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Motility (H Parkman and R Schey, Section Editors)

Botulinum Toxin as a Treatment for Refractory Gastroparesis: a Literature Review

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Abstract

Purpose of review Gastroparesis (GP) is a disorder of gastrointestinal motility which leads to delayed gastric emptying in the absence of mechanical obstruction. Treatment is limited as many patients are refractory to dietary modification and the use prokinetic medications carry significant adverse risks. These limitations necessitate more research into experimental therapies. The purpose of this article is to summarize the known information and guidelines on the diagnosis and management of GP and to review the latest literature on experimental treatments.

Recent findings Based on the current available literature, there is conflicting data regarding the efficacy of intra-pyloric botulinum injections (IPBIs) for refractory gastroparesis. There have been many open-label trials showing good clinical response, but the only two randomized controlled trials on the matter showed no objective improvement gastric emptying studies. However, both studies were likely underpowered and changes in gastric emptying may not correlate with symptom improvement. As such, these discouraging findings should not be used to exclude botox from the armamentarium of therapies for refractory GP.

Summary More large-scale, double-blinded, multicenter randomized control trials are needed to further validate the long-term efficacy and safety of IPBI, as well as gastric

peroral endoscopic myotomy (G-POEM), as compared to gastric electrical stimulation (GES) or surgical intervention (i.e., laparoscopic pylorotomy) for refractory gastroparesis.

Introduction

Gastroparesis (GP) is a disorder of gastrointestinal motility which leads to delayed gastric emptying in the absence of mechanical obstruction. It is often recognized as a clinical syndrome of nausea, vomiting, abdominal bloating or vague abdominal pain, early satiety, and constipation. Undiagnosed GP is responsible for a large portion of primary care and gastroenterology office visits. It is estimated to affect over four million people in the USA [1].

Symptoms can be debilitating and severe enough to lead to weight loss and malnutrition, resulting in increased hospitalizations, poor quality of life, and increased healthcare costs. Once diagnosed, based on symptoms and supportive gastric emptying scintigraphy, GP is managed largely through dietary modifications and medications for symptom control. Nevertheless, many patients are refractory to these treatments, leading patients to seek invasive and experimental therapies. The purpose of this article is to summarize the known information and guidelines on the diagnosis and management of GP and to review new literature on experimental treatments, focusing primarily on botulinum injections.

Incidence and epidemiology

There are few studies that have evaluated the epidemiology of gastroparesis in the general population, making the true incidence and prevalence of gastroparesis unknown [2–6]. Furthermore, epidemiologic studies in the past have looked at limited populations, i.e., diabetics and/or patients of tertiary referral centers, which could have falsely elevated their reported incidence or prevalence due to selection or referral bias. Jung et al. analyzed a more generalizable cohort by studying a small community population in Olmsted County, MN. They reported an age-adjusted incidence of 2.5 per 100,000 person-years for men and 9.8 per 100,000 person-years for women during the years of 1996–2006, with a prevalence of 9.6 for men and 37.8 for women in 2007 [3]. This study also reaffirmed the disorder's predilection for women with a 4:1 female to male ratio. Even though the Minnesota study was a large population study, it was limited in its use for extrapolation of the national incidence or prevalence of GP as it used a largely Caucasian cohort.

Despite the relatively low incidence and prevalence reported by the study, a follow-up study reported a 138% increase in GP-related hospitalizations during 1995–2004, with a significant increase occurring after 2000 [4]. This could represent an increase in diabetes-associated GP, with an overall increase in the prevalence of diabetes, as well as better recognition and diagnosis of GP in the new millennium. Regardless of the incidence or prevalence of GP, its related morbidity and increasing healthcare costs warrant further investigation into potential stabilizing or curative treatments.

Etiology and pathophysiology

The exact pathophysiology of GP has not been clearly elucidated, but it is theorized to involve a defect in the normal function of either the enteric smooth muscles or the enteric nervous system. These include defects in fundic tone, gastric dysrhythmias or gastroduodenal dyscoordination, and abnormal duodenal feedback. The etiology of these defects are varied, with the most common being idiopathic (50%), followed by diabetic (25%) [1]. Other etiologies include postsurgical, neurologic disorders (i.e., Parkinson's disease), connective tissue disorders, and medication-induced. This article will focus on the treatment of idiopathic and diabetic GP.

Idiopathic GP refers to delayed gastric emptying due to an unknown cause. It is thought to be associated with postviral damage and denervation of the gastric cells. Diabetic gastroparesis, on the other hand, is thought to be due to microangiopathic damage leading to autonomic neuropathy. Studies have shown that acute hyperglycemia delays gastric emptying by reducing proximal gastric tone [7–10]. However, GP in diabetes has not been proven to be related to autonomic neuropathy, but instead has a varied etiology including dysfunction of the interstitial cells of Cajal (ICC) and decreased neurotransmission [8–10]. Likewise, evidence is mixed regarding chronic, poorly controlled diabetes and association with severity of or progression of GP. Other than the optimization of glycemic control, the treatment of GP remains the same regardless of the etiology.

Diagnosis

Diagnosis of GP requires recognition of clinical symptoms (i.e., nausea, vomiting, abdominal pain and/or bloating, early satiety) and objective documentation of delayed gastric emptying with the absence of mechanical obstruction. Gastric emptying scintigraphy is the gold standard for diagnosis of GP, with gastric retention of solids at 4 h being the most reliable parameter for diagnosis [11]. Medications that cause delay in gastric emptying, such as opioids, anticholinergics, and GLP1 analogs, should be discontinued prior to testing. Likewise, prokinetic agents should be discontinued to avoid a false negative. Alternative tests that have been used include wireless capsule endoscopy and ^{13}C breath testing, but neither test have been validated or approved for the diagnosis of GP.

Treatments and management

Diet

The mainstay therapy for GP is largely dietary modifications, prokinetic agents, and medical management of symptoms. Dietary modification should be the first intervention attempted for decreasing symptoms of GP. Small but frequent, nutrient-rich meals that are low in fats and soluble fibers is recommended and has been shown to reduce symptoms in some GP patients. Optimal glycemic control is recommended in diabetic gastroparesis, but there is a lack of strong

evidence regarding glucose control and improvement in symptoms or objective gastric emptying.

Medications

Metoclopramide is the first-line prokinetic agent, and only medication approved by the Food and Drug Administration for the treatment of GP. It is a D2 receptor antagonist and works by increasing contractility in the GI tract and thus gastric emptying. It also acts on chemoreceptors to prevent nausea and vomiting. However, the approved duration of therapy with metoclopramide is limited to no longer than 12 weeks due to the association between long-term use of the drug and the development of tardive dyskinesia, a potentially irreversible disorder characterized by involuntary movements, particularly of the face [12–14].

Domperidone is another promotility agent that has been studied for symptom relief in GP. One large single-center study of 125 patients showed domperidone improved symptoms of postprandial fullness, nausea, and vomiting [15]. However, it is not without side effects and 12% of patients in that study discontinued treatment due to headaches, palpitations, and diarrhea. Due to its serious cardiovascular risks, including QTc prolongation leading to cardiac arrhythmias and sudden cardiac death, it is no longer available in the USA. It can, however, be used in refractory GP under the investigational new drug clearance if the benefit of treatment outweighs the risk. Erythromycin, a macrolide antibiotic and motilin agonist, has also been used off-label for its prokinetic effect, but has many drug interactions, being a CYP3A inhibitor, and can also lead to QTc prolongation [13].

Symptomatic treatment with antiemetics or antidepressants like ondansetron, promethazine, tricyclic antidepressants, or mirtazapine can improve quality of life by decreasing nausea or vomiting and stimulating appetite, but they do not improve gastric emptying. One study of 30 participants, largely Caucasian females, showed both qualitative and quantitative improvement in nausea and vomiting with mirtazapine [16]. Improvement was significant in patients with idiopathic GP more so than other etiologies. Statistically significant symptom improvement was noted more in older patients than younger study participants. The efficacy of antidepressants in GP symptom control may be multi-factorial in that it has physiologic antiemetic effects and also psychosomatic mood-enhancing effects. However, these medications do not solve the underlying cause of GP and still have adverse effects and risks, including QTc prolongation and put patients at risk of ventricular tachycardia, torsades de pointes, and sudden cardiac death, which limit their use in certain populations.

Implantable devices

Gastric electrical stimulation (GES) is an implantable device that is FDA-approved under Humanitarian Device Exemption for the treatment of severe, chronic nausea and vomiting due to idiopathic or diabetic gastroparesis that is refractory to maximal medical therapy [17]. Its mechanism of action is poorly understood, but it is thought to modulate the neuromuscular function of gastric tissue. The electrical stimulation it provides reduces gastric tone and thus decreases symptoms caused by gastric distension. Most of the published data on the efficacy of GES in treating the symptoms of GP have consistently shown

improvement in symptoms, overall nutrition and quality of life, and reduction in healthcare costs, particularly in diabetic gastroparesis more than idiopathic. However, this data comes from open-label trials. Given the lack of adequately powered, double-blind, placebo-controlled studies showing significant benefit of GES and the invasiveness of the treatment, it is not an ideal therapy for GP except in patients with truly refractory and severe symptoms. It is also extremely difficult to obtain the device due to insurance prior authorization and IRB approval.

Surgical intervention

Surgical intervention, including open or laparoscopic pyloromyotomy, gastrojejunostomy, and complete or subtotal gastrectomy, is a more invasive therapy for GP, but has been shown to improve symptoms and objective gastric emptying [18]. Dissecting the pyloric sphincter allows for easier gastric emptying into the duodenum. One study reported a symptom improvement rate of 82 and a 96% improvement rate in gastric emptying times after laparoscopic pyloromyotomy (LP) [19]. This study also reported postoperative complications of mainly persistent nausea and vomiting (12%), abdominal pain (4%), and diarrhea (6%) in < 30-day follow-up and 2% in > 30-day follow-up. More serious complications included pneumothorax in 2 % of patients that underwent LP [19]. Another case series not only showed improvement in symptoms and gastric emptying but also reduced the need for prokinetic agents at 3 months postsurgery [12]. These reports lead authors to suggest that laparoscopic pyloromyotomy possibly be considered first-line therapy for select cases of GP. However, it is unclear if the response to pyloromyotomy is dependent on residual antral motor function, making it inefficient in idiopathic or diabetic GP compared with postsurgical GP or in pylorospasms. One study echoed this concept, suggesting that patients who responded to intra-pyloric botulinum injections would be better candidates for pyloroplasty [20]. Overall, the general operative risk, postoperative complications, and irreversible nature of surgical intervention are major deterrents to this treatment option.

Gastric peroral endoscopic myotomy (G-POEM)

Peroral endoscopic myotomy (POEM) is a novel minimally invasive, endoscopic therapy that has been used in the treatment of achalasia and other esophageal motility disorders, but gastric peroral endoscopic myotomy (G-POEM) has recently shown to have success in the treatment of refractory GP. The procedure is similar to surgical pyloromyotomy but is undertaken endoscopically, under general or moderate sedation. The submucosa is first injected with a bolus of dye to separate the mucosal layer from the muscular layer. A mucosal incision is made, usually along the posterior wall of the greater curvature, and submucosal tunneling is performed to the area of the pylorus. An incision is made to provide laxity in the pyloric ring and the mucosal burrow in closed with endoscopic clips [21, 22, 23••, 24, 25••, 26••]. Patients do require at least 24 h postprocedure observation in an inpatient setting, but typically are discharged the day after the procedure if they can tolerate liquid and soft diets and do not show evidence of any complications, i.e., GI tract leakage.

Khashab et al. reported the first case of G-POEM in refractory diabetic GP in 2013 [21]. The patient was a young female with insulin-dependent diabetes and

severe symptomatic GP that was refractory to lifestyle modification and medical therapy. She was not a candidate for GES and refused surgical intervention but did achieve success with transpyloric stenting [22]. However, she experienced multiple incidents of stent migration with return of her symptoms every time. At that point, the patient underwent G-POEM without complication and with great reduction in GP symptoms for at least 12 weeks. Since then there have been many case reports and retrospective studies on G-POEM as both salvage therapy post failed gastric electrical stimulator and intra-pyloric botulinum toxin, as well as a stand-alone therapy for GP refractory to diet and medical therapy [27••, 28–30]. The reported cases of G-POEM in GP have shown largely positive results, with one study showing 86% clinical response post-G-POEM but only 47% of patients with normalization of GES [23], and another study reporting 85% of patient with statistically significant clinical improvement and 75% with improvement on GES [25••]. There has been only one prospective study that followed 29 patients during a median 10-month follow-up. In this study, 79% of patients reported clinical improvement at 3 months and 69% at 6-month follow- up. GES normalized in 70% of patients post G-POEM [26••].

Overall, G-POEM seems to be effective and generally safe, with low perioperative and postoperative complication rates when performed by an experienced operator. Most common complications include minor bleeding, perforation, and pneumoperitoneum, and less common complications include gastric or stricture formation. Despite the positive data in the aforementioned studies, there are no published randomized controlled trials on the use of G-POEM compared with placebo or other interventions in refractory GP. More trials are needed comparing G-POEM with surgical pyloromyotomy cases and also to assess which patients are better responders to G-POEM. It has been suggested that GP patients who show initial response to intra-pyloric botulinum injections or transpyloric stenting would be better candidates for G-POEM. However, one report did note previous endoscopic botulinum toxin injections to be associated with greater difficulty during submucosal tunneling due to fibrosis [29].

Experimental, anecdotal therapies: botulinum toxin

Thus far, we have reviewed the oldest, more conventional, and most studied therapies for the management of gastroparesis. Now, we will discuss the latest literature regarding experimental and anecdotal therapies, focusing on intra-pyloric botulinum injections (IPBI) in the management of GP.

Mechanism of action

Botulinum toxin (BTX) is a neurotoxic agent produced by the bacterium, *Clostridium botulinum*, a gram-positive anaerobic bacterium. It was first isolated in 1895, but its therapeutic properties were not developed until decades later. The toxin acts by cleaving soluble NSF (N-ethylmaleimide-sensitive factor) attachment protein receptor (SNARE) proteins, which normally function in forming synaptic fusion complexes between acetylcholine (ACh)-containing vesicles and the plasma membrane of the axon terminal. The cleaving of these SNARE proteins thus inhibit the docking of acetylcholine (ACh)-containing vesicles onto the axon terminal membrane and prevent the eventual release of ACh into the synaptic cleft of the neuromuscular junction. The end result is a

transient paralysis [31]. When injected intramuscularly at therapeutic doses, it produces a partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. Reinnervation of the muscle occurs over time, slowly reversing muscle paralysis. For this reason, BTX is theorized to be particularly useful in the treatment of GI disorders involving strictures or muscle spasms, including achalasia, esophageal strictures, sphincter of Oddi dysfunction, and gastroparesis.

Botulinum toxin A, commonly referred to as Botox® (Allergan Pharmaceuticals, Irvine, CA), is the variant of toxin that has been used in medical therapies. It is widely known for its use in cosmetic surgery, but it is also FDA-approved for the treatment of several medical conditions, including strabismus, blepherospasms, and cervical dystonia to name a few. In the past decade, there has been more research into the novel use of BTX in GI disorders, particularly involving the esophageal and pyloric sphincters.

The procedure for intra-pyloric botulinum toxin injection for the treatment of refractory gastroparesis is not overly complex. Patients undergo an upper endoscopy. Botulinum toxin A (80 to 200 units) is injected into the muscularis propria and submucosa layers of the pyloric sphincter and evenly distributed in four quadrants via endoscopy [32]. IPBI theoretically should cause a local, temporary paralysis of the pyloric sphincter, leading to relaxation and improved gastric emptying.

Literature review

There are a handful of case reports and case series describing the off-label use of BTX in the treatment of gastroparesis [32, 33••, 34–41]. However, the limited published studies on IPBI in GP have conflicting results. Several small, open-label studies using IPBI in GP of various etiologies have shown a significant clinical benefit and improvement in gastric emptying. One such study reported 48% of patients responded to botulinum toxin injection [34]. However, these studies are limited by their small sample sizes, lack of blinding, and lack of control groups, prompting a call for randomized controlled clinical trials.

Only two double-blind, placebo-controlled clinical trials have been done. The Temple trial, by Friedenberg et al., included 32 patients who were randomized into a treatment arm (IPBI 200 U) or placebo arm (saline injection). Symptoms were assessed before and after intervention using the Gastroparesis Cardinal Symptom Index, a validated questionnaire that measures symptom severity. Patients also underwent a gastric emptying scan before and after intervention. Although the treatment arm showed an improvement in symptoms and gastric emptying at 1-month follow-up, there was no significant difference between IPBI and placebo [41]. The Arts et al. clinical trial, performed in Belgium, showed similar results with no statistically significant difference in symptom improvement or gastric emptying between the two groups [40]. For this reason, the American College of Gastroenterology recommended against the use of IPBI in its 2013 clinical guidelines in the management of gastroparesis [12].

Criticisms of the abovementioned trials include use of a small sample size, short period of follow-up, and suboptimal dosing of BTX in the Belgium trial [32]. However, the study design mirrored many of the open-label studies that showed a significant difference with BTX. Another thought, based on the finding of these clinical trials and the proposed mechanism of action of

botulinum toxin efficacy in GP, is that IPBI may be of better efficacy in a specific cohort of GP patients, that being GP secondary to pyloric stenosis or spasm. Perhaps, studies including only patients who have been shown to have pyloric dysfunction will show greater rates of improvement on GES. Another idea is to use endoscopic ultrasonography (EUS) to guide intra-pyloric botulinum injections, as EUS use would allow for more precise delivery of botox into the muscularis propria of the pyloric sphincter, leading to optimal results from IPBI, as well as decreased risk of perforation or migration of BTA [33••, 34].

Although the reported studies of IPBI's efficacy in GP are contradictory, the lack of observed immediate or short-term adverse effects of IPBI in these trials are consistent, showing, at the least, that BTX injections are relatively safe and easy to perform. There have however been rare cases of adverse events reported in the literature, including hypersensitivity reaction, migration from the site of injection, and absorption into the stomach or intestine, leading to unwanted peripheral neuromuscular blockade, and one case of iatrogenic botulism as a result of an overdose in a pediatric patient [42, 43]. One of the few drawbacks to IPBI compared to other therapies is its relatively short duration of action (6 weeks to up to 5 months per some studies), need for multiple subsequent injections, and possible fibrosis from multiple injections, potentially leading to strictures and worsening pyloric stenosis long-term [18, 19].

Conclusion

The increased morbidity and poor quality of life associated with refractory GP warrants further study into newer investigational therapies. Based on the current available literature, there is no objective data supporting the effectiveness of intra-pyloric botulinum injections in improving gastric emptying. However, the correlation between gastric emptying, symptoms, and quality of life are lacking. The discouraging findings of the randomized controlled trials of IPBI should not be used to exclude this treatment option from the armamentarium of therapies for refractory GP if it has been shown clinically to improve symptoms. Given the low rate of observed adverse effects in these studies, IPBI is relatively safe at therapeutic doses. Given that it is less invasive, carries an overall lower risk, and its effects are temporary, intra-pyloric BTX may still be a considered therapeutic option prior to irreversible surgeries. More large-scale, double-blind, multicenter randomized control trials are needed to further validate the efficacy of IPBI, as well as its safety profile as compared to GES, surgical intervention, and G-POEM. G-POEM for refractory GP should also be investigated closer to assess for long-term efficacy and safety, as it may be a less-invasive intervention to attempt prior to surgery.

Compliance with ethical standards

Conflict of interest

Miguel Malespin reports research grants and support from AbbVie, Gilead, and Intercept and fees as a consultant for Gilead.

Ashley Thomas declares that she has no conflict of interest.
Silvio de Melo Jr. declares that he has no conflict of interest.
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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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