Gastric electrical stimulation for the treatment of diabetic gastroparesis

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Abstract

Diabetic gastroparesis is a component of autonomic neuropathy, and is the most common manifestation of gastrointestinal neuropathy. Diabetes is responsible for about one quarter of gastroparesis. The upper gastrointestinal symptoms are often non-specific and dominated by nausea, vomiting, early satiety, fullness, bloating. We also have to look for diabetic gastroparesis in case of metabolic instability, such as postprandial hypoglycaemia. The pathophysiology of diabetic gastroparesis is complex, partly due to a vagus nerve damage, but also to changes in secretion of hormones such as motilin and ghrelin. A decrease in the stem cell factor (SCF), growth factor for cells of Cajal (gastric pacemaker), was found in subjects with diabetic gastroparesis. These abnormalities lead to an excessive relaxation in the corpus, a hypomotility of antrum, a desynchronization antrum-duodenal-pylorus, and finally an abnormal duodenal motility. The treatment of diabetic gastroparesis is based on diabetes control, and split meals by reducing the fiber content and fat from the diet. The antiemetic and prokinetic agents should be tested primarily in people with nausea and vomiting. Finally, after failure of conventional measures, the use of gastric neuromodulation is an effective alternative, with well-defined indications. Introduced in the 1970s, this technology works by applying electrical stimulation continues at the gastric antrum, particularly in patients whose gastric symptoms are refractory to other therapies. Its efficacy has been recently reported in different causes of gastroparesis, especially in diabetes. Gastric emptying based on gastric scintigraphy, gastrointestinal symptoms, biological markers of glycaemic control and quality of life are partly improved, but not normalized. Finally, a heavy nutritional care is sometimes necessary in the most severe forms. The enteral route should be preferred (nasojunal and jejunostomy if possible efficiency). However, in case of failure especially in patients with small bowel neuropathy, the long-term parenteral nutrition is sometimes required.

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Keywords: Gastroparesis; Autonomic neuropathy; Diabetes mellitus; Gastric emptying; Gastrointestinal scintigraphy; Gastric electrical stimulation; Gastric neuromodulation; Review

Résumé

Neuromodulation gastrique pour le traitement de la gastropérapie diabétique.

La gastropérapie diabétique est une composante de la neuropathie autonome et constitue la manifestation la plus fréquente de la neuropathie digestive. Le diabète est responsable d’environ un quart des gastropérapies. Les signes digestifs hauts sont souvent frustres et dominés par des nausées, vomissements, satiété précoce, plénitude gastrique, ballonnements. Il faut donc savoir éviter une gastropérapie diabétique devant toute situation d’instabilité métabolique, comme les hypoglycémies postprandiales. La physiopathologie de la gastropérapie diabétique est complexe, en partie liée à une atteinte du nerf vague, mais aussi à des modifications de la sécrétion d’hormones telles la motiline et la ghréline. Une diminution du Stem Cell Factor (SCF), facteur de croissance des cellules de Cajal (pacemaker gastrique), est trouvée chez les sujets atteints de gastropérapie diabétique. Ces anomalies se traduisent par une relaxation excessive du fundus, une hypomotricité antrale, une mauvaise synchronisation antro-pyloroduodénale et enfin une motricité duodénale anormale. Le traitement de la gastropérapie diabétique repose sur l’équilibre du diabète et le fractionnement des repas, en réduisant la teneur en fibres et en lipides de l’alimentation. Les médicaments anti-émétiques et prokinétiques doivent être essayés en priorité chez les personnes souffrant de nausées et de vomissements. Enfin, après échec des mesures conventionnelles, le recours à la neuromodulation gastrique est une alternative efficace, avec des indications bien définies. Introduite dans les années 1970, cette technique consiste à appliquer une stimulation électrique continue au niveau de l’antrum gastrique, en particulier chez les patients dont les symptômes sont réfractaires à toute autre thérapeutique. Son efficacité a été récemment démontrée dans différentes causes de la gastropérapie, en particulier au

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cours du diabète. La vidange gastrique sur des critères scintigraphiques, les symptômes gastro-intestinaux, les marqueurs biologiques de contrôle glycémique, ainsi que la qualité de vie sont en partie améliorés, sans toutefois être normalisés. En outre, une prise en charge nutritionnelle lourde est parfois nécessaire dans les formes les plus sévères. La voie entérale doit être privilégiée (sonde nasojéjunale puis éventuelle jejunostomie en cas d’efficacité). En revanche, en cas d’échec en particulier chez les patients atteints de neuropathie grêlique, la nutrition parentérale au long cours est parfois justifiée.

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Mots clés : Gastroparesie ; Neuropathie végétative ; Diabète ; Vidange gastrique ; Scintigraphie digestive ; Stimulation électrique gastrique ; Neuromodulation gastrique ; Revue générale

1. Introduction

The gastric electrical stimulation (GES) is an emerging treatment for the patients with refractory symptoms related to gastroparesis. This review summarizes the mechanisms of action of the GES, the main results of studies that support the use of this therapy, and details recent clinical applications of GES in humans and some of its developments.

2. Physiology of the stomach

The stomach is composed of several regions with different but complementary actions: the fundus is a storage area for food, the antrum and pylorus that insure grinding and removal of the food bolus. The stomach is a muscle innervated and motor function is coordinated with that of the pylorus to ensure a fragmentation of the food bolus, and ensuring the regularity of digestion. The gastric emptying is also affected by the viscosity of the bolus and caloric density, explaining some variations depending on whether the food is solid and/or liquid, and more or less rich in fat and fiber.

In healthy individuals, the natural rhythmic contractile activity of the stomach serves to mix, compress and move the stomach contents from the fundus to antrum. The peristaltic activity is dependent on the pacemaker of the stomach located on the greater curvature (Cajal cells). The peristaltic activity propagates down to the antrum and pylorus at a frequency controlled by the natural rhythm related to the gastric slow waves, which occurs at a frequency of about three cycles per minute. The slow waves arrive continuously, while the activity of peristaltic contractions occur only after food intake [1]. Approximately half of the stomach contents will be externalized to the duodenum in 1 to 2 hours and only a very small part of the meal will be retained in the stomach after 4 hours.

3. Definition and pathophysiology of gastroparesis

Gastroparesis is a chronic condition characterized by delayed gastric emptying in the absence of mechanical obstruction. This pathology is sometimes associated with diabetes but also occurs in a number of other pathologies. In some cases where no cause is found, it is called idiopathic gastroparesis [2]. Gastroparesis is manifested clinically by gastrointestinal symptoms which can be particularly disabling. Symptoms include nausea, vomiting, early satiety, abdominal pain or abdominal bloating. In the case of diabetes, this complication is often poorly understood or poorly identified but must be suspected and confirmed clinically because it impacts inevitably on the glycaemic control: this results in an unstable blood glucose, a higher frequency of hypoglycaemia especially during postprandial state, or episodes of severe hypoglycaemia. Paradoxically, gastrointestinal symptoms in this case may be totally absent.

The pathophysiology of diabetic gastroparesis is complex and poorly understood. Gastroparesis is related in part to parasympathetic nerve damage, which explains why the clinical manifestations are similar to those observed after vagotomy. However, changes in secretion of hormones such as motilin and ghrelin are also involved in the pathophysiological process [3,4]. This results in an excessive relaxation in the fundus, an hypomotility of antrum, a desynchronization antrum-duodenum-pylorus, and finally an abnormal duodenal motility (Fig. 1) [5]. Moreover, recent pathophysiological advances were performed in this field: the alteration of the secretion of insulin and IGF1 results in decreased stem cell factor (SCF), the only known growth factor for cells of Cajal, that could explain the reduction or even the virtual disappearance of these cells in the muscular layers of the stomach in patients with diabetic gastroparesis [6].

4. History of gastric electrical stimulation

Gastric electrical activity was recorded for the first time in 1922. These recordings have subsequently become easier to perform and many authors have tried to stimulate gastric electrical
activity in a similar way to stimulation of the myocardium using various techniques with variable results [7].

At the beginning of the 1970s, many experimental studies conducted in dogs provided a better understanding of the nature of gastrointestinal myoelectric activity and its relationship with contractile activity, based on the similarity of gastric myoelectric activity and motility in dogs and man [8,9].

5. Single-channel gastric electrical stimulation

This is one of the techniques most frequently used. Two approaches can be distinguished (Fig. 2):

- low-frequency electrical gastric stimulation or gastric pacing, whose main effect is to accelerate gastric emptying;
- high-frequency electrical gastric stimulation that improves upper gastrointestinal tract symptoms (nausea and vomiting), but with little effect on gastric emptying [10]. This second technique has been applied in man.

5.1. Gastric electrical stimulation

This technique uses supraphysiological high frequency, usually fourfold higher than the physiological frequency of 12 Hz for gastric slow waves. The energy delivered is relatively low with a short pulse width of about 300 microseconds [10].

Several studies conducted in dogs have shown encouraging results. After altering gastric emptying by various methods, the stimulation frequencies used ranged between 3 and 12 Hz. Globally, these studies reported an increase of gastric contractions, sometimes associated with acceleration of gastric emptying [8,11]. Familoni et al. demonstrated that an optimal increase of gastric contractile activity was associated with a stimulation frequency fourfold higher than physiological gastric myoelectric activity [12]. This mode of GES was applied to a patient presenting a refractory form of diabetic gastroparesis. Temporary then permanent leads were implanted in the body of the stomach. Measurements of gastric emptying of liquids and gastrointestinal symptoms (nausea, vomiting, abdominal pain) were improved.

On the basis of these results, Medtronic® developed a totally implantable device (Enterra® system) able to deliver electrical stimulation with similar parameters to those used by Familoni et al. [12]. This implantable device was released onto the market at the end of the 1990s and a number of studies have been conducted: the Gastro Electro Mechanical Stimulation feasibility study (GEMS) [13] and the Worldwide Anti-Vomiting Electrical Stimulation Study international multicentre study (WAVESS) [14]. The WAVESS study constituted the basis for recognition of the humanitarian device exemption status of the Enterra® system in the United States. In 2000, the Food and Drug American Administration (FDA) granted humanitarian device exemption approval of the Enterra® therapy system for patients with chronic drug-refractory nausea and vomiting secondary to gastroparesis of diabetic or idiopathic origin. Enterra® therapy obtained the CE mark in August 2002.

5.2. Electrical gastric stimulation by Enterra® therapy

Enterra® therapy is reversible and consists of electrical stimulation of the lower part of the stomach (antrum). This electrical stimulation is generated by an entirely implantable system composed of two unipolar intramuscular leads and a neurostimulator. The neurostimulator is 60 mm long, 50 mm wide and 12 mm thick. The neurostimulator and the leads are implanted surgically. The various parameters of the neurostimulator can be adjusted noninvasively by using the clinician programmer (Medtronic N’Vision), which communicates with the implanted neurostimulator by telemetry. Basic stimulation parameters are defined by:

- an amplitude of 5 mA;
- a pulse width of 330 microseconds;
- a frequency of 14 Hz;
- a cycle of 0.1 second ON and 5.0 seconds OFF (Fig. 3).

Two different surgical approaches can be used (laparotomy or laparoscopy) to implant the two intramuscular leads. Laparoscopy is less invasive and is associated with a more rapid recovery time, but lead implantation is easier via laparotomy. The two leads are implanted about 1 cm apart in the muscle wall of the greater curvature of the stomach, approximately 10 cm from the pylorus. This anatomical site corresponds to the border...
between the body and the antrum of the stomach. Intraoperative gastroscopy is then performed to ensure that the needle and the lead have not perforated the stomach. The proximal part of the lead is then anchored by the trumpet anchor system, and the distal part is anchored by a sutured silicone rubber fixation disk. The leads are then connected to the neurostimulator and the neurostimulator is placed in a subcutaneous pocket created in the abdominal wall, generally in the superior quadrant of the abdomen. The neurostimulator is generally maintained in the OFF position until wound healing (several weeks). The battery life according to the nominal settings proposed for Enterra® therapy is 5 to 10 years depending on neurostimulator settings. As the battery is sealed in the neurostimulator, the device must be replaced after battery depletion, but the leads can be left in place and reused with a new neurostimulator. More than 3000 patients have now been implanted with this system (including more than 300 in Europe).

6. Pathophysiological hypotheses/Mechanism of action

Familioni et al. observed a marked improvement of gastrointestinal symptoms as well as gastric emptying. The favourable actions of this technique appear to be due to facilitated release of acetylcholine or may involve calcium channels [12]. According to Familioni et al., these effects induce an increased rhythmic electrical activity and consequently improvement of gastric motility. Many hypotheses have been proposed to explain the mechanism of GES. Most authors agree that the origin of the symptomatic improvement obtained with GES is multifactorial.

6.1. Mechanical factors

For many authors, improvement of symptoms can be explained by improved fundic relaxation, which increases the capacity of the stomach to receive food [15–24]. In the GEMS study, a gastric barostatic study with graduated isobaric distension was performed in patients with gastroparesis of idiopathic origin and the GES device was alternately turned ON and OFF [13]. This study demonstrated that GES decreased the sensitivity to gastric distension and improved gastric adaptation to a meal in patients with severe idiopathic gastroparesis. This hypothesis concerning decreased sensitivity to gastric distension was also reported by McCallum et al. [25].

6.2. Neural factors

6.2.1. Autonomic nervous system

Modifications of the autonomic nervous system also appear to participate in the beneficial effects of GES [8,11,16–18,21–24,26–28]. A study conducted in dogs by Chen et al. used vasopressin to induce gastric dysrhythmias and vomiting in healthy animals and in vagotomised animals [28]. The high-frequency GES applied to these animals induced a significant improvement of vomiting only in non-vagotomised dogs, suggesting a vagal action of the device. However, this action cannot explain all of the beneficial symptomatic effects of GES, as Abell et al. showed that GES also induced an antiemetic effect in patients with postoperative gastroparesis, including patients who had undergone vagotomy or operations at high risk of vagus nerve damage [13]. McCallum et al. studied autonomic nervous system function in a series of 10 gastroparetic patients by spectral power analysis of heart rate variability. This study demonstrated that the sympathetico-vagal balance was significantly decreased after GES therapy, resulting in a significant increase of vagal activity [25].

Luo et al. evaluated the autonomic nervous system in 39 patients included in the GEMS and WAVESS studies and described a reduction of sympathetic adrenergic function and a slight increase of vagal cholinergic function, concluding on a possible sympathetic blockade and cholinergic stimulation in subjects in whom the total gastrointestinal symptom score was significantly improved [29].

6.2.2. Enteric nervous system

The enteric nervous system has also been proposed to play a role in the mechanism of GES [13,16,21,26,27,30], but few objective data are available due to the difficulty of evaluating this system.

Tougas et al. reported that application of the Enterra® technique was likely to modulate gastric afferent neural activity [31]. Luo et al. observed a tendency to correction of electrogastrographic abnormalities after implantation of the GES device [29].

However, canine studies have described the absence of effect of gastric stimulation on gastric slow waves [28,32]. According to Yiannopoulos et al., this device acts more like an electrical stimulator than a true electrical pacemaker [20]. Finally, Lin et al. reported an increase of the propagation velocity and amplitude of gastric slow waves, partly explaining the significant improvement of nausea and vomiting symptoms [21].

6.2.3. Effects of gastric electrical stimulation on the central nervous system

This is by far the most widely accepted mechanism of action to explain the sometimes dramatic improvement of the symptoms of gastroparesis [8,11,15–19,21,22,25,27,33–38]. Activation of central control mechanisms of nausea and vomiting in the central nervous system would stimulate afferent pathways projecting onto central centres of perception of nausea and vomiting [18,36]. Yiannopoulos et al. reported that resolution of nausea and vomiting required blockade of afferent pathways of the vomiting centre in the brain [20].

In a recent study, 10 patients were examined by 18-Fluorodeoxyglucose positron emission tomography before and 6 and 12 weeks after implantation [25,38]. All regions of the brain were studied with specific assessment of quantitative changes of metabolism by using a 10-point colour scale. An increase of at least one point on the colour scale (10%) of bilateral thalamic activity was observed in all patients, reflecting substantial upregulation of metabolic activity at this site.
6.3. **Hormonal factors**

Hormonal factors are also considered to be involved in the mechanism of action of GES [11,14,17,18,21,22,24], but very few conclusive studies have been published. Improvement of vagal cholinergic function would increase pancreatic exocrine secretion, as suggested by elevation of pancreatic elastase and pancreatic polypeptide concentrations [39]. By inducing more isotonic pancreatic secretion, GES may therefore lead to the formation of less hypertonic duodenal chyme, resulting in reduction of nausea and vomiting. This action on pancreatic exocrine secretion would be related to adrenergic blockade or a combination of vagal cholinergic stimulation and sympathetic adrenergic blockade.

6.4. **In summary**

Decreased severity of symptoms is the primary factor subsequently leading to increased food intake, weight gain and decreased use of antiemetic and prokinetic medications [12,13]. The weak association observed between improvement of symptoms and improvement of gastric emptying suggests that the effects of GES are mainly related to factors other than simple modification of gastric motility [40].

7. **Evaluation of Enterra® therapy in the literature**

7.1. **Efficacy and safety of gastric electrical stimulation on gastroparesis**

7.1.1. **Methodology and study population characteristics**

Enterra® therapy was developed by Medtronic following the index case published by Familoni et al. [12]. The implantable device was marketed at the end of the 1990s. The first published study on this device was that by Forster et al. in December 2001 [15], followed by the large-scale GEMS [13] and WAVESS [14] feasibility studies that were the basis for FDA humanitarian device exemption approval of the device in 2003.

All studies on GES were non-randomized studies [34–36,41–45]. Most of them were prospective and single-centre studies. The level of proof of these studies is therefore relatively limited. Only one study, the WAVESS study [14], included a randomized, double-blind, 2 × 1-month crossover period during which the device was alternately turned ON and OFF. Most patients had a follow-up of 12 months. Only four studies reported a follow-up of at least 3 years [16,34,41,42]. A French study was published in 2007 [23].

At least two thirds of implanted subjects were women, corresponding to the known female predominance of gastroparesis. The cases of gastroparesis studied were of diabetic, idiopathic or postoperative origin. Two studies included exclusively diabetic populations [18,35]. Diabetic subjects represented between 11% and 100% of patients in each study. Unfortunately, clinical and laboratory data concerning diabetic patients were usually only partial or even non-existent. Diabetes was generally longstanding, present for an average of 19 years.

7.1.2. **Inclusion and exclusion criteria**

Delayed gastric emptying of solids and/or liquids was usually confirmed by isotope studies. The presence of refractory gastrointestinal symptoms also constituted an inclusion criterion. Finally, symptoms had to have been present for at least 12 months at the time of inclusion of the patients.

7.1.3. **Evaluation of the efficacy of gastric electrical stimulation**

7.1.3.1. **Gastrointestinal symptoms.** The primary objective of published studies was improvement of gastrointestinal symptoms.

In the original study, Familoni et al. [12] described a reduction of nausea and vomiting, as well as pain (decreased from three episodes per day to three episodes per week). This reduction of symptoms was associated with better food tolerance. Nausea and vomiting were generally studied by using a frequency and severity score.

The symptom questionnaire most commonly used was that used in the GEMS [13] and WAVESS [14] studies, evaluating the severity of six symptoms commonly associated with gastroparesis: vomiting, nausea, early satiety, bloating, postprandial fullness and epigastric pain. Nausea, vomiting and/or total symptom scores were improved in all studies and a statistically significant reduction was observed in the vast majority of cases [13–19,34–36,41,42,44,45].

Velanovich et al. used another gastrointestinal symptom score, the Gastrointestinal Symptom Rating Scale (GSRS) comprising a fairly complex assessment of three clusters of gastrointestinal symptoms [45]: dyspeptic symptoms, indigestion symptoms, and bowel dysfunction symptoms. This is a reliable and validated tool for a number of gastrointestinal diseases, but has never been evaluated in gastroparesis. Patients whose main complaints consisted of nausea and vomiting were more markedly relieved than those reporting abdominal pain and bloating. Many authors have concluded on the absence of any obvious link between improvement of gastric emptying and improvement of gastric symptoms [13,14,17,18,35,36,43,44].

7.1.3.2. **Gastric emptying.** In the index case reported by Familoni et al. [12], only gastric emptying of liquids was studied, as this patient did not tolerate any solids. Gastric emptying was severely delayed (98% retention at the 2nd hour) and was dramatically improved after 15 weeks of electrical stimulation.

In some cases, acceleration of gastric emptying was limited and not statistically significant [13,17,19,36]. However, several studies have reported more favourable results. Forster et al. reported a statistically significant improvement of gastric emptying of solids at 3 months, but this improvement was no longer significant after 6 and 12 months of GES [15].

In the WAVESS study [14], improvement of gastric emptying was significant at the 2nd hour at 6 months and at the 2nd and 4th hours at 12 months when analysing the overall study population. In a population exclusively composed of diabetic patients, Lin et al. observed an initially significant improvement of gastric retention of solids at the 2nd and 4th hours after 6 months of GES compared to baseline (65.5% and 38.5% vs 76.6% and
Non-pharmacologic Recommendations of management including electrical gastric stimulation for the most severe forms of diabetic gastroparesis.

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50%, respectively), but this difference was no longer significant after 1 year of GES (mean gastric retention of 74.5% and 38.0%) [18].

In contrast, van der Voort et al. reported a spectacular improvement of gastric emptying with normal gastric emptying scintigraphy in all subjects at the 2nd and in most subjects at the 4th hour [35]. These discordant results between studies could be related to differences in terms of glycaemic control between study populations.

In the series by Anand et al., gastric emptying was significantly improved at the 2nd and 4th hours at the last follow-up visit compared to baseline [42]. Gastric retention decreased from 55% to 42% at the 2nd hour \(P < 0.001\) and from 26% to 17% at the 4th hour.

Brody et al. reported improvement of gastric emptying at the 2nd and 4th hours after 1 year of GES, but this improvement was only significant at the 2nd hour [44]. In this study, gastric emptying was restored to normal in 41% of subjects and was improved by more than 50% in 37% of subjects. These differences between clinical trials can explain why the GES is indicated in patients with a delayed gastric emptying measured by scintigraphy, at least above 35% at 4 hours (Table 1).

7.1.3.3. Quality of life. Most published studies used the validated Short-Form Health Survey questionnaire (SF 36) [14,17,18,36,43,45] or a score called Independent Outcome Measure System (IDIOMS) [30,41].

In WAVESS, mean quality of life scores were altered at baseline. Statistically significant improvements of physical and mental scores were reported after 6 and 12 months of GES [14]. On subgroup analysis (diabetic and idiopathic gastroparesis), only the improvement of the physical score remained statistically significant for the diabetic subgroup.

In the series published by Lin et al., physical and mental scores were significantly improved at 6 and 12 months, with a mean mental score that could be considered to be normal (46.0 ± 2.0 at M12 vs 36.9 ± 1.8 at M0) [18]. In another study published by Lin et al., physical and mental scores were also significantly improved after 1 year of GES whether or not the patients continued their prokinetic medication [36].

The IDIOMS quality of life score (Independent Outcome Measure Score) was used in the study reported by Cutts et al. that compared medical management vs GES therapy in patients with drug-refractory gastroparesis over a 3-year period [41]. The IDIOMS score is a health-related quality of life measure evaluating three parameters associated with use of health resources:

- intensity of health resource consumption;
- severity of the impact of the disease;
- number of concomitant non-gastrointestinal diseases.

In the recently published study by Anand et al., a statistically significant reduction of the IDIOMS score (16.3 vs 10.6; \(P < 0.005\)) was observed in this population of 156 implanted subjects, most of whom had a follow-up of more than 3 years [42].

In the study by De Csepel et al. [19], quality of life was evaluated by the RAND 36 health questionnaire. A global improvement of quality of life was observed with a statistically significant improvement of role limitations due to physical health problems, energy/fatigue, role limitations due to personal or emotional problems and social functioning.

7.1.3.4. Nutritional outcome. The main nutritional parameters evaluated were weight and the need for nutritional supplements. Very early weight gain after initiation of GES, with medium-term and long-term maintenance of weight gain were usually observed. Weight gain was usually minor, but weight loss caused by gastrointestinal symptoms was nevertheless controlled. Mason et al. even reported that a weight-reduction diet had to be proposed to two subjects with excessive weight gain after GES [30].

Abell et al. evaluated serum albumin, cholesterol and circulating lymphocytes, but did not observe any significant variation of these parameters [16]. Weight gain was nevertheless significant during the first year, but no significant improvement of body weight was observed at 5 years.

Artificial feeding techniques (enteral or even parenteral nutrition) were used relatively frequently in published series. Almost one half of subjects required artificial feeding [13–15,18,30,34,36], usually enteral nutrition. The use of artificial feeding decreased dramatically after GES, thereby reducing the cost of treatment of gastroparesis and improving the patient’s quality of life.

Mason et al. reported that 45% subjects presented weight loss of at least 4.5 kg and two thirds of subjects required artificial feeding [30]. The significant weight gain observed after GES was associated with discontinuation of nutritional support at 20 months of follow-up in all subjects with diabetic or idiopathic gastroparesis.

7.1.3.5. Metabolic control: HbA1c. The first study to evaluate the metabolic outcome of diabetic subjects was that published by Forster et al. in 2003 [17]. A reduction of HbA1c after 6 months
of GES therapy and a more marked reduction after 1 year of GES (mean reduction of –1.3% compared to baseline, \( P < 0.05 \)) was reported. Two studies assessed the effect of GES in exclusively diabetic populations [18,35]. After 12 months of GES, HbA1c was decreased by –1.0 and –2.2% in these two studies, respectively (Table 2). A series published by Lin et al. in 2006, with a follow-up of 3 years, confirmed the statistically significant long-term improvement of HbA1c [34]. However, other more relevant analyses are required, particularly concerning the incidence of severe total and postprandial hypoglycaemia, and analysis of glycaemic variability.

7.1.3.6. Concomitant drug treatments. In the studies in which this variable was specified, almost one half of subjects used one or several antiemetic and/or prokinetic medications [13,34,36]. In every case, treatments were significantly less numerous after GES. In the study by Lin et al. [36], after 1 year of GES, GES alone was more effective than GES in combination with prokinetic and/or antiemetic agents. Patients who were able to decrease or stop medication probably had less severe gastroparesis or a better response to GES therapy.

7.1.4. Complications and adverse effects

The complication most commonly attributed to the device is infection of the subcutaneous pocket, affecting about 10% of subjects. Diabetic subjects would appear to be at greater risk of this type of complication [15]. Some authors have proposed antibiotic irrigation of the subcutaneous pocket to limit the risk of infection [30]. However, the most recently published series [43–45] did not report any infectious complications, due to progress in operative techniques and the more systematic use of prophylactic antibiotics.

The other main complications attributed to the device are:

- accidental deactivation by magnetic fields;
- gastric perforation by the leads: the index case was published by Becker et al. in 2004 [46];
- discomfort due to migration of the neurostimulator, requiring an operation to reposition and re-anchor the device;
- small bowel volvulus requiring partial small bowel resection [18,34];
- explantation of the neurostimulator due to erosion of the skin after injury to the abdominal wall;
- haematoma of the device implantation pocket.

In a large series of patients, Anand et al. reported 7.1% of cases of explantation, due to infection in about two thirds of cases and for technical reasons in one third of cases [42]. However, most patients were able to be successfully reimplanted. More recently, Liu et al. published two cases of delayed gastric erosion by neurostimulator leads occurring 16 and 21 months after implantation [47]. The most recent meta-analysis reports that the three most common complications were infection (3.87%), lead or device migration (2.69%), and pain at the implantation site (0.67%) [48]. First-line investigations are a plain abdominal X-ray, verification of electrode impedance and gastroscopy. Eroded leads can be safely removed and replaced by laparoscopy.

7.2. Effects of gastric electrical stimulation other than control of diabetic gastroparesis

7.2.1. Study of the effect of gastric electrical stimulation on pancreatic exocrine function

In an original study, Luo et al. investigated the effect of GES on pancreatic exocrine function in patients with gastroparesis and observed that faecal elastase levels were increased on GES [39]. Faecal elastase was also lower in non-implanted subjects with gastroparesis compared to healthy individuals. Postprandial levels of pancreatic polypeptide were also higher when the device was ON. GES therefore improves pancreatic exocrine secretion and autonomous nervous system control. This is the only study to have assessed the role of GES in the treatment of pancreatic insufficiency associated with gastroparesis.

7.2.2. Good responders to gastric electrical stimulation therapy

Forster et al. performed biopsies of the gastric pacemaker area containing interstitial cells of Cajal in patients with drug-refractory gastroparesis. Fourteen patients were studied (including nine patients with idiopathic gastroparesis) and electrogastrography was performed after surgery [49]. Interstitial cells of Cajal were absent in one third of patients, and the absence of these cells was associated with abnormalities of gastric slow waves, more disabling gastrointestinal symptoms and less marked improvement in response to GES therapy. Gastric biopsies could therefore be used to select patients likely to obtain a good response to GES. Patients with little or no interstitial cells of Cajal would be candidates for other gastric stimulation techniques such as gastric pacing.
7.2.3. Clinical factors predictive of a favourable response to treatment

Maranki et al. tried to identify predictive factors associated with a favourable response to Enterra® therapy by using the gastroparesis cardinal symptom index (GCSI) and additional questions concerning abdominal pain and global clinical response [50]. Clinical improvement was observed in 50% of subjects and three parameters were associated with a more favourable response:

- idiopathic rather than diabetic aetiology;
- nausea and vomiting as main symptoms rather than abdominal pain;
- absence of clinical dependence on opioid analgesics before neurostimulator implantation.

However, a recent meta-analysis indicates that high-frequency GES is an effective and safe method for treating refractory gastroparesis. This study was to assess the effects of GES on symptoms and gastric emptying in three subgroups of gastroparesis (diabetic gastroparesis, idiopathic gastroparesis and postsurgical gastroparesis). From 10 studies, 601 patients were included in this study and total symptom severity score, nausea severity score, vomiting severity score and gastric emptying were extracted and analyzed. But in addition, diabetic patients seem the most responsive to GES by improvement of symptoms and gastric emptying [48]. Moreover very little is known about the effect of varying stimulation parameters on symptoms of nausea and vomiting in most patients. In a pilot study of 22 patients (12 idiopathic, four diabetic and four postsurgical) with drug-refractory gastroparesis who did not respond optimally to initial settings, patients underwent an algorithmic approach to identify optimal stimulation parameters in GES on symptom improvement. The subgroup of patients with postsurgical gastroparesis required the most energy suggesting that the use of an algorithm for some patients with GES is feasible and may have potential for clinical application [51].

7.2.4. The advent of robotic surgery applied to gastric electrical stimulation

Robotic surgery is a rapidly growing field. Gould et al. compared seven patients undergoing robotic implantation of GES devices with 15 patients implanted laparoscopically [52]. Compared to standard laparoscopic techniques, robotic implantation was more precise and anchoring of sutures was achieved more effectively and more comfortably. Perforation of the gastric mucosa during passage of the leads was less frequent and the overall operating time was not prolonged.

7.2.5. Value of Enterra® therapy in children with refractory nausea and vomiting

Islam et al. recently published the first paediatric series of GES device implantation [53]. This series comprised nine children between the ages of 8 and 17 years with eight girls. All suffered from refractory nausea and vomiting, but did not necessarily present delayed gastric emptying. The aetiology was usually idiopathic with onset of symptoms following a viral infection in three subjects. One child presented postoperative gastroparesis.

After placement of a temporary device, improvement of symptoms was observed in nine children, leading to placement of a permanent device similar to that used in adults. A significant improvement of nausea, vomiting and total symptom scores was observed in this series. Gastric biopsies were performed in five of these children. The absence of interstitial cells of Cajal was associated with a less favourable clinical outcome.

These children consequently presented severe disease with the need for repeated hospitalisations, school absenteeism and frequent nutritional complications. This study raised new prospects for the treatment of children with refractory nausea and vomiting.

8. Conclusion

GES is a rapidly evolving technique. After the first controversial trials, the indications for this treatment have now been more clearly defined [54]. However, the mechanisms of action of this technique need to be further studied and elucidated. Those patients most likely to derive the greatest benefit from GES therapy (after evaluation of efficacy of all other therapies) also need to be identified, as the response to GES in terms of improvement of symptoms, quality of life, and metabolic and nutritional equilibrium appears to vary according to the type of population affected by this disease (Table 1). Large-scale randomized trials are therefore necessary to confirm the preliminary published data, and to more accurately define the medico-economic aspects of this technique [36,41].

Disclosure of interest

Bruno Guerci has participated on the boards, conferences and clinical trials for Medtronic.

Laurent Bresler has participated to clinical trials for Medtronic.

Caroline Bourgeois, Marie-Lorraine Scherrer and Philip Böhme have no conflict of interest to disclose regarding the subject of this paper.

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