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REVIEW

Endoscopic treatment of gastroparesis

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Abstract

Gastroparesis has traditionally been a largely medically managed disease with refractory symptoms typically falling under the umbrella of the surgical domain. Surgical options include, but are not limited to, gastrostomy, jejunostomy, pyloromyotomy, or pyloroplasty, and the Food and Drug Administration approved gastric electrical stimulation implantation. Endoscopic management of gastroparesis most commonly involves intrapyloric botulinum toxin injection; however, there exists a variety of endoscopic approaches on the horizon that have the potential to radically shift standard of care. Endoscopic management of gastroparesis seeks to treat delayed gastric emptying with a less invasive approach compared to the surgical approach. This review will serve to highlight such innovative and potentially transformative, endoscopic interventions available to gastroenterologists in the management of gastroparesis.

Key words: Botulinum; Gastrojejunostomy; Transpyloric; Pyloromyotomy; Gastric stimulator; Gastric pacemaker; Stenting

Core tip: Although a majority of gastroparesis patients respond to medical treatment, patients with refractory symptoms pose a therapeutic challenge and are often referred for surgical management. Endoscopic management of gastroparesis seeks to treat delayed gastric emptying with a less invasive approach compared to the surgical approach. Endoscopic treatment of gastroparesis most commonly involves intrapyloric botulinum toxin injection; however, there exists a variety of endoscopic approaches on the horizon that have the potential to radically shift the standard of care for refractory patients.

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INTRODUCTION

Gastric emptying is a highly regulated, carefully choreographed process that demands a harmony

of synchronized impulses working together as an impetus for which food can be delivered distally down the gastrointestinal tract. These propulsive forces are generated by proximal fundic tone, the interstitial cells of Cajal, distal antral contractions, and relaxation of the pyloric sphincter to create a scripted peristalsis[1]. Gastroparesis, or delayed gastric emptying, is characterized by physiologic disturbances in antral hypomotility, increased gastric outlet resistance, and pyloric dysfunction without evidence of obstruction[2,3]. Patients typically present with dyspepsia-like symptoms including early satiety, postprandial fullness, bloating, nausea, vomiting, and abdominal pain[2,4-6]. The most common etiologies of gastroparesis are idiopathic, diabetic, or post-surgical[2,7].

The epidemiology of gastroparesis is not well known though a small population-based study showed a prevalence in men and women of 9.6 and 37.8 per 100000 persons and an age-adjusted incidence of 2.4 and 9.8 per 100000 person-years, respectively[8]. Gastric-emptying scintigraphy is the gold standard for the diagnosis of gastroparesis and consensus recommendations for the procedure involve 99-m technetium sulfur-colloid labeled low fat, egg-white meal with imaging at 0, 1, 2, and 4 h[9]. The diagnosis of delayed gastric emptying is confirmed if there is > 90% gastric retention at 1 h, > 60% at 2 h, > 10% at 4 h[9,10]. Small, frequent meals along with medical therapy including prokinetic agents, such as dopaminergic (D2) antagonists - metoclopramide and domperidone, or motilin-analogue - erythromycin, are the first line of treatment.

The majority of data regarding the efficacy of conventional prokinetic agents for the treatment of gastroparesis is outdated[11-15]. It has been approximately 30 years since the first randomized controlled trials of the conventional prokinetic agents, metoclopramide, domperidone, and erythromycin, have been published, and despite this, they are still first-line agents for the treatment of gastroparesis[16]. Metoclopramide has been the most extensively studied and has been associated with less improvement in gastric emptying when compared to erythromycin[15]. A meta-analysis assessing benefits of four different drugs in 514 patients in 36 clinical trials reported the macrolide antibiotic erythromycin as the most potent stimulant of gastric emptying, while erythromycin and the dopamine receptor antagonist domperidone (not available in the United States) are best at reducing symptoms of gastroparesis[17]. Currently, several novel pharmacotherapies such as ghrelin receptor agonists (TZP-101, TZP-102, RM-131), mitemcinal, prucalopride, velusetrag, levosulpiride are in development, though their clinical efficacy and safety remains to be established[16,18,19]. While it is generally accepted that a significant percentage of patients require additional therapy beyond prokinetic agents, no clear data exists to determine the percentage of patients who fail medical management.

Patients with symptoms refractory to medical therapy pose a therapeutic dilemma. Patients are often referred for surgical treatment including a variety of potential procedures not limited to gastrostomy, jejunostomy, pyloromyotomy, pyloroplasty, and gastrectomy to improve gastric emptying. Poor and sometimes unpredictable response, in addition to the morbidity and mortality of surgical interventions, has led to the emergence of endoscopic therapies in management of gastroparesis (Table 1). While frequently under-utilized, endoscopic treatment strategies are at the cusp of altering traditional standard of care with exciting new developments that have the potential to radically shift the preferred management of refractory gastroparesis.

BOTULINUM TOXIN INJECTION

Endoscopic intrapyloric botulinum toxin injection (IPBI) is the most studied and perhaps the most commonly employed endoscopic treatment for those suffering from refractory gastroparesis, though this therapy still remains highly controversial. Botulinum toxin is a potent inhibitor of neuromuscular transmission used more commonly for the treatment of spasm in gastrointestinal sphincters. Botulinum toxin injection into the lower esophageal sphincter (LES), with or without endoscopic ultrasound (EUS)-guidance, is an established safe and effective therapy for management of achalasia in high-risk surgical patients. Low dose injection of botulinum toxin in the pylorus muscle decreases contractility secondary to decreased acetylcholine release by irreversibly binding to cholinergic receptors and directly affects muscle tone at higher doses[20]. The toxin also reduces substance P immuno-reactivity and disrupts pyloric myoelectric activity[21,22].

The procedure involves endoscopic access to the patient's pylorus with injection typically in a radial pattern at or within 2 cm of the pylorus, with a total dose of 100 to 200 units[23]. There is an alternative hypothesis that antroduodenal or pyloroduodenal manometry may be helpful to evaluate the baseline pylorus muscle tone to determine the best site for IPBI to predict response; however, this warrants further investigation[24]. The usual duration of benefit from IPBI ranges from 1 to 5 mo at which time worsening symptoms can be re-treated with repeated injections[23,25]. It is important to note however, that the effect of IPBI may not be limited simply to the pyloric muscle as there have been rare reports of gastric and intestinal absorption leading to peripheral neuromuscular blockade[26]. Despite this, the procedure is typically well tolerated and safe. There are a multitude of open-label studies in adults with gastroparesis (regardless of cause - idiopathic, diabetic, and post-surgical) reporting an improvement in symptoms and gastric emptying after endoscopic IPBI[25,27-31]. The largest observational study including 63 patients by Bromer *et al*[25] documented a 43% response rate to botulinum toxin treatment lasting

Table 1 Summary of endoscopic therapies for refractory gastroparesis

Endoscopic therapies	Technique/mechanism	Advantages	Disadvantages
Intrapyloric botulinum toxin injection	Radial or direct injection of 100-200 U of toxin around the pylorus Toxin binds to cholinergic receptors resulting in decreased acetylcholine release	Safe and well tolerated Easy to perform Observational studies report high response rate	No clear benefit in RCTs Need for repeat treatments
Gastric electric stimulation	Miniature wireless device placed through over-tube and secured to the gastric mucosa with endoclips Device stimulates gastric muscle resulting in more regular, constant amplitudes	Proof of concept design with proven benefit Currently used prior to definitive surgical placement Less invasive compared to surgical placement	Lack of human studies No comparative data to surgically placed gastric pacers
Transpyloric stenting	Through-the-scope self-expandable metal stents placed across the pyloric channel	Small case series demonstrating a proven benefit in symptoms	Limited data Potential for stent migration
Endoscopic pyloromyotomy	Submucosal dissection and tunneling with full separation of the pyloric ring (myotomy)	Less invasive alternative to traditional surgical pyloromyotomy	Limited data Technically challenging with limited expertise Potential for complications:
Endoscopic decompression or bypass	Percutaneous endoscopic jejunostomy (PEJ) and direct PEJ Direct post-pyloric enteral nutritional support	Safe and effective	Limited success Technical difficulty
endoscopic ultrasound-guided gastrojejunostomy	Transluminal anastomosis using self-expanding, lumen-apposing metal stents	Decreased morbidity and mortality compared to surgical approach	Lack of human trials Unknown long-term safety and patency issues

a mean of approximately 5 mo.

While observational data suggests that botulinum toxin injections reduce symptoms and accelerate gastric emptying in both idiopathic and diabetic gastroparesis, 2 independent, double-blinded, randomized controlled studies have shown little to no improvement in gastric emptying and no symptomatic improvement compared with placebo[32]. Friedenberg *et al*[33], using a randomized, double-blind, placebo-controlled trial, explored whether botulinum toxin improves symptoms to a significantly greater extent than placebo. In this study, 32 patients were randomized to botulinum toxin or placebo with 1-mo follow-up post endoscopic procedure measuring gastric retention at 2 and 4 h and symptoms based upon 2 validated scoring systems - the Gastroparesis Cardinal Symptom Index (GCSI) and the Gastroparesis Visual Analog Scale (GVAS). While endoscopic botulinum toxin injection did improve gastric emptying rates, the benefit was not superior to placebo at 1 mo (67% *vs* 64% at 2 h, $P = 0.56$ and 29% *vs* 28% at 4 h, $P = 0.86$, for IPBI *vs* placebo respectively). Additionally, there was no significant difference or improvement of symptoms between IPBI compared to the placebo (GCSI - 34.4 *vs* 36.4, $P = 0.21$; GVAS - 603 *vs* 584, $P = 0.68$, respectively). Another randomized-controlled crossover study including 23 patients, predominantly with idiopathic gastroparesis, also reported similar results, with no significant benefit of endoscopic injection of botulinum toxin over placebo in improving either symptoms or rate of gastric emptying[34].

This discrepancy between open-label and randomized controlled studies may be related to dose of toxin injected and patient population selected. In a retrospective cohort study of 179 patients by Coleski *et al*[23], patients treated with 200 units achieved a greater improvement in gastroparetic symptoms 1 to 4 mo post intervention compared to those treated with 100 units (76.7% *vs* 54.2%, $P = 0.02$). On multivariate analysis female gender, age < 50 years, and a non-diabetic or post-surgical etiology of gastroparesis were found to be associated with a significant response to therapy in this study.

While the use of botulinum toxin remains highly controversial, the American Gastroenterological Association (AGA) currently does not recommend the use of endoscopic IPBI for patients with gastroparesis[35]. However, given the small sample size of existing studies with conflicting data, there is an eminent need for larger randomized trials in the future before a definitive decision or treatment guidelines can be concluded.

ENDOSCOPIC GASTRIC STIMULATOR IMPLANTATION

In 2000, gastric electrical stimulation (GES) was approved by the United States Food and Drug Administration (FDA) as a humanitarian device exemption in patients with refractory symptoms of diabetic or idiopathic gastroparesis[36]. Often referred to as a gastric pacer, GES uses an implantable device consisting of a pulse generator that allows for electrical

stimulation at a variety of frequencies. Permanent GES for gastroparesis, typically 6 cm x 5.5 cm x 1 cm, requires a lengthy surgical implantation under general anesthesia. Several case series and small randomized controlled trials, the most important being the Worldwide Anti-Vomiting Electrical Stimulation Study (WAVESS), have shown clinical benefit from GES[37-43]. A subsequent meta-analysis by Chu *et al*[44] in 2012 confirmed significant improvement in symptom severity and gastric emptying times, though many of the analyzed studies were low quality observational studies lacking control groups. A more recent study by McCallum *et al*[40] also demonstrated improvement in weekly vomiting frequency amongst all patients with idiopathic gastroparesis with a median reduction of 61.2%. The National Institute of Health and Care Excellence issued guidelines in 2014 that stated current evidence is adequate to support the use of GES[45].

As of 2012, surgery was the only means available to implant the GES device. Although endoscopic placement of temporary gastric stimulators has been proven as a concept and is often used to determine whether a patient will respond to GES before undergoing a permanent implant surgery, the lack of a permanent endoscopic solution and the reliance on future surgery for symptomatic improvement has limited further endoscopic utilization at present[46,47]. However, Deb *et al*[48] has designed 5 innovative endoscopic gastric implantation techniques and developed a novel, wirelessly powered miniature gastrostimulator. While this early model was conducted in pig studies with no human data or patient trials, the study provides an important prototype for other dysmotility treatment paradigms and provides exciting new options that may translate in the future to less invasive endoscopic placement in gastroparetic patients. This miniature wireless GES device for endoscopic implantation can be easily inserted into the stomach through an over-tube with 2 GES electrodes endoscopically attached to the gastric mucosa and secured with endoclips[49]. Electro-gastrogram recordings have demonstrated that gastric slow waves become more regular with constant amplitudes when stomach tissues are stimulated, in comparison with no stimulation. The frequency-to-amplitude ratio also changes significantly with stimulation[49].

The miniature gastrostimulator and its attachment techniques have the potential to fundamentally shift the approach to refractory gastroparesis and provide a means for endoscopic implantation of gastric stimulator. Although further studies are required to prove the efficacy of such device, if shown to be effective, the possibility of FDA approval given a similar precedent set by GES would provide a clear indication for endoscopic management. The endoscopic gastric implantation device and technique may decrease the need for surgical implantation of GES and revolutionize the preferred management of refractory gastroparesis.

TRANSPYLORIC STENTING

A novel approach recently described by Clarke *et al*[50] at Johns Hopkins involves the use of through-the-scope transpyloric stent placement as a treatment for gastroparesis. In this small case series (n = 3), double-layered, fully-covered Niti-S self-expandable metallic stents (TaeWoong Medical, Seoul, South Korea) were used to successfully improve symptoms of gastroparesis. The procedure entails the placement of a self-expandable stent across the pyloric channel, deployed under endoscopic guidance without fluoroscopy. The stent is then fully deployed in the transpyloric position with its proximal end in the gastric antrum. Case 1 involved a 23-year-old woman with diabetic gastroparesis; case 2, a 15-year-old boy with chronic nausea and vomiting with markedly abnormal gastric emptying study; and case 3, a 45-year-old man with idiopathic gastroparesis. In all 3 cases, patient symptoms markedly improved or became asymptomatic at 115 d, 122 d, and 174 d follow-up respectively. While this includes only a case series of 3 patients, the stark improvement and lasting results at follow-up after the procedure suggest that transpyloric stent placement improves symptoms associated with impaired gastric emptying[50].

A major concern with transpyloric stenting is stent migration leading to recurrence of symptoms. Several stent securing methods such as endoscopic clips [through-the-scope clip (TTSC) and over-the-scope clip (OTSC)] and endoscopic suturing (ES) have been described to reduce stent migration. Despite the numerous options available, the question remains which stent securing method is superior. In a small case series by Saxena *et al*[51], transpyloric stent placement and fixation was performed in patients with refractory gastropariesis. The stent was anchored to the antral mucosa with either no device, TTSC, OTSC, or ES. A total of 17 patients underwent 28 transpyloric stent placements with 100% success rate regardless of method. Stent migration occurred as expected in 100% of those with no device; however stent migration was significantly lower in the ES *vs* TTSC group (16.7% *vs* 100%, P = 0.02). Stent migration occurred more frequently in the OTSC placement group as compared to the ES group (52.9% *vs* 16.7%, P = 0.075). With this data, albeit limited due to the number of the patients studied, there is evidence for concern regarding stent migration with transpyloric stent placement; however, it appears this can be minimized with OTSC and endoscopic suturing.

Currently, future studies are required to truly ascertain the long-term durability, utility, and preferred method for transpyloric stenting and fixation. Until that time, transpyloric stenting will remain a limited option for endoscopists in the management of patients with

refractory gastroparesis.

ENDOSCOPIC PYLOROMYOTOMY

Rao *et al*[52] demonstrated that phasic motor activity in the antrum and duodenum can be stimulated by fundic balloon distention. While there are no such studies to determine the effect of pyloric channel distention on the interstitial cells of Cajal in the stomach or gastric emptying, endoscopic pyloromyotomy and manipulation of the pylorus may improve gastroparesis refractory to medical management. With this notion of distention or disruption of the pylorus to improve gastroparetic symptoms, Khashab *et al*[53] demonstrated the feasibility and efficacy of this approach with a case report of the first human gastric peroral endoscopic myotomy (G-POEM) in a patient with severe refractory gastroparesis. The procedure was well tolerated with vast improvement in gastroparetic symptoms noted at 12-wk follow-up.

This technique is similar in principle to the submucosal dissection and myotomy performed for the treatment of achalasia[54]. Techniques through a submuscoal tunnel were first described in animal models by Pasricha *et al*[55] in 2007. Endoscopy is performed and involves myotomy of the inner circular and oblique muscle bundles 2-5 cm proximal to the pylorus on the anterior wall of the stomach, preserving the longitudinal muscle layers with larger vessels in the submucosa coagulated. This is then followed by endoscopic pyloromyotomy by dissecting the pylorus until deeper layers become evident with full separation of the pyloric ring[54,56].

In another study by Shlomovitz *et al*[56], endoscopic pyloromyotomy was performed in 7 female patients with early follow-up suggesting promising symptomatic improvement in 6 of the 7 and normal gastric emptying studies at 4 h noted in 4 of the 5 patients. One patient that did not respond subsequently underwent laproscopic pyloroplasty. Complications included gastrointestinal bleeding in one patient 2 wk after the procedure and pneumonia. Despite these complications, this endoluminal pyloromyotomy technique could provide an incision-less, less invasive alternative with similar functional outcome as compared to standard laparoscopic pyloroplasty[56]. While the small number of cases certainly limits the ability to determine the true impact of this procedure in the management of gastroparesis, with more frequent use, increasing technical experience, and more data, endoscopic pyloromyotomy has exciting potential to be at the forefront in the endoscopic management of gastroparesis.

ENDOSCOPIC DECOMPRESSION OR BYPASS

Enteral nutrition and feeding is sometimes required for more severe symptoms and can be seen in up to 30% of grade 3 gastroparesis[57,58]. Direct percutaneous endoscopic jejunostomy (DPEJ) is a push enteroscopy technique that was first described by Shike *et al*[59], and offers another approach to provide direct postpyloric enteral nutritional support. Percutaneous endoscopic jejunostomy (PEJ) is a safe and effective means to palliate malnutrition in patients with severe gastroparesis[60,61]. Maple *et al*[62] demonstrated, in the largest cohort study to date, clinical outcomes with DPEJ and included 307 attempts at PEJ placement with a success rate of 68%. While this study included multiple indications for DPEJ placement, gastroparesis was a substantial proportion (n = 61 or 21%). A case series by Toussaint *et al*[63], showed a PEJ technical success rate of 78.6% with no immediate complications reported; however, this was based upon a small sample size of 14 patients total. Based on these data, PEJ should be considered in the algorithm of enteral access for nutritional support before jejunostomy is considered.

The main limitation of DPEJ is technical difficulty as the jejunum is narrow, making it more difficult to advance a needle directly into the lumen[64]. This difficulty can be alleviated with balloon-assisted enteroscopy (BAE)[65]. Aktas *et al*[66] reported the first prospective study in which single-balloon enteroscopy (SBE)-assisted DPEJ was successful in 11 of the 12 procedures (92%). In this prospective case study, SBE was shown to facilitate the identification of an ideal DPEJ insertion site for the placement of a direct percutaneous jejunal feeding tube. While again this study is limited in size, the results were similar to previous small case series using double-balloon enteroscopy (DBE)-assisted DPEJ placement[65,67].

ALTERNATIVE TO SURGICAL GASTROJEJUNOSTOMY

While surgical gastrojejunostomy is a potential treatment option for patients with gastroparesis, the procedure is associated with substantial morbidity and mortality when patients are in less than ideal clinical condition[68-71]. Fritscher-Ravens *et al*[72,73] and Binmoeller *et al*[74] first described EUS-guided gastrojejunostomy in pigs by using a compression button and lumen-apposing metal stent, respectively. These studies were built upon the success of previous studies - notably Cope *et al*[75] creating the first transluminal anastamosis using self-expanding metal stents (SEMS) and Chopita *et al*[76] reporting the first clinical trial using fully covered version of the flared stent. While the Fritscher-Ravens *et al*[72,73] and Binmoeller *et al*[74] studies were performed as possible alternatives to surgical bypass for the palliation of malignant gastric outlet obstruction, more benign conditions such as gastroparesis may potentially benefit from this transluminal therapy.

An additional study performed by Itoi *et al*[77], developed a new enteric tube that allowed for the entrapment of fluid between the double balloons without the need to use tissue-opposing devices such as tilt tags. This maintains distention of the small bowel between the double balloons at the initial FNA needle puncture site. Although simply a pilot study, all stents, with exception of one stent, were successfully deployed without complication. All animals showed normal eating behavior without signs of infection at 1-mo follow-up post procedure. Endoscopic gastric imaging showed patent stents in all pigs. While this study lacks power, the initial findings are impressive. The development of a EUS-guided gastrojejunostomy appears to be promising as a minimally invasive treatment.

Although surgical gastrojejunostomy has been shown to improve gastroparetic symptoms, EUS-guided gastrojejunostomy warrants further investigation owing to unknown long-term stent safety and patency issues[74]. Ideally, the stent can be removed after an interval of time, leaving a permanent fistula tract. However, studies are needed to determine the necessary pressure gradient and initial gastrojejunostomy tract diameter in order to maintain long-term fistula patency after stent removal. The minute amount of data available to date, while optimistic and potentially transformative, requires repeat analysis and trials with human study before implementation into the gastroenterologist's everyday arsenal. However, given the technical success of studies above, the future of endoscopic gastrojejunostomy using EUS-guided lumen-apposing metal stents is bright with the potential to diminish the need for invasive surgeries and improve symptoms of gastroparesis refractory to medical management.

CONCLUSION

In summary, there is a wealth of potential endoscopic approaches that may one day be at the disposal of endoscopists. While many of these procedures and pioneering approaches have the potential to be ground-breaking and radically transform the standard management algorithm of refractory gastroparesis, all of them require more studies to validate, corroborate, and substantiate early optimistic data. The opportunities for less invasive endoscopic treatment of gastroparesis are abundant and inspiring. From further studies to evaluate the true effectiveness of IPBI to the potential for EUS-guided lumen-apposing metal stents for gastrojejunostomy, the role of endoscopic therapies in management of gastroparesis is likely to expand in near future.

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