G-POEM for Gastroparesis: Is There Pressure to Go with the Flow?

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Distressing symptoms such as post-prandial nausea, bloating, a sense of fullness, and vomiting are associated with the syndrome of gastroparesis, a condition associated with abnormal retention of food and fluid in the stomach. A subset of gastroparesis patients have “pylorospasm”, initially described by Mearin et al. [1] as abnormally prolonged, high-amplitude pyloric contractions in a 1986 study of 14 of 24 diabetic patients with nausea and vomiting. Following publication of this study, the contribution of the pylorus to symptoms and gastric emptying delays in gastroparesis has been the focus of several investigations. Recent histologic studies observed loss of the putative pacemaker cells controlling enteric smooth muscle contractions, the interstitial cells of Cajal, and collagen fibrosis in full-thickness pyloric biopsies from gastroparesis patients, further implicating abnormal pyloric motility and pyloric obstruction in the etiopathogenesis of pylorospasm [2]. Several therapies have been devised to correct pylorospasm in gastroparesis, including pyloric botulinum toxin A injection, surgical pyloromyotomy, and transpyloric stent placement. A drawback of botulinum toxin is the transient duration of the response whereas migration has limited adoption of stent placement. Gastric per-oral endoscopic myotomy (G-POEM) is a technique first described in 2012 in a study conducted in pigs that was subsequently described in several case series of 7–46 patients that was promoted as a less invasive alternative to surgery as a means to permanently minimize the impact of pyloric dysfunction in gastroparesis [3–5].

In this issue of *Digestive Diseases and Sciences*, Malik et al. [6] report their experience with G-POEM in 13 gastroparesis patients. At first glance, the results appear promising. All patients successfully underwent G-POEM and 8/11 subjects with follow-up data reported somewhat or considerably improved symptoms as assessed by the Clinical Patient

Grading Assessment Score (CPGAS). Nonetheless, several items require closer examination. First, these subjects almost all had mild symptoms at baseline with an average Gastroparesis Cardinal Symptom Index (GCSI) score of 2.1, even though they were labeled as “refractory gastroparesis” by the authors. It is unclear why the authors used the validated Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM) survey as their baseline questionnaire and CPGAS as their primary therapeutic endpoint. GCSI, a 9-item questionnaire contained within PAGI-SYM, has been validated as a reliable and responsive instrument for detecting symptom severity in gastroparesis [7]. This contrasts with CPGAS which has not been validated for use in gastroparesis and has no evidence regarding its reliability or responsiveness to changes in gastroparesis symptoms. When examining changes in GCSI, only 5/11 subjects reported a clinically significant improvement (change in GCSI by 0.5) after G-POEM. None of the individual symptom scores as assessed by PAGI-SYM were statistically significantly different after G-POEM, raising the question of whether a potentially morbid procedure such as G-POEM is appropriate treatment for a patient cohort with mild gastroparesis symptoms. There were no improvements in gastric emptying by scintigraphy; furthermore, G-POEM was not associated with any clinically meaningful changes in pyloric function using the Endoscopic Functional Luminal Imaging Probe (EndoFLIP), an endoscopically deployed balloon catheter that simultaneously measures cross-sectional area and intraluminal pressure as measures of flow impedance and distensibility. Although EndoFLIP measurements may have been affected by post-POEM inflammation and edema that limited distensibility, as suggested by the authors, the mean < 1 mm²/mmHg increases in distensibility observed are disappointingly less than the ~ 13 mm²/mmHg increases observed in ten gastroparetics after pyloric dilation in a study by Gourcerol et al. [8].

The findings of this study are contrasted with other uncontrolled case series of G-POEM as well as prior investigations of other pyloric therapies in gastroparesis. There are nearly a dozen published case reports or series of G-POEM

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in this condition, many of which are reviewed in detail by the authors of this article. All studies to date describe symptom benefits similar to or greater than those reported by Malik et al. (Fig. 1a). Some investigations report superior improvements in gastric emptying than in the current study, but it is uncertain if this is secondary to differences in endoscopic technique or in the composition of patient populations (Fig. 1b) [3, 4]. Notably, only six patients in this series underwent serial gastric scintigraphy—too small of a sample on which to base definitive conclusions about efficacy. Nevertheless, these observations bring to mind similar uncontrolled reports about pyloric botulinum toxin circa 2002 or gastric resection therapies circa 1988 for gastroparesis. Indeed, the early literature was similarly optimistic about the utility of botulinum toxin to relax the pylorus in gastroparesis, with some studies reporting symptom improvements in up to 90% of patients. Furthermore, several investigations showed similar or greater improvements in pyloric pressure or the gastric emptying rate after botulinum toxin therapy comparable to the modest effects seen in the current study. In contrast, functional responses to surgical pyloroplasty are more robust, with normalization of gastric emptying in 60–71% of patients. The practice climate for injecting botulinum toxin in gastroparesis was substantially altered by publication of two underpowered sham injection-controlled studies a few years later that reported no symptom benefits of this therapy, including one protocol with a debatable crossover design where active and sham injections were separated by only 1 month even though the drug has a 3–6 month duration of action [9, 10]. As a consequence, botulinum toxin was the only therapy that earned

a strong recommendation to not be performed for gastroparesis in the 2013 American College of Gastroenterology (ACG) guideline [11]. Similar trends were observed with subtotal gastrectomy for postsurgical gastroparesis where early series reported response rates approaching 90% followed by later reports of responses in only ~40%. Time will tell if G-POEM research follows a similar trajectory.

The potential utility of G-POEM in gastroparesis should be contrasted to benefits of POEM for achalasia. Achalasia differs significantly from gastroparesis in that its dominant symptom (dysphagia) can be readily attributed to impaired intraluminal flow. Although the disorder involves dysfunction of both the esophageal body and lower esophageal sphincter (LES), all effective therapies of achalasia, including surgical myotomy, endoscopic dilation, POEM, and botulinum toxin provide relief of the functional LES obstruction. POEM effectively increases LES distensibility in achalasia and has been endorsed as being comparable to laparoscopic myotomy for all of the achalasia syndromes by the American Gastroenterological Association Clinical Practice Updates Committee [12]. The importance of a delay in gastric emptying in causing the clinical manifestations of gastroparesis is less clear. None of the cardinal symptoms of gastroparesis (nausea, vomiting, fullness, early satiety, bloating, pain) or composite scores of gastroparesis symptom severity correlate with scintigraphic measures of gastric emptying. Furthermore, although prokinetic medications improve symptoms, the symptom benefits of these drugs correlate poorly with gastric emptying acceleration, suggesting a possible central or placebo effect of these medications. Management of gastroparesis includes the implementation

Fig. 1 Benefits of the G-POEM procedure are shown for the study by Malik et al. and 3 prior studies that employed validated measures of symptoms and gastric emptying. Effects of G-POEM on overall gastroparesis symptom severity measured by the validated Gastroparesis

Cardinal Symptom Index score (0 = none, 5 = very severe) are shown (a). Effects of G-POEM on 4 h scintigraphic gastric retention (10–20 mildly delayed, 20–35% moderately delayed, >35% severely delayed gastric emptying) are shown (b)

of a range of therapies, including gastric stimulation, which has no consistent effects on gastric emptying. Thus, it would not be surprising if G-POEM is ultimately found to be less effective for gastroparesis than esophageal POEM is for achalasia.

A major focus of future research should be to define which patient subsets are most likely to respond to G-POEM. These investigators chose to focus on patients with postsurgical gastroparesis due to the belief that this etiology would be most likely to respond to pylorus-directed therapies. This decision is logical from a physiological standpoint as postsurgical patients commonly exhibit more severe gastric emptying impairments than individuals with idiopathic or diabetic gastroparesis. Yet, a subgroup analysis of patient subsets likely to report symptom reductions from botulinum toxin injection identified idiopathic gastroparesis as the etiology most likely to respond to that form of pyloric therapy [13]. One can envision using EndoFLIP to stratify patients into those with normal versus poor pyloric distensibility who would then be referred for pyloric treatment. Indeed, Gourcerol et al. [8] correlated symptom severity with blunted pyloric compliance in gastroparesis. A number of patients in the study by Malik et al. had undergone prior botulinum toxin injection; positive responses to botulinum toxin mostly correlated with improvements after G-POEM. Using botulinum toxin responsiveness as an inclusion criterion for future G-POEM studies will have to be judiciously considered due to the theoretical concerns about injection-induced scarring which has been observed with therapies for achalasia, although these changes were not reported in this study.

In their conclusion, Malik et al. advocate performing randomized sham-controlled studies to confirm the efficacy of G-POEM. Still, it is not at all clear how a blinded, controlled trial of this endoscopic technique would be undertaken. Sham treatments with a therapy that does not alter the gastric anatomy are easy-to-design, as has been done for pyloric botulinum toxin injection [9, 10]. Nonetheless, devising a sham methodology as a control arm for any G-POEM study is problematic, in particular since many patients who undergo G-POEM are admitted or undergo barium contrast radiography to exclude leaks, similar admissions or radiographic testing for patients receiving the sham treatment would raise important ethical and financial considerations, including questions regarding payment for these additional procedures. Furthermore, even in the most experienced hands, G-POEM performance adds significantly more time and equipment charges to the endoscopy session than would any sham treatment. Taken together, these issues suggest that conducting a trial that is truly blinded to the patient, caregivers, and third-party payers would be nearly impossible to accomplish in practice. Non-inferiority trials comparing G-POEM versus other therapies including medications (e.g. metoclopramide) or surgical pyloromyotomy could be considered to minimize some of these considerations,

although these might not be definitive if the comparator treatment itself has not of proven benefit on the basis of controlled investigations.

Despite these concerns, G-POEM and other pyloric therapies will continue to be employed in selected gastroparesis patients. In our own practice, we acknowledge the use of many treatments for this condition, the efficacy of which has not been confirmed in controlled investigations, including botulinum toxin as well as a broad range of neuromodulators, antiemetics, and surgeries including gastric electrical stimulator implantation. Accumulating more clinical experience will define if G-POEM is useful as sole therapy of gastroparesis or in combination with agents with other mechanisms of action.

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