Gastric Electrical Stimulation for the Treatment of Gastroparesis: Ready for Prime Time?

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Gastroparesis is a symptomatic chronic disorder of gastric motility characterized by severely and chronically delayed gastric emptying without any evidence of mechanical obstruction [1]. The clinical presentation can vary from mild intermittent nausea to refractory vomiting, chronic abdominal pain, and a compromised nutritional state. In severe cases, total parenteral nutrition or a feeding jejunostomy may be required. Poorly controlled symptoms often lead to frequent hospital visits and contribute to an impaired quality of life.

The treatment of gastroparesis remains a clinical challenge. The currently available standard medical therapy is based on the use of anti-emetics and prokinetic agents, although the evidence for the efficacy of this therapy is not impressive. In addition, based on uncontrolled studies, intrapyloric injection of botulinum toxin seems able to relieve the symptoms of gastroparesis [2, 3], but preliminary controlled data do not confirm efficacy [4]. Where medical therapy fails, surgery is considered, and there are anecdotal reports of favourable outcomes with creation of a stoma, to provide access for enteral nutrition and decompression, or with major gastric resections reserved as a last resort [5].

In the light of the unsatisfactory results from conventional medical therapy, there has been growing interest in the use of gastric electrical stimulation (GES) as a treatment option. The development of an implantable gastric

stimulator, using low-amplitude and high-frequency stimulation, which received the Food and Drug Administration approval as a humanitarian device in March 2000 (Enterra; Medtronic, Minneapolis, Minn., USA), provided a potentially attractive alternative for medical or surgical treatment of difficult gastroparesis.

To date, the beneficial effects of GES that have been reported from uncontrolled case series include improvements in nutritional status and symptoms of nausea and vomiting as well as improved quality of life [6–14]. In addition, a pilot study on the use of GES in patients with postgastric surgery gastroparesis showed improvements in symptoms and gastric emptying times at 1-year follow-up [15]. Favourable results with the use of GES in patients with intractable vomiting regardless of whether gastric emptying was delayed or normal have been recently reported [16]. However, many of these reports have included small patient numbers (<30) [6–8, 11, 14–16], and in an uncontrolled use, the results may be influenced by a natural history with spontaneous improvement and by placebo effects. In addition, there are insufficient long-term data, with only two studies [14, 17] providing 3-year results.

In this issue, Anand et al. [18] report on the largest series of 214 patients with drug-refractory gastroparesis followed up for a median duration of 4 years in three regional centres. The patients were divided into three

groups: (1) group 1 comprised 25 patients who consented to but did not receive a GES implant due to reimbursement issues; (2) group 2 comprised 156 patients with permanent GES implants, and (3) group 3 comprised 33 patients with temporary implants. The authors report a significant reduction in both nausea and vomiting, reduced total symptom scores, and enhanced gastric emptying in the patients who received GES at the latest follow-up as compared with baseline. Life table analysis results showed no survival benefits in patients who received GES as compared with non-implanted patients.

Although the findings from this paper suggest that GES implantation conveys long-term persisting benefits, no comparison data on symptom scores and quality-of-life measurements are available for the non-implanted patients (control group) at baseline and at latest follow-up. It is assumed that the control group received standard medical therapy, and it is conceivable that similar beneficial effects could have occurred. Furthermore, information on the long-term outcome of severe gastroparesis is very scarce in the literature, but follow-up case series of patients with intractable diabetic or idiopathic gastroparesis who require tube feeding suggest an overall improvement over time, with ability to resume oral feeding [19, 20]. Similar to earlier reported studies, in the absence of a control arm, a contribution of a placebo effect in the treatment arm also cannot be excluded. To date, the multicentre Worldwide Anti-Vomiting Electrical Stimulation Study (WAVESS) [11] is the only randomized double-blind crossover trial reported. In the first part of the study, which was double blinded, there was a significant reduction in the vomiting frequency during the month, when the device was in the 'on' mode as compared with the 'off' mode, but the overall symptom score did not differ between both modalities. Moreover, the efficacy on the vomiting frequency seemed to be confined to the diabetic gastroparesis subgroup. During the second part of the study, which was open labeled, significant improvements in vomiting and quality of life were reported at 6 and 12 months. However, this trial involved a small number of patients (33 in total), having mixed idiopathic and diabetic gastroparesis, and the duration of the double-blind arm of the study was restricted to only 2 months. The authors of the WAVESS trial [11] recommended that 'future protocols should 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'. Unfortunately, results of newer studies of this type have not been reported until now.

Various theories have been postulated concerning the mechanism of action of GES. These include altered autonomic nervous system tone, altered enteric nervous system function, reduced gastric sensitivity to gastric distension, and enhanced fundal relaxation [21–23]. However, the pathophysiological pathways that are directly implicated in the symptomatic improvement from GES remain unknown. Despite the reported improvement in nausea and vomiting and a selection of patients with proven gastroparesis, there is little or no correlation between symptom improvement and objective assessment of accelerated gastric emptying. No data are available on the effects of GES on the gastric contractility patterns. Undeniably, these findings highlight the present status of our ignorance of the mechanisms of action of GES. In the setting of such unknown mechanisms of action, a placebo effect cannot be ruled out, and the optimal mode and site of stimulation remain unclear.

Only one study has compared medical therapy to GES, but this was done in a non-randomized setting [14]. Whilst this study reported improved long-term symptom control and a decreased use of health care resources in the GES-treated group for up to 3 years of follow-up, the extremely small sample size (9 patients in each treatment arm), the unusually high mortality rate in the medical therapy group, and the lack of population-based control data were severe limitations of this study.

In the absence of convincing evidence of efficacy, and lack of good predictors of responsiveness, all patients undergoing Enterra implantation should preferably be involved in a follow-up program to document short- and long-term outcomes and to contribute to the scientific basis for this treatment. With that respect, Anand et al. [18] certainly must be commended for providing the largest and longest follow-up study reported to date. Still, many burning questions remain, before we can convincingly conclude that GES is efficacious and ready for generalized application. Except for the WAVESS study [11], none of the other studies have utilized well-controlled trial designs. Given the high costs involved (approximately USD 20,000.00), the unknown mechanism of action, and the absence of rigorous well-controlled randomized trials, we should exercise caution before embracing GES as a standard of care. Taking into account the unpredictable nature of gastroparesis and the poorly studied natural history, more long-term studies would be welcome, in addition to properly designed, well-controlled, randomized placebo-controlled studies, before we can draw scientific and objective conclusions.

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