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Pyloric Therapies for Gastroparesis

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Opinion statement

Gastroparesis is a syndrome that can be difficult to treat effectively and likely represents the common clinical presentation of multiple underlying mechanisms. One of these presumed mechanisms involves pyloric dysfunction, tied perhaps to spasm or fibrosis, manifesting as functional gastric outlet obstruction. Various diagnostic modalities have been used to better characterize this hypothesized abnormality, including most recently antroduodenal manometry and impedance planimetry. A variety of therapeutic interventions specific to the pylorus have also been proposed in the last several years, including intrapyloric injections of botulinum toxin, transpyloric stenting, surgical pyloroplasty, and endoscopic pyloromyotomy. The clinical application of these maneuvers has been mostly empiric thus far, but efforts are ongoing to identify the subset of patients whose physiology best positions them to benefit from such therapy. Early results for many of these interventions have been promising and will serve as the basis for larger and more systematic research frameworks moving forward.

Introduction

Gastroparesis is typically defined by delayed emptying of the stomach in the absence of mechanical obstruction. The associated clinical syndrome is chronic and usually includes some combination of nausea, vomiting, early satiety, postprandial fullness, bloating, and abdominal pain. Gastroparesis is well known to reduce overall quality of life, with the severity of gastric emptying delay offering little predictive information regarding the degree of functional impairment [1].

Over time, various treatment strategies have been proposed to address this major symptom burden. Dietary restriction favoring low-fat, low-residue foods has been associated with milder symptoms [2, 3]. Metoclopramide, a dopamine agonist with prokinetic activity, remains the only

medication that is FDA approved for the treatment of gastroparesis, though its long-term applicability is limited by the risk of neurological side effects. Gastric electrical stimulation, an investigational modality that has yielded mixed results, is limited by the need for surgical implantation and the risk of structural complications requiring later revision [4, 5].

Mechanistic understandings of gastroparesis continue to evolve but generally acknowledge that a diverse set of etiologies lead to a common clinical presentation. In terms of causative conditions, gastroparesis is commonly seen in diabetic, postinfectious, and postsurgical contexts, though infiltrative and neurological disorders such as amyloidosis and Parkinsonism are also associated [6]. With regard to pathophysiology, hypothesized abnormalities include gastric arrhythmia, reduced contractility, various forms of neuronal damage, and upstream mechanical effects from dysmotility of the small bowel [7].

In attempting to bring a mechanistic perspective to therapeutic decision-making, multiple investigators have attempted to define clinically relevant subtypes of the general gastroparetic population. Distinctions have been made, for example, with attention to basic demographics, histomorphology, and background disease state [7–9]. Work is also ongoing to identify genetic and neurohormonal markers with potential implications for responsiveness to specific medical therapies [10]. These associations remain tenuous, however. Even gastric emptying time, the major objective criterion at present for defining gastroparesis, may be limited in its clinical utility, since chronic unexplained nausea and vomiting without gastric emptying delay is a process that is in most practical regards indistinguishable [11]. This fact underscores the importance of developing novel methods for subcategorizing this patient population, with particular attention to grounding the use of targeted therapeutic strategies.

Pyloric dysfunction in theory and practice

Among the functional abnormalities that have been demonstrated in particular subsets of gastroparetic patients, dysfunction of the pylorus continues to receive special attention given its ready association with anatomically focused intervention. The hypothesis that gastroparesis could be mediated at least partially by pyloric dysfunction was first formally tested in 1985 through a manometric evaluation of 24 diabetic patients with nausea and vomiting compared with 12 healthy controls. Mearin et al. showed that over 5 h, pyloric contraction tended to be longer in duration and higher in amplitude among the diabetic patients, corresponding with a tonic pattern they dubbed "pylorospasm." Mechanistically, this departure from normal pyloric motility was presumed to correlate with increased resistance to flow and thus aberrancies in gastric emptying [12]. Additional studies have shown that local mechanical changes at the pylorus also impact antral and duodenal motility, suggesting the existence of more complex underlying feedback mechanisms [13].

Recent histologic studies have reinforced the potential importance of pyloric dysfunction to gastroparesis symptomatology. Evaluation of full-thickness biopsies obtained from 17 patients with refractory gastroparesis symptoms showed that 12 patients demonstrated evidence of pyloric depletion of interstitial cells of Cajal (ICC) in comparison with healthy controls. Pyloric fibrosis was also noted in a significant majority of gastroparetic patients regardless of disease etiology. Gastric emptying times correlated with ICC dropout at the antrum but not at the pylorus, a finding that could be attributed to

the study's sample size but that again raises questions about the clinical relevance of scintigraphic analysis for primary diagnostic categorization [14•].

In practice, however, clinical characterization of pyloric function has been challenging, in part because of the region's dynamic neuromuscular complexity and in part because of limitations in diagnostic technique. Assessments of pyloric patency and contractility under endoscopic visualization are of course limited given that these views are short, subjective, and contingent upon numerous uncontrolled procedural variables. Fluoroscopic evaluation has been used historically in clinical and research settings to estimate pyloric diameter and thus to suggest functional obstruction, but this modality is likewise limited by short diagnostic intervals and interpretive subjectivity [15].

Antroduodenal manometry, involving placement of a pressure-sensitive catheter across the distal stomach and proximal small bowel, remains a commonly recognized option for reliable characterization of pyloric muscle activity, though the procedure can be technically challenging and is limited in its availability. Conventional manometry catheter sensors are typically spaced centimeters apart, resolution that may be insufficient for recording activity at a sphincter of relatively short length [16]. Moreover, operator expertise is required as these catheters remain prone to frequent migration, undermining the accuracy of readings that are critically dependent on position. High-resolution manometry has also been employed, but data are limited at present. There is also evidence to suggest that the manometry procedure itself might alter pyloric function [17].

More recently, attention has shifted toward the measurement of sphincter compliance as a potentially useful quantitative metric of pyloric function. In particular, the commercially available endoluminal functional lumen imaging probe (EndoFLIP®, Crospon, Inc., Galway, Ireland) exploits the principles of impedance planimetry to measure the diameter and pressure of any hollow structure and thereby extrapolate information about tissue distensibility at that location. The probe consists of uniformly spaced ring electrodes arranged within a distensible, non-compliant bag, and thus far, it has demonstrated utility in distinguishing functional pathology at multiple sites along the gastrointestinal lumen [18–21].

Three recently published studies, all using the EndoFLIP device, have attempted to characterize abnormalities in pyloric distensibility in the setting of gastroparesis. Gourcerol et al. studied 27 gastroparetic patients and found that mean fasting pyloric compliance was significantly lower than in healthy controls and correlated with symptom severity and gastric emptying time [22]. Malik et al. evaluated 54 patients with gastroparesis and found that pyloric diameter and cross-sectional area were inversely correlated with symptom severity but not gastric emptying time [23]. Lastly, Snape et al. prospectively performed sequential manometric and distensibility measurements of the pylorus in 114 patients with some combination of nausea, vomiting, and postprandial abdominal pain. Within this otherwise undifferentiated cohort, the authors identified a significant correlation between pyloric distensibility and

pressure and showed that reduced pyloric distensibility was associated with delayed gastric emptying [24•].

As a relatively young diagnostic modality, EndoFLIP is still subject to justifiable skepticism, including challenges to its constant geometric assumption of radial symmetry that allows for cross-sectional area to be calculated from the measured diameter. This assumption may misrepresent the anatomic complexity of muscles like the pylorus [25]. Even so, impedance planimetry remains the subject of active investigation as a complementary metric for isolating a clinically relevant subset of patients with gastroparesis. In their study, Gourcerol et al. also isolated ten patients with the lowest pyloric compliance measurements for hydraulic dilation of the pylorus and demonstrated significant posttreatment symptom improvement among these patients [22]. This sub-analysis provides intriguing proof of concept for future approaches to other kinds of pyloric therapy.

Recently, Koch and colleagues at Wake Forest University used electrogastrography to evaluate pyloric dysfunction from another angle. They hypothesized that patients with impaired gastric emptying, an unremarkable endoscopy excluding obstruction and a normal electrogastrography with a rate of 3 cycles/min pattern were more likely to have pyloric dysfunction as opposed to other potential etiologies such as dysrhythmia—with the hypothesis that a normal electrogastrography pattern showing of 3 cycles/min implied that gastric antral contractions were grossly normal and dysfunction must lie at another foci of the emptying algorithm. By limiting pyloric-directed therapy to that subgroup, they were able to demonstrate improvement in 78% of their 33 selected patients. While electrogastrography is not widely viewed as a typical test to evaluate pyloric function, the presence of a normal electrogastrography in the context of documented gastroparesis may help raise concern for a potential pyloric etiology and could potentially have a role in tandem with other pyloric-directed diagnostic studies—if the results of this intriguing study can be corroborated by other investigators and in larger numbers [26].

The current lack of reliable methods for identifying a predominantly "pylorospastic" phenotype has not hindered the empiric application of anatomically focused interventions. Anecdotal experience of therapeutic success has driven their continued use, despite the fact that randomized controlled trials, where available, have yielded negative results. In explaining this discrepancy, advocates of pyloric therapies in gastroparesis often cite the presumed heterogeneity of these study populations, noting that a prescreened set of patients physiologically predisposed to benefit from pyloric therapy might demonstrate more robust effects than patients recruited on the basis of delayed gastric emptying or symptoms alone.

Botulinum toxin

Botulinum toxin is a protein natively produced by the bacterium *Clostridium botulinum* that blocks neuromuscular conduction, an effect that has been

exploited clinically for the past several decades. Within the gastrointestinal tract, the compound's first application was reported by Pasricha et al. in 1995 as an injection to the lower esophageal sphincter in the context of achalasia [27]. Botulinum toxin is necessarily temporary in its effectiveness and requires repeated administration after several months, but its low harm profile and minimal invasiveness underscore its favorability as a therapeutic option. Thereafter, experiments proliferated to evaluate the utility of this agent in other processes involving smooth muscle dysfunction, ranging from esophageal spasm to chronic anal fissure [28].

In the context of gastroparesis, Sharma et al. provided the first case report of intrapyloric injection of botulinum toxin as a 1998 conference abstract [29]. This report was followed 4 years later by three published open-label case series ranging from 6 to 10 patients in size, each demonstrating that botulinum injection led to significant improvement in both symptom scores and gastric emptying delay [30–32]. A larger retrospective review from 2005 analyzed 63 patients with symptomatic gastroparesis who underwent botulinum toxin at a single institution and found that 43% of the study population experienced a therapeutic response, defined as subjective symptom improvement for at least 4 weeks [33].

Two subsequent randomized placebo-controlled trials yielded less impressive findings. Arts et al. performed a crossover trial of 23 patients with gastroparesis, randomizing them to undergo intrapyloric injection of either botulinum toxin (100 units) or saline followed by repeat injection with the alternative agent 4 weeks later. Significant improvements were noted in gastric emptying after the first injection but not after the second injection, regardless of interventional sequence. Postprandial fullness and bloating improved significantly 1 month after botulinum toxin injection, but improvements in cumulative symptom scores did not achieve statistical significance [34]. Friedenberg et al. studied 32 patients with gastroparesis, randomizing them to intrapyloric injection of either a higher dose of botulinum toxin (200 units) or saline. Again, symptomatic improvement was noted in both study arms at 1-month follow-up, more prominently in the placebo group and with a difference between the two that was not statistically significant. Gastric emptying delay was significantly reduced after botulinum toxin injection but not after saline [35].

The shared conclusion of these trials, that botulinum toxin was no better than placebo in the treatment of gastroparesis, was recapitulated in a later systematic review, likely weighted toward the high level of evidence implied by a randomized controlled study design [36]. In addition to heterogeneous study populations, however, these trials may have been limited by their small sample sizes, designed as they were to detect relatively large effects [37]. Clinical guidelines put forward by the American College of Gastroenterology in 2013 also strongly recommended against the use of intrapyloric botulinum toxin for patients with gastroparesis but cautioned that "there is a need for further study in patients with documented 'pylorospasm'." [38] To further cloud the issue, a retrospective analysis by Coleski et al. of 179 patients—the largest study to date involving botulinum toxin and gastroparesis—identified specific predictors of therapeutic response, including higher dose injection (200 units); female gender; younger age; and non-diabetic, non-surgical etiologies [39]. These findings support the existence of a definable subset of patients for whom intrapyloric botulinum toxin injection might be particularly beneficial. While botulinum

toxin cannot be recommended at this time for all patients with gastroparesis based on the inconsistent data detailed above, it may have a role in the treatment of select subgroups and remains in the gastroparesis treatment armamentarium, in large part perhaps due to the absence of other safe established treatments. It may also perhaps have a diagnostic role in selecting patients more likely to benefit from other pyloric interventions.

Stent placement

Transpyloric stent placement represents another recently explored option for addressing presumed functional obstruction at the gastric outlet. Results of this intervention were first reported in a 2013 case series of three relatively young patients with gastroparesis who had failed multiple medication trials. In each case, a double-layered, fully covered, self-expandable metallic stent was placed across the pylorus with resultant normalization of gastric emptying times and improvement in subjectively reported symptoms [40].

These investigators subsequently published a larger retrospective analysis of 30 patients undergoing a total of 48 procedures involving transpyloric stent placement (with 9 patients undergoing at least 1 repeat stent placement) by the same method. All patients in this study had gastroparesis refractory to at least one prokinetic medication, and just over half were treated in the context of hospitalization for intractable symptoms. Symptoms subjectively improved in three-quarters of patients for whom follow-up data were available, though importantly, the degree of improvement was not quantitated, and validated questionnaires were not used. Of the 16 patients who underwent repeat scintigraphic evaluation, gastric emptying times improved in 11 cases [41].

As with studies involving botulinum toxin injection, transpyloric stents were placed on the basis of symptoms and gastric emptying time rather than dedicated measures of pyloric function. A relatively high rate of stent migration was reported (59% over a mean follow-up interval of 146 days) despite the use of various modes of stent fixation, also limiting this intervention's durability over time. Many of these patients had not received any prior pyloric therapy, so it is also unclear how the efficacy of transpyloric stent placement might compare with that of botulinum toxin injection or other pyloric interventions. The authors suggest that transpyloric stent placement might serve as a means of identifying appropriate candidates for more permanent means of sphincter disruption, such as pyloromyotomy. Further research is certainly needed to clarify the role of stent placement within the larger suite of gastroparesis therapies.

Surgical pyloroplasty

Surgical disruption of the pylorus is a longstanding therapeutic concept that originated in the care of infants with idiopathic hypertrophic pyloric stenosis [42]. More recently, the concept has been translated to cases of presumed functional gastric outlet obstruction. Among relevant surgical approaches, the most common and best studied is the Heineke-Mikulicz pyloroplasty, now typically performed laparoscopically, in which pyloric diameter is increased by

making a longitudinal incision across the pylorus that is then sutured in a transverse orientation.

Building on the apparent success of surgical pyloroplasty in mitigating postprocedural bloating after fundoplication, Hibbard et al. described their experience with this procedure in 28 gastroparetic patients, with 83% of patients indicating symptomatic improvement at 1-month follow-up and 71% experiencing normalization of gastric emptying time after the procedure [43]. Toro et al. published a similar retrospective study of 50 patients with refractory gastroparesis, the majority of whom underwent concomitant surgical procedures at the time of pyloroplasty. Symptoms improved in 82% of patients for whom follow-up data was available, and 96% of those undergoing repeat scintigraphy had an improvement in gastric emptying. While these results are impressive, interpretation is again limited by the use of qualitative and non-validated symptom assessments [44]. Mancini et al. reported results for 46 patients undergoing surgical pyloroplasty for gastroparesis, augmenting their analysis with preoperative and postoperative Gastroparesis Cardinal Symptom Index (GCSI) scores. Scores were significantly improved after the procedure across all nine included symptom domains. Gastric emptying times improved in 90% of patients and normalized in 60% of patients for whom a follow-up scintigraphic evaluation was performed [45].

In the largest retrospective cohort analysis to date, Shada et al. reported on 177 patients undergoing laparoscopic pyloroplasty for a presumed diagnosis of gastroparesis. Inclusion criteria were somewhat more liberal than other studies, including endoscopic visualization of retained food and clinical suspicion of vagal nerve injury, and the majority of included patients had undergone various concurrent operative interventions, perhaps limiting the extent to which operative results could be attributed to pyloroplasty alone. Procedural complications included four reoperations due to suspected leak (two of which were confirmed), four wound infections, and seven readmissions within 30 days for medical management of symptom exacerbation. The median length of the index hospitalization was 2 days. Mean symptom severity, reported in aggregate, improved significantly after surgery for eight of nine prespecified symptom domains, excepting early satiety [46•].

Endoscopic pyloromyotomy

Progress within the relatively novel paradigm of submucosal tunneling, driven in large part by the continued imperative toward minimizing procedural invasiveness, has led to the development of endoscopic approaches to pyloric disruption as well. Gastric per-oral endoscopic myotomy (G-POEM), alternately termed per-oral endoscopic pyloromyotomy (POP), conceptually recapitulates per-oral endoscopy myotomy (POEM), which targets functional obstruction at the lower esophageal sphincter for patients with achalasia and other spastic disorders of the esophagus. Despite a relatively established procedural sequence (mucosal entry, tunneling, myotomy, and mucosal closure), technical refinement by its limited number of currently active practitioners is ongoing, with experimental models continuing to shed light on clinical application [47].

Endoscopic pyloromyotomy was first documented in a porcine model by Kawai et al., with a significant reduction in sphincter pressure demonstrated by

postintervention manometry [48]. Khashab et al. reported the first successful human application of this procedure in a patient who had experienced significant relief with transpyloric stenting but reliable symptom recurrence with stent migration. Endoscopic pyloromyotomy led to significant symptomatic improvement despite persistently delayed gastric emptying on repeat scintigraphic analysis [49]. Multiple additional case reports have since been published with generally favorable results regardless of gastroparesis etiology [50]. Descriptions of G-POEM for mechanical gastric outlet obstruction comment on the risks of a transient postprocedural dumping syndrome with episodic hypoglycemia, but this seems to have been noted less frequently in the gastroparetic population [51].

The first reported case series of endoscopic pyloromyotomy was reported by Shlomovitz et al. and involved seven patients with gastroparesis, six of whom underwent the procedure with laparoscopic assistance given concurrently planned surgical procedures. Technical success was achieved in all cases, though three were associated with postprocedural complications, namely, bleeding, dysphagia, and hospital-acquired pneumonia. Six of the seven patients reported symptomatic improvement, which was significant in the domains of nausea and epigastric burning, and four of five patients who underwent follow-up scintigraphy had normalized gastric emptying times [52•]. Additional case series were presented earlier this year in abstract form, including a European analysis of nine gastroparetic patients, eight of whom reportedly experienced significant clinical improvement after 1 month as reflected by preprocedure and postprocedure GCSI [53]. A larger, multicenter trial of 30 patients, several of whom had already undergone prior pyloric therapy with botulinum toxin or stenting, demonstrated that G-POEM led to clinical response in 86% of patients according to an unspecified symptom scale [54].

Despite the optimism of this early data, both surgical and endoscopic methods of pyloric disruption require larger and more rigorous study designs to justify regular use in the setting of gastroparesis. At least in the context of G-POEM, prospective and sham-controlled trials are already planned. There is also some interesting precedent for research into particular clinical circumstances in which mechanical disruption of the pylorus might prove especially valuable; for instance, Sarosiek et al. studied a retrospective cohort and identified an additive benefit of laparoscopic pyloroplasty to gastric electric stimulator placement [55]. Continued exploration of novel schema by which to organize the larger gastroparetic population will likely strengthen indications for all of the interventions discussed above.

Conclusion

In summary, multiple therapeutic interventions have been proposed in the past several years to address presumed pyloric dysfunction in patients with typical gastroparesis symptoms. Data are limited in some cases by mixed results (botulinum toxin) and in others by a lack of large and methodologically rigorous trials (transpyloric stenting, pyloromyotomy). Certainly, it is hoped that future investigation will overcome these limitations. Despite the consistent attention paid by existing studies (and, by extension, this review) to the effects of mechanical therapy on gastric emptying delay, the clinical relevance of

traditional metrics for gastroparesis diagnosis and management seems ever more debatable. Developing more precise and reliable methods for defining pyloric dysfunction is a research priority that ideally will be pursued in parallel with the refinement of anatomically targeted therapies.

Compliance with ethical standards

Conflict of interest
Nitin K. Ahuja declares that he has no conflict of interest. John O. Clarke declares that he has no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance;
•• Of major importance

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