Systematic review of endoscopic botulinum toxin injections for refractory gastroparesis

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ABSTRACT

Endoscopic botulinum toxin injections (EBTI) are used to treat refractory gastroparesis in various patient populations, but their use still needs to be standardized. The PubMed, Web of Science, and Cochrane databases were searched for studies focusing on using endoscopic, intrapyloric botulinum toxin injections to treat refractory gastroparesis. Reports published more than 5 years ago and studies that evaluated EBTI in conjunction with another treatment were excluded. Case reports were included in this analysis due to the limitations of recently published literature. 57 unique citations were identified and screened, and 31 items were excluded based on the pre-determined exclusion criteria. Of the remaining 26 citations, 6 items met the criteria for final review. Most reports determined that EBTI is promising as a treatment for refractory gastroparesis, but concluded that further, large-scale, randomized control trials should be performed before a definitive conclusion can be made. Our search also found that using EBTI to prevent refractory delayed gastric emptying is a questionable practice and should be used with caution at this time. According to reports published in the past 5 years, it appears that EBTI is an effective treatment for refractory gastroparesis. However, a significant amount of additional investigation is needed before EBTI can be widely recommended as an effective treatment for gastroparesis. Additional large-scale randomized, controlled trials should be conducted as there is insufficient data on the topic to make definitive conclusions.

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Key words: endoscopic botulinum toxin injection; gastroparesis; refractory; delayed gastric emptying.

Contributions: all authors listed have made a direct and intellectual contribution to the work and approved for publication.

Conflict of interest: the authors declare that they have no competing interests, and all authors confirm accuracy.

Availability of data and material: data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Funding: no funding or sponsorship was received for this study or publication of this article.

Received: 27 June 2024.
Accepted: 23 December 2024.

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Advancements in Health Research 2025; 2:20
doi: 10.4081/ahr.2025.20

Introduction

Gastroparesis is a syndrome that is caused by a delay in gastric emptying in the absence of mechanical obstruction.[1] This delay is often associated with decreased amplitude and frequency of contractions of the gastric antrum.[2] It is often thought that gastroparesis occurs as a result of vagal dysfunction but it can also occur with decreased gastric fundic tone, antroduodenal dyscoordination, gastric arrhythmias and pyloric dysfunction.[2,3] Gastroparesis can be an idiopathic condition, a complication of diabetes mellitus, a post-surgical complication, or can be the result of a viral or bacterial illness such as *Salmonella* gastroenteritis, norovirus, Epstein-Barr virus, cytomegalovirus, and herpes virus. Among these subtypes, idiopathic gastroparesis remains the most prevalent, followed by diabetic and post-surgical gastroparesis. The pathophysiology of idiopathic gastroparesis is still poorly understood; thus, treating the condition remains difficult. However, certain cellular and histopathological clues

can give insight into the pathophysiology of idiopathic gastroparesis, and how the motility of the gut is affected by such changes. Histopathological examination of biopsies taken from gastric tissue in patients with idiopathic gastroparesis demonstrates loss of interstitial cells of Cajal in the gastric body, antrum and pylorus.[4-7] Diabetic gastroparesis describes a delay in gastric emptying with other accompanying symptoms, such as abdominal pain and nausea without an actual mechanical obstruction. Patients with both type I and type II diabetes are at risk of developing gastroparesis due to oxidative stress placed on the enteric nervous system from chronic hyperglycemia.[5] The most common procedural cause of post-surgical gastroparesis is fundoplication for the treatment of gastroesophageal reflux disease. Gastroparesis in these cases, arises from the vagus nerve being damaged or entrapped. This can also result from bariatric surgeries as well.[8,9]

The cardinal symptoms of gastroparesis include early satiety, postprandial fullness, bloating, nausea, and vomiting. Other than the cardinal symptoms, patients can experience abdominal pain, gastroesophageal reflex, anorexia, constipation, and diarrhea.[7,10-12] Because of its pathophysiology, gastroparesis is diagnosed with tools assessing gastric emptying, such as a 4-hour scintigraphic study using a test meal or a stable isotope 13-carbon spirulina breath test.[13,14] As gastroparesis has varying etiologies and degrees of severity, multiple treatment options are available to alleviate the problem and address its sequelae.[15] This is important since gastroparesis significantly affects healthcare costs, morbidity and mortality.[16] Gastroparesis also significantly affects the quality of life in patients who suffer from the disease. A study using the 36-item Short Form revealed that average scores for mental health and overall social functioning in patients with gastroparesis were similar to scores of patients suffering from disorders such as irritable bowel syndrome and depression.[17] Main treatment modalities for gastroparesis in rough order of implementation include nutritional support and balance, pharmacological treatment, surgical options.[16,18]

Endoscopic botulinum toxin injections

When one cannot attain adequate relief from conservative treatment modalities, it may be necessary to opt for more invasive modalities of treatment.[19] Prerequisites to these therapies often involve upper gastrointestinal (GI) imaging and emptying studies to determine anatomy, presence or lack of mechanical obstruction, and baseline measurements for follow-up.[19] Botulinum toxin A injections, first used for achalasia, have been proposed to be a helpful tool in those with gastroparesis; very few controlled trials have assessed efficacy.[20,21] Botulinum toxin A decreases the release of acetylcholine into nerve endings, which can help reduce tone or spasm of the pyloric sphincter.[22,2]. The goal of an intramuscular endoscopic botulinum toxin injection (EBTI) is to cause inhibition of smooth muscle and pyloric relaxation, allowing for easier passage and digestion of stomach contents.[24] While higher doses have been deemed to have better effects in some cases, the improvements generally only last a few months at best.[25,26] The overall utility is uncertain, as there is conflicting evidence surrounding botulinum toxin injections and their ability to improve symptoms and quality of life.[27] Currently, there is not an accepted, standardized parameter that supports the benefit of EBTI. According to our preliminary search, the use of EBTI for refractory gastroparesis was systematically reviewed in 2010 and 2018 - those reviews concluded that further investigation was necessary to determine whether this is an effective treatment. This systematic review will serve to examine more recent literature to review results from studies published in the last 5 years and summarize their conclusions.

Methods

Data sources and searches

A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[28] A systematic search of the Pubmed, Web of Science, and Cochrane databases was performed using the search terms *botulinum*, *toxin*, *refractory*, *gastroparesis*, *injection*, and *endoscopic* on July 24, 2023. To properly evaluate more current literature on the topic, the search was limited to reports published in English from 2019 to 2023.

Study selection

Initial database searches yielded many citations focused on other types of gastroparesis treatment besides EBTI. After the initial screening, studies that focused only on the use of EBTI for the treatment of gastroparesis and studies that had an outcome measure of improvement of symptoms associated with gastroparesis were selected to be included in the systematic review. Reports focused on the use of EBTI on both children and adults were included in the search. Because published literature on this topic is limited, case studies were also included in the search. Studies were excluded if they were published prior to 2019 or if they evaluated improvements in gastroparesis with EBTI in combination with another therapy. One researcher (Flanagan, C) screened all references obtained from the literature search and organized them according to the predetermined inclusion and exclusion criteria. Figure 1 details the systematic review method and results.

Results

The initial search across the three databases yielded a total of 220 citations. After filtering these citations only to include those published in 2019 or later, 67 citations remained. These citations were uploaded into Zotero reference manager, where 10 of them were identified as duplicates and were subsequently removed. The remaining 57 unique citations were identified and screened, and 31 items were excluded based on the pre-determined exclusion criteria. Of the remaining 26 citations, 6 items met the criteria for final review (Table 1). In a prospective open label trial, Reichenbach *et al.* evaluated the efficacy of EBTI in patients with gastroparesis over a 6 month period.[24] More specifically, 34 patients who were symptomatic and diagnosed with refractory gastroparesis were enrolled in the study. The diagnosis of delayed gastric emptying was made by scintigraphy showing greater than 10% gastric retention of a solid meal after a 4 hour period.[29] The authors defined the primary outcome of the study as the improvement in gastroparesis-associated symptoms. In order to evaluate this primary outcome, patients completed the Gastroparesis Cardinal Symptom Index (GCSI), which is a validated questionnaire that quantifies the severity of gastroparesis symptoms. The GCSI was administered at the initial encounter and at 1-, 3- and 6-months post-injection. Once

enrolled in the study, patients underwent pyloric EBTI using standard endoscopic procedures in combination with propofol sedation. At the conclusion of the study, 24 out of 34 initial patients were available for symptom follow up - 64% of these patients demonstrated an improvement in their symptoms at the one-month mark. Of the patients who reported an improvement in their symptoms one month after the injection reported continuous improvement in their symptoms for up to 6 months after the injection. Notably, no adverse events were reported during this study. Nevins *et al*. also conducted a prospective study evaluating patients who developed delayed gastric emptying (DGE) after undergoing oesophagogastrectomy with gastric conduit reconstruction.[30] 97 patients underwent either an open, two-stage Ivor-Lewis left thoracoabdominal oesophagogastrectomy or a three-stage McKeown oesophagogastrectomy; no patients had an intraoperative pyloric drainage procedure. For patients who developed DGE, the first line management was a subcutaneous infusion of metoclopramide (150 mg/24 h). If patients did not have resolution of their symptoms after the first line management within 24 h of its initiation, they were diagnosed with refractory DGE and underwent pyloric EBTI. The primary outcome measured in this study to evaluate efficacy of pyloric EBTI was nasogastric (NG) tube output. In total, 29 patients developed DGE refractory to metoclopramide within 30 days after surgery. Prior to undergoing pyloric EBTI, the median pre-procedure average NG aspirate was 780 ml. After the procedure, average NG aspirate was 125 ml. 16 patients developed DGE more than 30 days after surgery, presenting to outpatient follow up with complaints of chest pain, vomiting and weight loss. This cohort also received pyloric EBTI and all patients reported symptom improvement. Notably, six patients required a repeated pyloric EBTI procedure and all 6 patients had complete resolution of their DGE prior to discharge. Although one study participant developed aspiration pneumonia while awaiting their EBTI procedure, there were no procedural complications reported in this study. In 2019, Bhutani detailed the case of a 51-year-old man who developed severe gastroparesis after undergoing esophagectomy for distal esophageal cancer.[31] The patient initially presented with complaints of gastroesophageal reflux (GERD), chest pain, early satiety and chest fullness which were refractory to medical treatment. Consequently, the patient underwent pyloric EBTI which resulted in a "greater than 80% symptomatic benefit for 3 months". The patient experienced a relapse in symptoms after 3 months and then underwent pyloric balloon dilation which provided relief for 6 months. Rashid *et al.* also described a case of a patient with severe gastroparesis treated with pyloric EBTI.[32] In their case study, a 43-year-old male initially presented with complaints of chest pain and odynophagia and was diagnosed with a linear, deep, mid-esophageal perforation. The perforation was closed with 6 hemostatic clips and patient was stable on discharge. He returned 2 weeks later with complaints of shortness

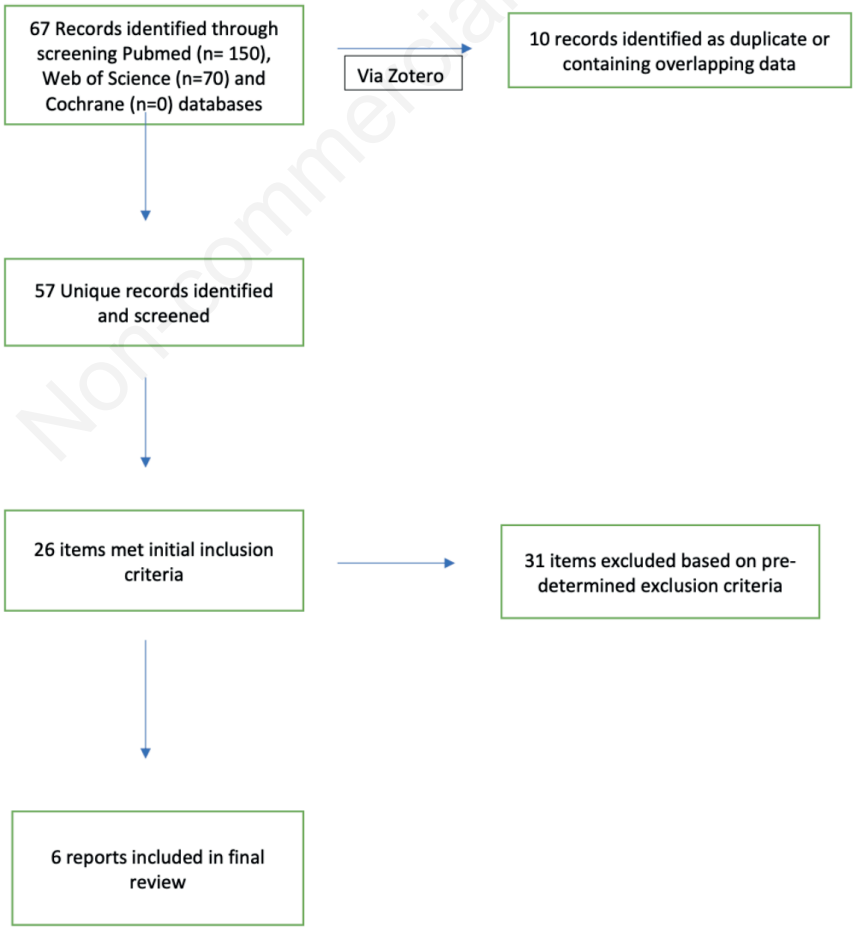

Figure 1. Systematic review method and results.

of breath and chest discomfort and was found to have a pericardial effusion with early signs of cardiac tamponade. He subsequently underwent emergent pericardiocentesis and a chest CT showed left sided-pleural effusion and empyema. He then underwent intra-pyloric EBTI after developing gastroparesis likely secondary due to vagal nerve injury after undergoing thoracotomy, decortication of an empyema, esophageal repair, omental transfer and repair of inferior/pulmonary vein/atrial margin. The patient reported a 60 percent improvement in his symptoms after pyloric EBTI. Lastly, Ezaizi *et al.* conducted a

Table 1. Summary of citations.

Author/Year	Type of study	Intervention	Outcome	Study conclusion
Reichenbach *et al.* (2019)[24]	Prospective, open label trial	Patients (n = 34) with refractory gastroparesis were treated with pyloric injections of botulinum toxin A and completed the Gastroparesis Cardinal Symptom Index (GCSI) at the initial counter and at 1-, 3- and 6-months post-injection.	25 out of 34 patients were available for symptom follow-up at the 6-month period and 64% of these patients demonstrated an improvement of their symptoms at one month. Patients who improved at one month reported continuous improvement for up to 6 months.	The authors concluded that EBTI improved gastroparesis-associated symptoms in over half of the patients enrolled in the study, and those that showed initial response reported improvement in their symptoms up to 6 months after the injection.
Nevins *et al.* (2020)[30]	Prospective study	Patients undergoing oesophagogastrectomy with gastric conduit reconstruction (n=90) were included in the study; 29 of them (30%) were diagnosed with postoperative DGE resistant to systemic pharmacotherapy and subsequently underwent pyloric EBTI.	After performing EBTI, the median NG tube aspirate output decreased from 780 ml to 125 ml. 6 patients required a second course of EBTI, but ultimately all patients had 100% successful resolution of DGE before being discharged from the hospital.	Patients who developed DGE refractory to systemic pharmacotherapy responded well to EBTI treatment and had a minimized risk of developing biliary reflux.
Bhutani (2019)[31]	Case study	EBTI was performed on a 51-year-old man who developed severe postoperative gastroparesis after undergoing esophagectomy for distal esophageal cancer.	After treatment, the patient reported a >80% improvement in his symptoms for 3 months – he experienced a relapse in his symptoms after the 3-month mark. Symptoms resolved after repeat EBTI, and the patient had a marked response to treatment and improvement in symptoms for 6 months afterward.	The author concluded that EBTI proved beneficial for this specific patient but reported that conducting more prospective studies on the topic would be worthwhile.
Rashid *et al.* (2020)[32]	Case study	A 43-year-old man underwent emergent pericardiocentesis after he was found to have a pericardial effusion with early signs of cardiac tamponade. He then underwent thoracotomy and decortication of an empyema. Postoperatively, the patient developed gastroparesis likely secondary to vagal nerve injury.	The patient was treated with intra-pyloric EBTI after his gastroparesis symptoms were noted, and reported an improvement in his gastroparesis-associated symptoms of greater than 60%.	The authors concluded that EBTI is a treatment that is effective in the treatment of post-operative gastroparesis.
Ezaizi *et al.* (2022)[33]	Retrospective cohort study	EBTI was performed in 20 children who were identified as having upper GI symptoms; of the 20 children, 9 of them were found to have gastroparesis.	A response to the intervention was reported in 10 children (50%) and it was found that the response to EBTI did not differ in the presence or absence of gastroparesis. Overall, 68% of the children who underwent EBTI reported a reaction to the treatment.	The authors concluded that EBTI can relieve refractory upper GI symptoms in patients with and without gastroparesis.
Tham *et al.* (2019)[34]	Retrospective cohort study	228 patients undergoing ILGO participated in the study; 65 received intraoperative EBTI, and 163 had no intervention.	The incidence of DGE was 11 (16.9%) in the treatment group and 29 (17.8%) in the control group.	The authors concluded that intraoperative EBTI during ILGO was ineffective at preventing DGE and that a better understanding of the disease process will guide the assessment and use of procedures to manage the condition.

DGE, delayed gastric emptying; EBTI, endoscopic botulinum toxin injection; NG, nasogastric; GI, gastrointestinal; ILGO, Ivor-Lewis gastroesophagectomy.

retrospective study in which they assessed the efficacy of intrapyloric EBTI in children with gastroparesis.[33] The authors retrospectively searched the electronic health records at Mayo Clinic to identify children (aged 18 years or younger) who underwent esophagogastroduodenoscopy, subsequently developed persistent upper gastrointestinal symptoms associated with gastroparesis and then underwent intrapyloric EBTI. Their search yielded 20 children with a mean age of 9.7 years who underwent EBTI. Of these 20 children, 17 underwent gastric emptying scintigraphy and 9 of them were found to have gastroparesis. In total, response to intrapyloric EBTI was reported in 10 children and this response did not differ based on the presence or absence of gastroparesis. Of the 10 children who had a response after EBTI, four children underwent repeat EBTI and interestingly none of them reported any benefit from the second EBTI.

Discussion

Of the few studies that have been published on the use of EBTI for gastroparesis, most have concluded that EBTI can be an effective treatment for gastroparesis and its use should be considered in patients who develop gastroparesis of various etiologies, including post-operatively. Interestingly, one study has shown that intra-pyloric EBTI is ineffective when performed at the time of the initial surgery as they found no difference in the rate of development of delayed gastric emptying between patients who received the treatment and those who did not. This systematic review has a few limitations. In this regard, the main limitation is the small number of randomized controlled trials performed to evaluate EBTI and its effects on refractory gastroparesis. Because the literature was so limited, case studies were included in the search. While these case reports demonstrated that EBTI was helpful in the management of gastroparesis, the results cannot be generalized as only one patient was the subject of the case report. Similarly to previous published systematic reviews, our systematic review concluded that the response to EBTI in patients with gastroparesis is variable and it cannot be definitively concluded to be a reliable, effective treatment for refractory gastroparesis. While there are a few studies that have reported that EBTI is effective in the treatment of gastroparesis that have been published in the last few years; there is still a significant amount of information to be determined before EBTI can be widely recommended as an effective treatment for gastroparesis. Additional large-scale randomized controlled trials should be conducted as there is not sufficient data on the topic to draw definitive conclusions.

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