Gastric Electrical Stimulation Results in Improved Metabolic Control in Diabetic Patients Suffering From Gastroparesis

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Article

Abstract

Aims/hypothesis: Symptoms of gastroparesis possess a heavy impact on the quality of life; delayed gastric emptying may result in poor metabolic control in diabetics. Gastric electrical stimulation (GES) has recently been introduced as a treatment option in patients with drug refractory gastroparesis to increase the quality of life by alleviating nausea and vomiting frequencies. However, the effect of GES on metabolic control has not been assessed yet.

Methods: We performed a prospective single center study on the long-term effect (12 months) of continuous high-frequency/low-energy GES on symptoms, gastric emptying (measured scintigraphically), and metabolic control (HbA1c) in insulin-dependent diabetic subjects suffering from drug-refractory gastroparesis for more than one year.

Results: Seventeen (12 female, 5 male) patients entered the study; all were available for analysis at all time points. No therapy-associated adverse events occurred. Weekly vomiting and nausea frequencies decreased significantly at 6 and 12 months. Gastric retention rates improved significantly from 83% (2 h) and 38% (4 h) to 35% (2 h)/14% (4 h) and 25% (2 h)/17% (4 h) at 6 and 12 months, respectively. HbA1c values were lowered in all 17 subjects; initially, all HbA1c values were above 7.5%; at 6 and 12 months, mean values had significantly decreased from 8.6% to 6.2% and 6.5%, respectively.

Conclusions/interpretation: Gastric electrical stimulation offers symptom control in diabetics with drug-refractory gastroparesis and decreases gastric retention. This study, for the first time, documents a positive effect of this therapy on metabolic control as indicated by HbA1c, a surrogate marker of the risk of diabetic complications.

Key words
Diabetes · gastroparesis · gastric electrical stimulation · glycohemoglobin · HbA1c

Introduction

Multiple disorders, especially insulin-dependent diabetes mellitus, can result in gastroparesis, which is defined as a delayed passage of gastric contents into the intestine in the absence of mechanical obstruction. Typical symptoms include nausea, abdominal bloating, early satiety, and protracted vomiting, in severe cases weight loss and malnutrition. Such symptoms may occur in up to 60% of patients with long-standing diabetes, resulting in heavy impact on quality of life as well as glycemic control. This

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may be associated with frequent hospital admissions and loss of employment (Soykan et al., 1998).

The management of gastroparesis remains a challenging problem: dietary modifications alone often fail to improve symptoms, therefore most patients require prokinetics or antiemetics such as metoclopramide, domperidone, or erythromycin. Their use is limited by adverse effects or tachyphylaxis. Patients with severe refractory symptoms may require gastrostomy and/or jejunal feeding (Rabine and Barnett, 2001), or total parenteral nutrition. A recent review suggested that caution is warranted before surgical therapies such as jejunostomy or gastrectomy in diabetic gastroparesis are used (Jones and Maganti, 2003).

Gastric electrical stimulation (GES) is a new therapeutic option for patients with drug-refractory gastroparesis. Taking into account that the underlying pathology of gastroparesis is supposed to be a dysfunction of gastric myoelectrical activity like gastric dysrhythmias, this new technology stimulates the gastric wall with electrical pulses. To accomplish this task, a pulse generator is implanted into the subcutaneous fatty tissue of the abdominal wall and two electrodes are inserted into the muscularis propria of the greater curvature of the stomach. Although the idea of gastric electrical stimulation was already born in 1963 (Bilgutay et al., 1963), it took decades to develop suitable devices for use in humans because of the complexity of gastric innervation. Therefore, there is only limited data about the efficacy and safety of this promising new technique, most studies were not controlled and/or published as an abstract only.

Two recently fully published multi-center studies by Abell et al. (2002, 2003a), called Gastric Electro-Mechanical Stimulation (GEMS) and Worldwide Anti-Vomiting Electrical Stimulation Study (WAVESS), described the effect of gastric electrical stimulation in a heterogeneous study population. The most recently published one (WAVESS) documented a high efficacy and safety of active treatment in patients suffering from diabetes associated gastroparesis, but the influence of treatment on metabolic control was not documented and objective parameters of gastric emptying could only be evaluated in nine diabetic subjects.

Aim of the present study was therefore to investigate the effect of this electrical therapy on gastric emptying, gastrointestinal symptoms, and metabolic control in patients with long-standing insulin-dependent diabetes mellitus suffering from severe gastroparesis.

Material and Methods

Patients

Seventeen diabetic patients (12 female, 5 male, age 25 – 73 years; type I insulin-dependent diabetes mellitus known for at least 10 years) with gastroparesis refractory to conventional medical therapy were included in this single center study. Refractory gastroparesis was defined as (a) vomiting frequency of more than 7 episodes per week; (b) delayed gastric emptying (> 60% retention at 2 hours and > 10% at 4 hours), on the basis of a standardized scintigraphic method for solid meals; (c) symptoms consistent with gastroparesis for longer than 12 months; (d) 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 (antihistaminics, serotonin receptor antagonists, and dopamine receptor antagonists).

Patients with documented intestinal pseudo-obstruction, previous gastric surgery, vagotomy, organ transplantation, pregnancy, primary swallowing disorders, seizures, psychogenic vomiting, and those at high surgical risk (evaluated by an experienced surgeon [K. H. D.]; being category III or higher according to the criteria of the American Society of Anesthesiologists' Physical Status [ASA-PS]) were excluded from the study. Prior to entry, upper gastrointestinal endoscopy was performed to exclude mechanical causes of gastric outlet obstruction such as peptic ulceration. The patients were allowed to continue their current antiemetic or prokinetic therapy during the study and were asked not to substantially alter their antidiabetic therapy.

The design of the study was approved by the appropriate local ethical committee and each patient gave written, informed consent prior to entering the study.

Symptoms, gastric emptying, and HbA1c were measured at baseline (defined as the 4-week period before surgery), 6, and 12 months after implantation of the gastric electrical stimulator.

All included patients received an electrical stimulation system consisting of a stimulator (Itrel 3, Model 7425, Medtronic Kerkrade, the Netherlands) and two unipolar intramuscular electrodes (Model 4300, Medtronic Kerkrade, the Netherlands); surgery was performed by the same experienced surgeon (K. H. D.) utilizing an open approach in all cases. Positioning and programming of the device were performed as previously reported (Abell et al., 2003a); briefly, the pair of electrodes was inserted into the muscularis propria of the greater curvature, 10 cm from the pylorus and separated from each other by approximately 1 cm. The neurostimulator was positioned subcutaneously in the abdominal wall, typically in the right midquadrant, and was programmed to standardized parameters (frequency, 14 Hz; intensity, 5 mA; pulse width, 330 µs; cycle ON, 0.1 seconds; cycle OFF, 5.0 seconds) by using a physician console programmer (Model 7432, Medtronic Kerkrade, the Netherlands). As proposed by the manufacturer of the device, impedance testing was performed during surgery to verify optimal lead placement and documented to be appropriate in each case.

Symptoms

Each patient was asked to record daily nausea and vomiting episodes over periods of four weeks prior to implantation and, subsequently, for the follow-up visits at 6 and 12 months. Mean nausea and mean vomiting frequencies were calculated based on these standardized forms which had already been evaluated and used in the GEMS and WAVESS studies (Abell et al., 2002; Abell et al., 2003a).

Gastric emptying

A standardized scintigraphic method (Tougas et al., 2000) utilizing a solid low-fat test meal was used to measure gastric retention at baseline, 6, and 12 months after implantation. Prior to

performing this test, blood glucose levels were tested to secure values of less than 180 mg/dl (10 mmol/l), because hyperglycemia *per se* causes a temporary delay of gastric emptying (Ishiguchi et al., 2002; Petrakis et al., 2002). Patients were asked to discontinue prokinetic medications 3 days before the test to ensure identical test conditions for all participants.

HbA1c

The concentration of glycohemoglobin HbA1c in blood was determined by high power liquid chromatography (HPLC); in a healthy population, lower and upper limits of normal are 3.4 and 4.7%, respectively.

According to the Diabetes Control and Complications Trial Research Groups (DCCT), intensive therapy in a subject suffering from insulin-dependent diabetes mellitus should aim to control glycohemoglobin levels to remain below 6.05% (DCCT, 1993). Values of less than 7% indicate sufficient therapy and are associated with a lower incidence of long-term complications (American Diabetes Association, 2000); we therefore chose these thresholds to assess treatment efficacy with respect to long-term metabolic control.

Statistical analysis

Analysis of variance (ANOVA) and paired Student's *t*-test were used to investigate the effect of gastric electrical stimulation on emptying, symptoms, and HbA1c. P values of less than 0.05 were considered to indicate statistical significance.

Results

All 17 patients were available for analysis at baseline, 6, and 12 months after device implantation. No adverse events associated with the implanted device were documented at either time point.

Symptoms

All patients had high weekly nausea and vomiting frequencies at baseline. Both significantly decreased at 6 and 12 months compared to baseline (Table **1**). The mean vomiting frequency decreased from 26 episodes per week to 3 (88% reduction) and 4 (85% reduction) at 6 and 12 months, respectively. The mean nausea frequency was diminished from 34 episodes to 8 (76% reduction) and 12 (65% reduction) at 6 and 12 months, respectively. All differences between baseline and follow-up data were statistically significant ($p < 0.01$).

Gastric emptying

The gastric emptying results at baseline, 6, and 12 months are illustrated in Fig. **1**. Two-hour and 4-hour gastric retention of the isotope-labeled meal was 83% ± 3 and 38% ± 5 at baseline, respectively. Six months after implantation of the stimulator gastric retention was significantly reduced to 35% ± 10 (2 h, $p < 0.01$) and 14% ± 5 (4 h, $p < 0.05$). At twelve months, the gastric emptying values were also significantly reduced to 25% ± 5 (2 h, $p < 0.01$) and 17% ± 2 (4 h, $p < 0.05$). At all time points, emptying rates were statistically significantly improved compared to baseline values.

Table **1** Weekly vomiting and nausea frequencies before and after stimulator implantation

n = 17	*Weekly vomiting frequency*	*Weekly nausea frequency*
Baseline	26 (19 – 41)	34 (21 – 49)
6 months	3 (0 – 10)*	8 (1 – 18)*
12 months	4 (0 – 13)*	12 (2 – 20)*

Values are reported as mean and range. * denotes $p < 0.01$ compared to baseline

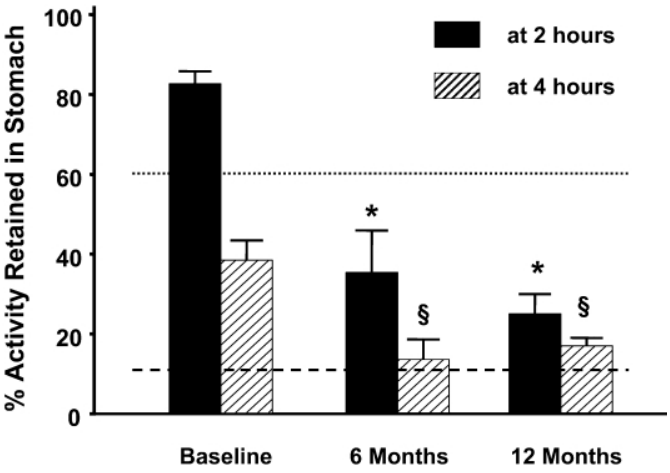

Fig. **1** Gastric emptying at baseline, 6, and 12 months after stimulator implantation. * $p < 0.01$, § $p < 0.05$; all compared to baseline. Values are presented as mean ± SEM; dotted line – upper limit of normal at 2 hours; dashed line – upper limit of normal at 4 hours.

At 6 and 12 months, in all patients gastric retention values were within the normal range at 2 hours (< 60%), in most patients (11/17) at 4 hours (< 10%) as well.

HbA1c

In all 17 patients glycemic control measured as HbA1c values improved. Fig. **2** illustrates the dynamics of HbA1c levels of each patient. The HbA1c values of the diabetic patients were significantly reduced at 6 months and 12 months compared to the baseline values ($p < 0.05$, Fig. **2**). Compared to baseline, the mean value improved by 28% at 6 months and 24% at 12 months. In 5 and 4 subjects HbA1c levels fell below 6.05% at 6 and 12 months, respectively; only in 4 out of 17 patients HbA1c was measured to be above 7% at both time points. Prior to implantation of the device, no patient had presented with HbA1c values of less than 7.5%.

Discussion

Gastric electrical stimulation appears to be a very promising therapeutic option for patients suffering from drug refractory gastroparesis. Bortolotti (Bortolotti, 2002; in addition, see Lin et al., 2003, for further review) has recently summarized the different, currently discussed, and applied methodological approaches. The first option, gastric electrical pacing, utilizes frequencies just

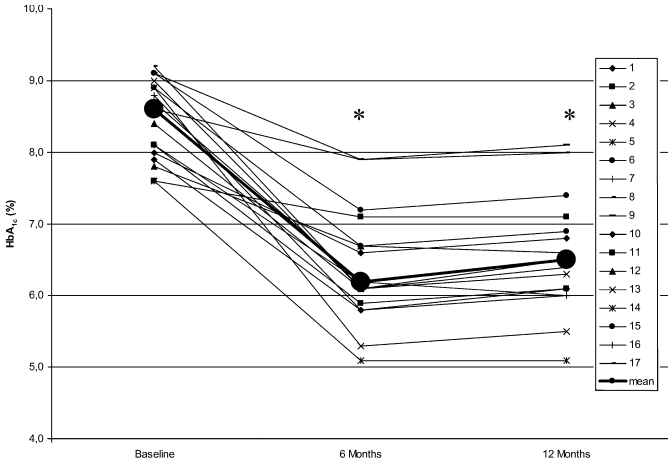

Fig. **2** Individual HbA1c values of all patients at baseline, 6, and 12 months of follow-up. In all cases, HbA1c levels were lowered. * denotes $p < 0.01$ compared to baseline.

above the native slow wave activity (up to 4.7 cycles per minute), which is supposed to entrain a normal slow wave activity in gastric dysrhythmias. In contrast, high frequency gastric electrical stimulation uses stimulation frequencies ranging from 10 to 1200 cycles per minute. The effect on propagated slow waves and thereby on gastric emptying is supposed to be minor (Bortolotti, 2002). On the other hand, dyspeptic symptoms significantly improve in patients treated with higher frequencies (Abell et al., 2002; McCallum et al., 2000), which may also affect afferent nerves directed to central perception structures for nausea and vomiting. A stimulator utilizing this therapeutic approach was applied in the present study and is now CE-certified and commercially available (Enterra™ Therapy, Medtronic Inc., Minneapolis, MN, USA).

The first comprehensive, fully published trial (GEMS) by Abell et al. (2002), described some adverse events to occur within 12 months following the implantation of the device; the most important being inadvertent deactivation of the pulse generator. This problem has been solved by the use of a different neurostimulator (Medtronic type Itrel 3, Model 7425, versus the previously used Medtronic Model 7424) and we therefore did not encounter such an event. Adverse events described in the study report of the WAVESS trial (Abell et al., 2003a) were all related to local complications caused by the stimulator system (e.g., infection of the neurostimulator pocket in 3 of 34 patients included in the analysis, pain, discomfort from migration). In the patients included in the present study, no therapy-associated adverse event occurred, most probably due to the fact that all surgical interventions were performed by a surgeon highly experienced in the use of this device. We have, however, experienced adverse events as described above in other patients and even a gastric wall perforation caused by a stimulator lead in one (Becker et al., 2004).

It has been noticed that objective parameters such as scintigraphic tests of gastric emptying not necessarily parallel the quite regularly observed improvement of clinical symptoms in patients treated with GES (Abell et al., 2002). This finding seems to occur in untreated patients (De Block et al., 2002) as well as in those receiving medical treatment of gastroparesis (Soykan et al., 1997; Horowitz et al., 1987).

In the present study, the cohort of diabetic patients experienced improvement of subjective as well as objective parameters of gastric emptying. In addition, HbA1c levels were consistently and lastingly lowered. Since HbA1c levels can be used as a surrogate marker of sufficient long term metabolic control in diabetic subjects (Krishnamurti and Steffes, 2001) and levels achieved in the patients after treatment with the stimulator correlate with fewer diabetes-related complications, the use of such a device – despite its complex nature – may be cost-efficient in the long run. This does contrast with findings of medical therapy – in that the most potent, yet due to cardiac side-effects unavailable drug, cisapride, is able to accelerate gastric emptying, but does not enhance metabolic control in diabetics (evidenced by HbA1c levels) (Braden et al., 2002). Further studies will be needed to determine whether other aspects of diabetes therapy (such as daily insulin dose, frequency of hypoglycemia) can be positively influenced by gastic electrical stimulation as well.

In summary, gastric electrical stimulation seems to be a safe and effective treatment option in diabetic patients suffering from gastroparesis refractory to conventional medical therapy. GES does not only reduce symptoms of gastroparesis, enhance quality of life, and induce weight gain as previously described (Abell et al., 2002; Abell et al., 2003a), but also results in acceleration of gastric emptying. It has been shown before that GES improves nutritional parameters (Abell et al., 2003b), but to the best of our knowledge, this study documents for the first time that GES enhances metabolic control in diabetics as evidenced by a significant reduction of HbA1c values. Further studies will be needed to evaluate if this type of treatment may in the long term reduce the incidence of diabetic sequelae and may therefore add to the quality of life of diabetic patients beyond its direct effect on the symptoms of gastroparesis alone.

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