# **Endoscopic Approaches to Gastroparesis**

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Corresponding author: Dr Aziz Aadam 676 North Saint Clair St, Suite 1400 Chicago, IL 60611 Tel: (312) 695-3364 E-mail: abdul.aadam@northwestern.edu **Abstract:** Gastroparesis is a complex syndrome with multiple underlying etiologies and pathophysiologies that can cause significant morbidity for patients. Currently, there are limited effective and durable medical and surgical treatments for patients with gastroparesis. As such, there has been recent innovation and development in minimally invasive endoscopic treatments for gastroparesis. Endoscopic therapies that have been investigated for gastroparesis include enteral feeding tube placement, intrapyloric botulinum toxin injection, transpyloric stenting, gastric peroral endoscopic myotomy, and gastric electrical stimulation. This article aims to assess the effectiveness of current endoscopic therapies, as well as discuss future directions for endoscopic therapies, in the management of gastroparesis.

G astroparesis is defined as a complex syndrome of symptoms, including early satiety, postprandial fullness, nausea, vomiting, bloating, and upper abdominal pain, with a corresponding objective delay in gastric emptying in the absence of mechanical obstruction.<sup>1</sup> The primary etiologies of gastroparesis include diabetic, postsurgical, and idiopathic causes. The pathogenesis underlying gastroparesis is complex and driven by multiple overlapping mechanisms, including impaired gastric accommodation, autonomic neuropathy, vagal nerve injury, uncoordinated gastric contractility, pyloric dysfunction, degeneration of interstitial cells of Cajal, and neurohormonal disruption, as well as inflammatory and postinfectious changes.<sup>2,3</sup>

Effective and durable medical treatment of gastroparesis remains a clinical challenge. Currently, the only medication approved by the US Food and Drug Administration (FDA) for gastroparesis is metoclopramide, which is associated with the potential side effects of QT prolongation and irreversible tardive dyskinesia.<sup>4,5</sup> Surgical treatments for gastroparesis include pyloroplasty, pyloromyotomy, subtotal gastrectomy, and gastric electrical stimulation (GES) implantation, which is currently approved by the FDA for compassionate use.<sup>6-8</sup>

Keywords Gastroparesis, endoscopy, treatments, myotomy, transpyloric, stent



**Figure 1. A:** A lumen-apposing metal stent is deployed across the pylorus. **B:** Endoscopic suturing is used to fixate the stent to the gastric wall to prevent migration. **C:** A transpyloric lumen-apposing metal stent is fixated in place after endoscopic suturing.

The need for minimally invasive, effective, and durable treatment for refractory gastroparesis has led to research and innovation in endoscopic therapies. Initial endoscopic treatment for gastroparesis focused on bypassing the affected stomach with enteral feeding tube placement.<sup>9,10</sup> Subsequent studies investigating underlying mechanisms of diabetic gastroparesis revealed prolonged elevations in pyloric pressure by antroduodenal manometry, which were called pylorospasms and thought to be a contributing etiology to delayed gastric emptying.<sup>11-13</sup> Pyloric physiology measured by the endoscopic functional luminal imaging probe (EndoFLIP, Medtronic) has also demonstrated decreased pyloric distensibility and compliance in patients with gastroparesis.<sup>14-16</sup>

As such, endoscopic therapies that specifically target the pylorus, including intrapyloric botulinum toxin injection, transpyloric stent (TPS) placement, and gastric peroral endoscopic myotomy (G-POEM), have been more recently investigated as potential treatments for gastroparesis. This article discusses the landscape of current and potential future endoscopic therapies for gastroparesis.

## **Endoscopic Therapies**

# Endoscopic Placement of Enteral Feeding Tubes

When meeting nutritional needs through oral intake is not feasible due to severe symptoms related to gastroparesis, consideration for endoscopic placement of an enteral feeding tube is appropriate. Endoscopic enteral tube options include percutaneous endoscopic gastrostomy tubes with or without jejunal extensions, as well as direct percutaneous endoscopic jejunostomy.<sup>1</sup> Percutaneous endoscopic gastrostomy is typically performed by the standard pull method described by Gauderer and colleagues and allows for venting of secretions and air to alleviate symptoms of bloating, fullness, and nausea.<sup>9</sup> However, gastric feedings through percutaneous endoscopic gastrostomy are not recommended due to delayed gastric emptying.<sup>9</sup>

Prior to consideration of jejunal tube feedings, temporary placement of a nasoduodenal or nasojejunal tube should be performed under endoscopic or radiologic guidance to determine whether jejunal tube feedings are tolerated. Jejunal tube feeding can be accomplished by a J-tube extension placed through a percutaneous endoscopic gastrostomy, a percutaneous endoscopic jejunostomy, surgical placement, or radiologic placement. Surgical jejunostomy for refractory gastroparesis has been previously studied and found to improve symptoms and reduce hospitalizations. However, there are limited data on percutaneous endoscopic jejunostomy in the setting of gastroparesis, and the optimal method of jejunostomy placement remains unclear.<sup>10,17</sup> Although enteral tube placement can provide relief of gastroparesis symptoms as well as an alternative route to maintain appropriate enteral nutrition, gastrostomy and jejunostomy tubes can be associated with significant patient discomfort and anxiety along with potential complications, including infection, bleeding, and tube dislodgement.<sup>18</sup>

## Intrapyloric Botulinum Toxin Injection

Botulinum toxin inhibits the release of acetylcholine, which causes flaccid paralysis, and has been utilized to induce muscle relaxation in other spastic disorders, such as achalasia. Intrapyloric botulinum toxin injection is thought to reduce pyloric pressure and thereby improve gastric emptying. In a matched control study, Lacy and colleagues demonstrated pylorospasm by manometry in all 8 patients with diabetic gastroparesis; pylorospasm was absent in matched control patients.<sup>12</sup> Furthermore, pyloric injection of 200 units of botulinum toxin was found to significantly reduce pylorospasm in patients with diabetic gastroparesis.<sup>12</sup>

A small case series investigating intrapyloric botulinum toxin injection in idiopathic and diabetic gastroparesis revealed modest results, with most patients showing statistically significant benefits in solid-phase gastric emptying and subjective symptom improvement.<sup>19-21</sup> These results were consistent with large retrospective studies, which found that 43% to 51% of patients demonstrated a symptomatic response to intrapyloric botulinum toxin injection.<sup>22,23</sup>

Despite promising results seen in initial retrospective studies and case series, subsequent randomized, controlled trials found no significant improvement compared to placebo. A randomized, controlled trial by Arts and colleagues of 23 patients found significant improvement in Gastroparesis Cardinal Symptom Index scores compared to baseline with botulinum toxin injections of 100 units.<sup>24</sup> However, these findings were not statistically significant compared to the control of saline injections. A randomized, double-blind, placebo-controlled trial by Friedenberg and colleagues of 32 patients comparing 200 units of botulinum toxin to saline injections also revealed

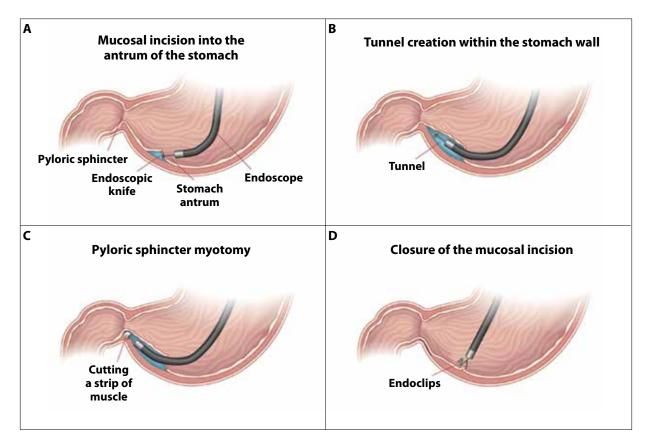


Figure 2. A diagram depicting the 4 principal steps of gastric peroral endoscopic myotomy.

significant improvements in solid gastric emptying times.<sup>25</sup> Interestingly, these improvements were not statistically different from those of the saline group, which also showed significant improvements compared to baseline.<sup>25</sup> As of 2013, the American College of Gastroenterology guidelines on gastroparesis do not recommend the use of intrapyloric botulinum toxin. However, the guidelines noted that there may be utility in further investigation of botulinum toxin injection in patients with documented pylorospasm.<sup>1</sup>

## Transpyloric Stenting

Transpyloric stenting was initially reported in 2013 by Clarke and colleagues in 3 patients with refractory gastroparesis who underwent placement of a self-expandable metal stent across the pylorus, with improvement in gastric emptying and symptoms in all of the patients.<sup>26</sup> Endoscopic TPS placement involves deployment of a self-expandable metal stent across the pylorus with the proximal flange of the stent positioned in the prepyloric antrum and fixated to the gastric wall by endoscopic suturing or clip placement (Figure 1). A study of 30 patients with refractory gastroparesis who underwent transpyloric stenting demonstrated high technical success of stent placement (98%), with improvement of clinical symptoms in 75% of patients and 4-hour gastric emptying studies in 69% of patients. The major limitation of TPS placement is the risk of stent migration, which occurred in 59% of patients in the aforementioned study.<sup>27</sup> Typically, esophageal self-expandable metal stents are placed transpyloric, and the long design of the stent may contribute to the high risk of stent migration. Lumen-apposing metal stents are only 10 mm in length, and the overall stent design may be better suited for transpyloric placement and potentially reduce the risk of stent migration.<sup>28</sup>

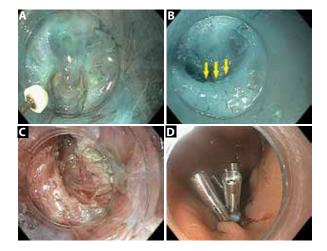
Complications of TPS placement include stent migration, perforation, and bleeding. Stents that migrate proximally can be grasped by forceps endoscopically and withdrawn through the stomach and esophagus, whereas stents that migrate distally are typically monitored with radiographic imaging until spontaneous passage is ensured. Given that TPS placement is not a durable therapeutic option, its role is currently limited to temporizing treatment in patients hospitalized with refractory gastroparesis or as a predictor to help identify patients who may respond to subsequent pylorus-directed therapies, such as G-POEM. In a single-center study of 24 patients who underwent TPS placement prior to G-POEM, clinical improvement with lumen-apposing metal stent placement was found to be associated with improved Gastroparesis Cardinal Symptom Index scores and decreased 4-hour residuals on gastric emptying studies after G-POEM.<sup>28</sup> Further studies are currently needed to better understand optimal stent selection (lumenapposing vs self-expandable metal stents) and optimal fixation technique, as well as to validate the role of TPS placement as a potential predictor of success for further pylorus-directed therapies.

## Gastric Peroral Endoscopic Myotomy

G-POEM was first described by Khashab and colleagues in 2013 as a potential endoscopic treatment for refractory gastroparesis in a single patient with refractory diabetic gastroparesis.<sup>29</sup> Similar to the principles of submucosal endoscopy that underlie peroral endoscopic myotomy for the treatment of achalasia, G-POEM is typically performed under general anesthesia and involves 4 main steps (Figure 2). First, a mucosal incision is made a few centimeters proximal to the pylorus using an endoscopic knife. Next, a submucosal tunnel is created to expose the pyloric ring. Then, a full-thickness myotomy is performed and is slightly extended into the muscularis propria of the antrum. Finally, closure of the mucosal incision is performed using either endoscopic clips or endoscopic suture (Figure 3). Adverse events related to G-POEM are infrequent, with a reported incidence of 0% to 6%. Mild and moderate adverse events include capnoperitoneum, postprocedural abdominal pain, and intra- or postprocedural bleeding related to mucosotomy. Capnoperitoneum is typically asymptomatic and can be managed with needle decompression. Bleeding related to mucosal injury is generally treated endoscopically. Perforation is a potential severe adverse event related to G-POEM and may require surgery.30-32

A multicenter study of 30 patients with refractory gastroparesis who underwent G-POEM demonstrated a technical success rate of 100%, with 86% of patients having clinical improvement at 5.5-months follow-up. Repeat gastric emptying studies after G-POEM also normalized or improved in 47% and 37% of patients, respectively.<sup>33</sup> A subsequent international multicenter study of 33 patients undergoing G-POEM for refractory gastroparesis demonstrated similar outcomes, with 85% of patients having symptomatic improvement with a decrease in Gastroparesis Cardinal Symptom Index score as well as significant improvement of mean gastric emptying studies from 222 minutes to 143 minutes.<sup>30</sup>

As gastroparesis is a chronic, debilitating disease, improvement in quality of life is also an important metric



**Figure 3. A:** Creation of a submucosal tunnel using an endoscopic knife. **B:** Exposure and identification of the pyloric ring (arrows). **C:** Full-thickness myotomy with exposure of the serosal layer. **D:** Closure of the mucosal incision with endoscopic clip placement.

of effective treatment. A retrospective study by Dacha and colleagues of 16 patients with refractory gastroparesis who underwent G-POEM found significant improvements in multiple quality-of-life domains, as measured by the Short Form 36 (SF36) quality-of-life survey, that persisted at 1 year after the procedure.<sup>34</sup> A subsequent retrospective study of 30 patients with refractory gastroparesis who underwent G-POEM found similar outcomes, with significant improvement in SF36 scores at 1 year after the procedure. Patients were also noted to have significant reductions in emergency department visits (2.2 ± 3.1 to  $0.3 \pm 0.8$  visits) and hospitalizations (1.7 ± 2.0 to 0.2 ± 0.4 hospitalizations per month) after G-POEM.<sup>35</sup>

Although G-POEM is a promising endoscopic treatment for refractory gastroparesis, the current literature remains limited to small retrospective studies and prospective studies without long-term follow-up. Future studies are needed to understand the effectiveness of G-POEM for differing etiologies of gastroparesis, the durability of clinical improvement, and the optimal selection of patients who would benefit from G-POEM. Reimbursement for G-POEM also remains a barrier, as there is presently no approved or listed Current Procedural Terminology for the procedure. G-POEM should be considered in patients with medically refractory gastroparesis with primary symptoms of nausea and vomiting.

#### Gastric Electrical Stimulation

Surgical placement of GES for gastroparesis is performed by laparoscopic surgery or laparotomy and consists of

implantation of a pulse generator subcutaneously and placement of an electrode that leads into the muscularis propria of the greater curvature of the stomach. Two methods of GES have been investigated. One method involves the delivery of high-frequency, low-energy stimulation, which leads to excitation of the interstitial cells of Cajal that serve as pacemaker cells for the stomach and improve gastric emptying.36,37 The second method involves the delivery of low-frequency, high-energy stimulation known as gastric pacing to entrain the gastric slow wave and normalize gastric dysrhythmias, which improves gastric emptying.<sup>38,39</sup> A prospective study by Brody and colleagues of 50 patients who underwent surgical implantation of GES found that patients had significantly improved gastroparesis symptoms at 6 and 12 months without any significant difference in gastric retention.<sup>40</sup>

The placement of temporary GES electrodes endoscopically or via percutaneous endoscopic gastrostomy has been investigated as a predictor of subsequent success of permanent surgical GES placement. Ayinala and colleagues first described these techniques in 2005 and found that 17 of the 20 patients who underwent either endoscopic or percutaneous endoscopic gastrostomy placement of temporary GES electrodes for refractory gastroparesis had symptomatic improvement with temporary and later permanent GES placement.<sup>41</sup> A subsequent double-blind, placebo-controlled trial by Abell and colleagues in 2011 of 58 patients who underwent endoscopic temporary GES placement showed a nonsignificant trend toward symptom improvement with stimulation but found that electrode dislodgement occurred in 22% of patients.<sup>42</sup> More long-term wireless gastrostimulators for gastroparesis that can be placed endoscopically have been developed and investigated in porcine models but have not yet been reported in patients.43 Currently, endoscopic placement of temporary GES is not widely available and is only performed at specialized tertiary medical centers.

# **Future Considerations**

The measurement of pyloric physiology by EndoFLIP has recently been demonstrated to be a potential tool to predict response to pylorus-directed endoscopic therapies for gastroparesis. In a recent study by Desprez and colleagues, 19 patients with gastroparesis who had altered pyloric distensibility as measured by EndoFLIP were found to have significantly improved symptom response and gastric emptying study results after intrapyloric botulinum toxin injection.<sup>44</sup> In 16 patients with gastroparesis who have normal pyloric distensibility, there was no significant improvement in symptom response or gastric emptying after intrapyloric botulinum toxin injection. Pyloric distensibility has also been investigated to predict success for G-POEM.

In a multicenter study, 37 patients who underwent G-POEM for refractory gastroparesis had pyloric EndoFLIP measurements before and after G-POEM. The pylorus cross-sectional area was found to be a predictor of 1-year clinical success after G-POEM.<sup>16</sup> Further studies are needed to better understand the role of EndoFLIP in assessing pyloric dysfunction in gastroparesis and in guiding endoscopic therapies.

Endoscopic ultrasound (EUS)-guided gastrojejunostomy is another potential endoscopic treatment for gastroparesis that requires further investigation. This treatment involves using a therapeutic echoendoscope and fluoroscopic guidance to identify and puncture a jejunal bowel loop adjacent to the gastric wall followed by direct placement of a lumen-apposing metal stent across the stomach into the jejunum. This tract serves as an alternative route for enteral drainage.<sup>45</sup> There are limited data supporting the use of EUS-guided gastrojejunostomy for benign and malignant gastric outlet obstruction.<sup>45,46</sup> As gastric outlet obstruction and gastroparesis have overlapping underlying pathophysiologies, further research is needed on whether EUS-guided gastrojejunostomy has a role in the treatment of refractory gastroparesis.

# Conclusion

Despite recent advances in endoscopic therapies for gastroparesis, this chronic disease causes significant morbidity for patients and has limited effective treatment options. Recent research on pylorus-directed endoscopic therapies has demonstrated promising results, and endoscopic therapies will likely become an important component of step-up therapy in refractory gastroparesis. It is important to recognize that there remains a large population of patients with gastroparesis symptoms without objective delayed gastric emptying in whom the impact of endoscopic therapies has not been investigated. Further understanding of the pathophysiologies underlying gastroparesis will help drive future innovation and advancement of endoscopic therapies, as well as the identification of which patients will best benefit from them.

## Disclosures

The authors have no relevant conflicts of interest to disclose.

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