Gastric Electrical Stimulation in Gastroparesis: Where Do We Stand?

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Key Words

Gastroparesis · Gastric myoelectric activity · Gastric electrical stimulation · Gastric pacing/low-frequency stimulation · High-frequency stimulation

Abstract

Gastroparesis is a chronic disabling condition of impaired gastric motility that results in decreased quality of life. Currently available medical therapy consists of prokinetic and/or antiemetic therapy, dietary modifications, and nutritional supplementation. For patients with medication-resistant gastroparesis a non-pharmacological therapy, gastric electric stimulation, has evolved over the last decade. Based on the frequency of the electrical stimulus, gastric electric stimulation can be classified into low- and high-frequency gastric electric stimulation. The first method aims to normalize gastric dysrhythmia and entrain gastric slow waves and accelerates gastric emptying, whereas high-frequency gastric electric stimulation is unable to restore normal gastric emptying, but nevertheless stunningly reduces symptoms, such as nausea and vomiting, re-establishes quality of life, nutritional state in all patients, and metabolic control in patients with diabetic gastroparesis. Gastric electric stimulation presents a new possibility in the treatment of gastroparesis.

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Introduction

Gastroparesis is a chronic disorder which is characterized by delay in gastric emptying in the absence of mechanical obstruction that presents with variable symptoms including nausea, vomiting, bloating, early satiety, and discomfort. In severe cases this can lead to dehydration, and weight loss, electrolyte disturbances, and malnutrition [1, 2].

The two main causes of gastroparesis are idiopathic and diabetes mellitus. More than 30% are idiopathic, whereas approximately 25–30% of cases with gastroparesis result from long-standing diabetes mellitus, usually type 1 [2]. Other causes of gastroparesis include: collagen vascular diseases as scleroderma and amyloidosis; post-surgical after partial gastric resection, vagotomy, post-bariatric surgery, or Nissen fundoplication; eating disorders as anorexia; gastrointestinal disorders as gastroesophageal reflux disease, achalasia, functional dyspepsia, chronic intestinal pseudo-obstruction, gastric ulcer, and celiac disease; neurological disorders; gastric infection, and paraneoplastic and medication-associated conditions [3]. The majority of patients with gastroparesis (up to 82%) are women [2].

In some cases of idiopathic gastroparesis the pathogenesis is believed to be post-infectious after a viral infection, resulting in temporary or permanent damage to the myenteric plexus [4]. Others have reported myenteric hypoganglionosis and reduction in numbers of interstitial cells

of Cajal as cause of idiopathic gastroparesis [5]. Diabetic gastroparesis is likely to result from impaired neuronal control of gastric motility, possibly at the level of the vagus nerve [6]. Other factors, as impairment of inhibitory nitric oxide-containing nerves [7], damage of the pacemaker interstitial cells of Cajal [8], and underlying smooth muscle dysfunction, have also been described in animal models and patients with diabetic gastroparesis [9–11], as well as sensory nerve dysfunction in patients with type 1 diabetes [12].

Standard therapy of gastroparesis includes dietary measures and medication with prokinetic and antiemetic agents, such as cisapride (the availability of which has been severely restricted), domperidone, metoclopramide, and erythromycin [13–16]. Some patients do not tolerate these drugs, due to the occurrence of side effects, such as anxiety, tremors, dystonia in metoclopramide, hyperprolactinemia using domperidone, or abdominal cramps and vomiting caused by erythromycin due to its narrow therapeutic window. Recently, tegaserod, a partial 5-HT₄ receptor agonist, has been suggested to be of use in the treatment of gastroparesis [17–19], but further investigation is needed to prove its benefit for this condition. Other therapeutic options include pyloric injection of botulinum toxin [20–22], placement of feeding jejunostomy [23, 24], or gastric surgery as last resort in carefully evaluated patients with profound gastric stasis [25, 26].

Due to the limited efficacy of the standard therapeutic options in patients with medication refractory gastroparesis, new approaches for treatment were developed. One of these approaches is the stimulation of gastric motor activity with an implantable electrical device.

Gastric Myoelectric Activity

The gastric myoelectric activity originates from the gastric pacemaker area located in a small zone of the proximal gastric corpus near the greater curvature from interstitial cells of Cajal type I [27–29]. These produce a so-called slow wave, i.e. myoelectrical activity at a frequency of about 3/min which propagates circumferentially and distally towards the pylorus in form of incomplete depolarization-repolarization annular bands. It is known that frequency and propagation of gastric contraction are determined by the gastric slow wave. This occurs when spikes are superimposed on the slow wave indicating electromechanical coupling [30, 31].

Gastric motility is controlled by myoelectrical activity of the stomach, and impaired motor activity due to dis-

turbed myoelectrical activity can play a role in gastroparesis [32–36]. Gastric electrical stimulation is an approach aiming to restore recurring myoelectrical activity.

Gastric Electrical Stimulation

Investigators have used two different pacing frequencies in gastric electrical stimulation (GES); the first is at or just above the intrinsic gastric slow-wave frequency, which is able to induce propagated slow waves [37], this is also called gastric pacing or low-frequency stimulation. The second type of GES is at a high frequency, at a frequency much higher than that of the native slow waves, which is unable to induce propagated slow waves, and its frequency is about 10–1,200 cycles/min.

Gastric Pacing/Low-Frequency Stimulation

As early as 1972, research showed entrainment of slow waves with gastric pacing in dogs using 0.8–1.6 times the intrinsic slow-wave frequency [37–39]. In other canine studies, impaired gastric emptying was induced by vagotomy in combination with injection of glucagon [40, 41] or evoked by atropine [42]; electrical stimulation at 1–1.1 times the intrinsic gastric slow-wave frequency normalized the dysrhythmic activity. In the vagotomy plus glucagon investigation it produced a significant acceleration in gastric emptying of a solid meal. However, gastric emptying was not altered in intact or normal dogs [40, 41]. Other studies could confirm that gastric pacing had no effect on gastric emptying of a mixed [43] or liquid meal [44] under normal conditions. It can be concluded that low-frequency electrical stimulation may restore normal frequency of slow-wave activity in gastric dysrhythmia, and has no effect on gastric emptying in healthy dogs but improves gastric emptying in animal models of gastroparesis.

Several human studies using gastric pacing (low-frequency gastric stimulation) have been published [45–53]; all of them showed that this leads to entrainment of gastric slow waves. An effect on gastric motility was observed in two of these, one study reported the reappearance of phase III activity [48] and the other an increase in spike activity [49]. Both studies were only published as abstracts, with a total of 4 patients. Improvement of gastric emptying has been reported by Courtney et al. [49] in 3 patients with severe gastroparesis in a single-patient

case report [45], both published as abstracts. A study by McCallum et al. [47] investigated 9 patients with medication-resistant gastroparesis (5 diabetic, 3 idiopathic, and 1 post-surgical). After 1 month of daily gastric pacing before and after meals with a portable stimulator, symptoms of gastroparesis were substantially reduced at the end of the outpatient treatment of 1–3 months. Eight of 9 patients no longer relied on jejunostomy tube feeding. A significant improvement of gastric retention was observed at 2 h after a solid meal compared to baseline without pacing, and 6 out of 9 patients had normal values for gastric emptying at 2 h after the test meal. However, this study had no controls and permitted the continued use of prokinetic medication (cisapride). Therefore, further studies under controlled conditions are needed to convincingly investigate the efficacy of gastric pacing in treating gastroparesis.

High-Frequency Stimulation

Eagon and Kelly [43] studied proximal GES over a wide range of frequencies (3, 6, 30, and 1,200 cpm) in 4 conscious dogs while fasting, after feeding, and during pentagastrin infusion. Electrical stimulation at frequencies from 6 to 30 cpm, but not at 1,200 cpm, increased the frequency of slow waves during fasting and feeding. Pentagastrin increased the intrinsic slow-wave frequency such that electrical stimulation no longer altered the frequency of the slow waves. However, they observed that at frequencies of 6 and 30 cpm, GES had no effect on gastric contractile activity or gastric emptying of liquids. In contrast, an increase in gastric contractions and more rapid gastric emptying of contrast media was shown by a study in 8 vagotomized dogs using serosal electrodes sewn to the antrum and duodenum for electrical stimulation at a frequency of 1,200 cpm [54]. Familoni et al. [55] and Johnson et al. [56] also found an increase in contractile activity and gastric emptying, with the greatest increase in amplitude of the gastric myoelectric activity and contractile response occurring at GES with a frequency of 30 cpm. Also, prevention of vomiting induced by vasopressin was reported in an abstract at a frequency of 20 cpm [57].

Based on study results of a canine model [55], where GES at 20 cycles/min elicited the largest motility index of all frequencies tested (which is about 4 times of the physiological rate), Familoni et al. [58] report the use of electrical stimulation at 12 cpm (4 times the rate of the nominal physiologic frequency) in a patient with refrac-

tory diabetic gastroparesis. GES was first delivered via temporary mucosal electrodes inserted through a percutaneous gastrostomy and subsequently via serosal implanted electrodes. Gastric emptying of a liquid meal over a period of 120 min improved from less than 2% at baseline to 28% after 1 week of pacing via the temporary electrodes. At weeks 4, 15, and 52 following placement of the permanent electrodes, the amount emptied from the stomach in 120 min was 28, 97, and 56%, respectively [58]. Following this case report, a study of the so-called GEMS (gastric electromechanical stimulation) group was presented at several national meetings [59, 60] and published in 2002 [61]. Thirty-eight patients with documented gastroparesis were recruited, 24 patients had idiopathic gastroparesis, 9 patients diabetic gastroparesis, and 5 subjects post-surgical gastroparesis. The study consisted of two phases. Phase I involved temporary stimulation via percutaneous electrodes for 2–4 weeks at a frequency of 12 cpm. Patients with a reduction of more than 80% of nausea and vomiting were eligible for phase II; the patients in the USA were additionally required to have an improvement of at least 35% in the gastric emptying test prior to inclusion into phase II. In the second phase, permanent electrodes were placed in the gastric serosa and connected to a neurostimulator implanted in a subcutaneous abdominal pocket. The neurostimulator was activated to the same parameter as in phase I for 12 months, except for a 1-week period at 6 months where the device was deactivated. Nausea, vomiting, body weight, medication use, and nutrition were serially evaluated, and gastric scintigraphy was repeated at 3, 6, and 12 months [61]. Although uncontrolled, this study showed that most patients reported a reduction in nausea and vomiting of more than 90%. Further, beneficial effects on body weight, antiemetic and prokinetic drug needs, and the use of supplemental nutrition were reported. This study was published quite some years after the implantation; follow-up data was not available for all patients still in the trial at 6 and 12 months. Furthermore, in the study, device deactivation at 6 months did not elicit recurrent nausea and vomiting in a large patient subset, raising the possibility that symptom improvements are unrelated to the electrical stimulus or that device activation time of 1 week was not sufficient to observe this. Gastric emptying had not changed or worsened at 12 months in 53% of the patients. A study in 25 patients with gastroparesis (19 with diabetic gastroparesis) showed that this benefit was sustained at 12 months [62]. A weight gain of up to 8 lb (3.63 kg) at 6 months and 15 lb (6.80 kg) by 12 months was observed, and 79% of study participants had their

jejunostomy tubes removed by 6 months. Gastric emptying was not affected overall, only 25–30% of patients did have normalization of their gastric emptying rate at 1 year. The most commonly seen complication has been pacemaker hardware infection requiring device removal. This has been observed in approximately 5% of patients, most of them having long-standing diabetes.

The first double-blind trial was published in 2003 and involved 33 patients with idiopathic or diabetic gastroparesis [63]. This international, multicenter trial had a randomized, cross-over design with the device being on for 1 month, off for 1 month and with follow-up for 12 months. Patients included in the study had symptoms of gastroparesis for more than 1 year, were drug refractory, and had a vomiting frequency of more than 7 times/week. Gastric retention of a radionuclide-containing standardized, low-fat egg meal was abnormally slow at 2 and 4 h after ingestion. Many of these patients had lost more than 10% of their body mass index and had been hospitalized frequently. Results from this study showed significant reductions in the frequency of nausea and vomiting for the 'on' vs. 'off' period, as well as sustained effects at 6 and 12 months for both the diabetic and idiopathic patient groups. Overall, 79% of patients had a 50% or greater decrease in vomiting. The benefit for the whole symptom spectrum, as measured by total symptom score (i.e., nausea, vomiting, bloating, fullness, satiety, and pain), was not as dramatic as for vomiting alone, but was still significant. Two-hour gastric retention decreased significantly at 6 and 12 months for all patients but was not decreased for the diabetic and idiopathic groups if analyzed separately. Four-hour gastric retention only decreased significantly at 12 months for all patients and for the diabetic patients. No correlation between changes in vomiting frequency and changes in gastric emptying was established [63].

Further uncontrolled studies have been reported showing an improvement of nutritional parameters throughout the first 12 months, as nausea and vomiting decreased and oral intake increased in 12 patients with gastroparesis [64]. This improvement in nutritional measures could be maintained over a long period of time (up to 5 years) and was associated with improvement in quality of life [64], but this publication did not report the results of gastric emptying tests over time. Forster et al. [65] reported on a large series of 55 patients with gastroparesis of diverse origin. Total symptom scores, physical and mental composite scores of quality of life improved significantly, but gastric emptying was only significantly improved at 6 months, not at 12 months. However, a third of the pa-

tients had normal gastric emptying. At 12 months the hemoglobin A_{1c} level was significantly reduced in diabetic patients [65]. In a study of 48 diabetic gastroparesis patients [66] and 17 diabetic gastroparesis patients [67], the significant reduction in hemoglobin A_{1c} could be confirmed. The later study was able to display a significant difference in gastric emptying at 6 and at 12 months. A study in 16 patients with post-surgical gastroparesis showed an improvement in symptoms, without an improvement in gastric emptying [68]. A recent study used temporary electrodes placed via an endoscope or PEG, which produced a rapid, significant, and sustained improvement in the vomiting score that corresponded to the effects achieved with permanent GES [69]. The investigators concluded that effects at short-term placement of an electrode for GES may be predictive of long-term response to this treatment [69].

A recent study by Cutts et al. [70] analyzed the financial impact of GES on the overall care of gastroparesis, and concluded that GES is more cost-effective than medical therapy in long-term improvement of gastrointestinal symptoms, and decreasing use of healthcare resources in their patient population.

Conclusion

Numerous studies have been conducted to find the ideal parameters in GES. As mentioned before, mainly two different approaches have been employed in the chronic treatment of gastroparesis.

The first is gastric electrical pacing or also called low-frequency GES, which has been shown to induce a regular electrical rhythm, but it is unable to restore efficient contractions, and in one uncontrolled study in humans improved gastric emptying and symptoms at continued use of prokinetics [47].

The second type of GES is high-frequency GES. This method does not significantly modify slow-wave activity and does not influence gastric emptying in most studies. Nonetheless, it is able to significantly reduce symptoms of nausea and vomiting in various types of gastroparesis. The only controlled study was performed by Abell et al. [63], where improvement in symptoms of nausea and vomiting was significant compared to the sham stimulation.

In general, the effect of high-frequency GES on gastric contractility is unclear, as is the mechanism of action in decreasing symptoms. Accelerations in gastric emptying times have been noted in some patients; however, this

response is unpredictable and the majority of treated patients continue to have abnormal gastric emptying times after implantation.

Furthermore, there have been poor correlations for both procedures between changes in symptoms and gastric emptying. Therefore, well-controlled studies in well-defined patient populations will be needed to assess the clinical efficacy of GES in the treatment of gastroparesis.

Few studies have investigated the possible mechanisms involved in the effects of GES. It has been hypothesized that the symptomatic improvement that has been observed is caused by modulation of enteric or afferent neural activity that consequently influences symptom perception or a central nausea and vomiting control mechanism [71]. Also, there have been recent reports indicating that GES therapy changes various electrogastrographic parameters, fundic relaxation, the autonomic nervous system, and gastrointestinal hormone levels [72–74]. Forster et al. [75] could show that one third of patients with idiopathic and diabetic gastroparesis have absent cells of Cajal on full-thickness gastric biopsies, and

that these patients have increased abnormalities of gastric slow waves and a more severe symptom status, as well as a poorer outcome with GES therapy. Further studies are needed to investigate the possible mechanisms which might play a role in GES.

Newer methods that have been proposed include a device that uses a series of chains of electrodes that encircle the gastric corpus and antrum and are activated sequentially [76, 77]. These successive rings of electrodes affixed to the gastric mucosa deliver current pulses 1,000 times the frequency of the intrinsic slow wave. Results from dog studies have shown that gastric contractions are reliably produced and gastric emptying accelerated with this technology [78]. Also, high-energy gastric pacing (3 cpm) that pass impulses segmentally from the proximal to distal stomach through 3–4 electrodes have been developed. Such a high-energy system has already been shown to be effective in preliminary studies [47].

The results of these developments are encouraging and suggest that in the future an improved GES therapy for gastroparesis will be available.

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