesis who are unresponsive to medical therapy, we believe that an $\geq 50\%$ reduction in weekly vomiting frequency reflects a meaningful reduction in patient symptoms. Applying this criterion to our study, we observed that 70% of idiopathic and 77% of diabetic patients experienced a $\geq 50\%$ reduction in weekly vomiting frequency at 12 months compared with baseline. However, we observed a reduction in weekly vomiting frequency of $< 25\%$ in 13% of patients, whom we consider therapy nonresponders.

We observed significant improvement in HQOL scores in our patients with MCS, who improved to within 1 SD of the normal US range for the combined group at 6 and 12 months. These findings are consistent with previous research in which effective drug treatment of severe dyspepsia or gastroparesis was highly correlated with enhanced quality of life.¹⁶⁻¹⁸ At 12 months, our diabetic patients experienced greater improvements in mean PCS and MCS (+9.4 and +10.8, respectively) than did diabetic patients in a recent domperidone trial (+3.57 and +5.23, respectively).¹⁷

The symptom improvement observed in this study was more consistent in the diabetic (vs. idiopathic) subgroup. This may be because the idiopathic patients reflect a relatively heterogeneous population when compared with the diabetic patients. More specifically, idiopathic gastroparesis may be related to any of a number of factors, including viral illness, gastroesophageal reflux, nonulcer dyspepsia, abdominal pain, and depression. Idiopathic patients tend to have a longer symptom duration and poorer quality of life than that seen in other subgroups with gastroparesis, perhaps explaining the more limited improvement we observed with that etiology.¹⁹

The mechanism of action of GES in this study is unclear. The intensity of stimulation used is insufficient to cause either direct contraction of smooth muscle or entrainment in the gastric electrical rhythm. Although gastric emptying did normalize in approximately 50% of patients evaluated at 12 months, improvement varied widely, and there was no association between changes in symptoms and gastric emptying ($r = -0.04$ to $r = 0.1$); this is consistent with earlier studies in gastroparesis.^{18,20-22} Thus, it seems likely that the effect of GES is due to factors beyond gastric motility or dysrhythmias. Short-pulse stimulation, similar to the parameters used in this study, was evaluated in a canine model by using vasopressin to induce gastric dysrhythmias and vomiting in both intact and vagotomized animals.²³ Short-pulse stimulation produced a significant reduction in vomiting in the intact animals, but not in those with acute vagotomy, and the authors concluded that the antiemetic effect of short-pulse stimulation was vagally mediated. A recent clinical report, however, indicated that GES had an antiemetic effect in gastroparetic patients, including those with long-standing postsurgical gastroparesis,⁹ suggesting that the effects of GES stimulation may not be solely vagally mediated. GES has been shown to affect the dominate power of the slow wave,¹⁰ and other recent work indicates that fundic relaxation,²⁴ the autonomic system,²⁵ or GI hormones²⁶ may all be affected by GES. Further research will be necessary to clarify the major contributing mechanisms.

Although relatively few complications were identified during the 12-month follow-up, those that occurred required active interventions. Infections at the implant site almost always necessitate the surgical removal of the device, so we recommend that the implant site be irrigated with antibiotic solution during surgery and that IV antibiotics be administered perioperatively. Although most surgeries in this study used laparotomy, laparoscopy is less invasive and may reduce the infection rate. Simultaneous intraoperative endoscopy is now routinely performed to permit immediate detection of gastric wall perforation, and then electrode repositioning can take place.

On the basis of the number of patients who are refractory to, or cannot tolerate, standard medical therapy for gastroparesis, it is estimated that 25%–50% of those referred to major medical centers may be candidates for GES. Future research trials should account for the study design deficiencies noted previously. Despite this caveat, GES therapy represents a major advance in the treatment of medically refractory gastroparesis and may open the door for the application of GES technology to the GI tract for other indications.

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Received September 17, 2002. Accepted May 15, 2003.

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Supported in part by Medtronic, Inc.

Portions of the study were presented in abstract form at the American Gastroenterological Association meetings in 2001 and 2002.

The authors would like to acknowledge the following individuals who supported this study: G. Voeller, M.D., P. Eaton, R.N., and R. Werkman (University of Tennessee); Theresa Cutts, Ph.D. (University of Tennessee); Lesa Gann (University of Arkansas); C. Sninsky, M.D., and S. Fitz William, R.N. (University of Florida); R. Delcore, M.D., J. Forster, M.D., Z. Lin, M.S., G. Raju, M.D., and I. Sarosiek, M.D. (University of Kansas); G. Kaufman, M.D., L. Xu, M.D., and S. Bingaman, R.N. (Penn State University); H. Lonroth, M.D., and M. Capocci, R.N. (University of Göteborg); P. Ducrotté, M.D., and A. M. Leroi, R.N. (Hospital Charles Nicolle); S. Ramel, M.D., S. Bringman, M.D., and M. Iwarzon, R.N. (Karolinska Institute); M. Dietel, M.D., and I. R. van der Voort, M.D. (University of Münster); J. Hammond, M.D. (St. Vincent's Hospital); J. Thompson, M.D., J. DiBaise, and F. Park, R.N. (University of Nebraska); W. E. Waterfall, M.D., and U. Chauhan, R.N. (McMaster University); J. P. Galmiche (University of Nantes); and G. Vantrappen (University of Leuven). Michael Hull also assisted with the statistical analysis.