



Gastric POEM for gastroparesis: Panacea, placebo, or pathway to the future?

Gastroparesis (GP) is a syndrome defined by delayed gastric emptying in the absence of mechanical obstruction.¹ Typical symptoms include abdominal pain, nausea, vomiting, early satiety, bloating, and/or weight loss.² It is 1 of the 2 most common sensorimotor disorders of the stomach, the other being functional dyspepsia.³ It is estimated that approximately 5 million adults in the United States have GP symptoms.⁴ The causes of GP are diverse; there are more than 50 recognized causes, although diabetes accounts for the majority of known cases (25%).^{1,2,5} Medications, vascular disorders, connective tissue disorders and postsurgical conditions are other common causes of GP.^{1,2,5} Not surprisingly, given the multiple causes of GP, the pathophysiology of GP is complex (see below).⁵ This explains, in part, why no single treatment has proved uniformly effective at treating the global symptoms of GP and why continued research in this field is critical.

In healthy patients, gastric emptying is a subconscious event that does not cause distress. However, in patients with GP, eating can create a variety of symptoms and cause significant physical, and even emotional, distress. In a healthy patient, the proximal part of the stomach (fundus and upper body) relaxes to accommodate ingested food (ie, receptive relaxation), whereas the distal part of the stomach (antrum and lower body) generates strong muscular contractions to triturate and then expel ingested food. The pylorus plays a critical role in gastric emptying. Normally, in a series of tightly coordinated events, antral contractions are intimately linked with pyloric relaxation, to maximize the flow of triturated material out of the stomach. Although data are limited, abnormalities of pyloric tone and pressure (eg, “pylorospasm”) and dyscoordination between antral contractions and pyloric relaxation are thought to impair normal gastric emptying and contribute to symptom generation in some patients.^{5,6} Accurately measuring pyloric function (eg, resting tone, phasic pressures, relaxation) is difficult, however. Endoscopy does not provide information on pyloric physiologic function; fluoroscopy provides information only on the flow of liquids, which is not relevant to symptom generation in most patients. Antroduodenal

manometry has provided some of the best information on pyloric function, although this technique is not widely performed. Analysis of deep pyloric biopsy specimens has demonstrated that a reduction in the interstitial cells of Cajal and the presence of pyloric fibrosis may also play key roles in pyloric dysfunction in some patients with GP.⁷ These findings prompted researchers to investigate endoscopic therapies designed to reduce pyloric pressure and tone.

Clinicians and endoscopists enthusiastically endorsed the use of intrapyloric endoscopic injection of botulinum

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toxin after early studies showed that the procedure was safe and improved GP symptoms in diabetic patients.⁸ However, although initial case reports and small uncontrolled studies appeared promising, larger placebo-controlled studies demonstrated that botulinum toxin of the pylorus benefited few patients.⁹ Concurrently, investigators were evaluating the safety and efficacy of a novel endoscopic technique to treat symptoms of achalasia. Peroral endoscopic myotomy (POEM), developed in Japan and used since 2010, was rapidly taken up by endoscopists as a method to treat achalasia. Success in this area led investigators to evaluate the role of endoscopic myotomy for the treatment of GP. The results of the first case were reported in 2013; since then, several case reports and small uncontrolled studies have been published, and many academic centers are now performing gastric POEM (G-POEM), although data from large, randomized, sham-controlled studies are lacking, as are long-term follow-up data.

In this edition of *Gastrointestinal Endoscopy*, Gregor et al¹⁰ report the performance of G-POEM in 52 patients in whom medical therapy for their GP symptoms had

failed. Patients were surveyed by several validated measures (Gastroparesis Cardinal Symptom Index (GCSI), Patients Assessment of Gastrointestinal Disorders Symptoms Severity Index (PAGI-SYM), and Short Form 36 at baseline and 1, 3, 6, 12, and 24 months after G-POEM. Upper endoscopy, gastric scintigraphy (4-hour solid phase study), and pyloric EndoFLIP were performed before G-POEM and at the 6-month follow-up mark. Patients were categorized both by underlying cause (diabetes, postsurgical, idiopathic) and were phenotyped by the predominant symptom (vomiting, dyspepsia, regurgitation). A patient was defined to be a clinical responder if there was an improvement in the GCSI by ≥ 1 points.

In the current study, 52 patients were treated with G-POEM. Similar to other GP studies, the majority of patients were female (88%). A responder definition of a 1-point improvement in the GCSI score was used; 58% and 48% of patients were classified as responders at the 6- and 12-month follow-up mark, respectively. The clinical response rates did not differ on the basis of cause. The mean gastric emptying improved at 6 months (10% retention) compared with baseline (36% retention), and PAGI-SYM scores improved at each predefined follow-up point. Finally, with regard to the impact on health care utilization, the number of emergency department visits and hospital days decreased overall.

This study confirms prior studies showing that G-POEM is technically feasible and safe when performed by endoscopists with experience (>100 prior procedures in this study). A technical success rate of 100% was achieved, with an adverse event rate of 5.8% (3 of 52 procedures; GI bleeding in 1 patient; submucosal mucosotomy leaks in 2 patients). Although the median hospital stay was just 1 day, there was quite a range, with hospital stays of up to 1 week reported. In contrast to many G-POEM studies, these investigators coordinated a long follow-up period, although the sample size diminished greatly, with only 23 patients studied at 12 months and 11 at 24 months. This study demonstrates that G-POEM improved GP symptoms in some, but not all, patients. However, several critical questions remain unanswered. First, how does G-POEM really work? In the current study, mean gastric retention time was shown to improve. However, extensive data demonstrate that improving gastric emptying does not predictably lead to global GP symptom improvement.^{3,5} The concept of endoscopic pyloromyotomy reducing pyloric pressures, thereby improving gastric emptying and GP symptoms, is likely far too simplistic. That said, it is curious that prior symptom improvement with intrapyloric Botox injection seemed to predict a favorable response to G-POEM among the 25 patients who had previously been treated with Botox, although the details regarding the timing, frequency, and dosing of Botox in those patients was not provided. The response to intrapyloric Botox injection, as the authors suggest, may be useful in selecting appropriate patients for G-POEM in

the future and warrants additional research. Similarly, the role of EndoFLIP warrants further study. Future investigations will also need to evaluate other pathophysiologic mechanisms that may be affected by G-POEM, including changes in gastric accommodation, neurohumoral factors, and sensory afferent function. Second, no significant differences in response rates were identified when analyzed by cause, which is interesting because GP is a heterogeneous disorder, and the pathophysiology of GP secondary to a surgical adverse event (eg, postfundoplication GP) is quite different from that of GP secondary to long-standing diabetes. Third, although EndoFLIP at 6 and 12 months after the procedure identified a reduction in pyloric cross-sectional area and in the distensibility index, this did not correlate with treatment response or with gastric emptying. Importantly, there appeared to be a loss of compliance in the pylorus with longer follow-up times; this requires further investigation because it may mean that healing and tissue remodeling over time leads to a less compliant pylorus. Whether this correlates to a worsening of gastric emptying over time is not known. Fourth, the patients enrolled in this study were categorized as medically refractory. However, there is no consensus on what defines a “medically refractory” GP patient, and this likely differs greatly according to the clinicians’ experience and comfort level with the multiple currently available options to treat nausea, vomiting, and visceral pain.

The study by Gregor et al¹⁰ provides new and interesting information on quality of life and the impact of G-POEM on the healthcare system. These results, when combined with other published studies, should spur researchers on to help answer some of the key questions outlined above. Large prospective multicenter studies, including a sham procedure arm, are required to determine whether G-POEM has a permanent role in our array of therapeutic choices for GP patients. Similarly to the work in the field of achalasia, these studies may help refine our understanding of this complicated disorder and help identify a specific patient population that will gain long-lasting benefits from this endoscopic procedure.

DISCLOSURE

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Abbreviations: GCSI, Gastroparesis Cardinal Symptom Index; GP, gastroparesis; G-POEM, gastric POEM; PAGI-SYM, Patient’s Assessment of Gastrointestinal Disorders Symptoms Severity Index; POEM, peroral endoscopic myotomy.

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