

Endoscopic botox injections in therapy of refractory gastroparesis

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Abstract

Gastroparesis (GP) is a common disease seen in gastroenterology practice particularly in western countries, and it may be underdiagnosed. The available drug

therapies for this condition are quite disappointing. Botulinum toxin type A (BT) has been found to be effective therapy in various spastic disorders of smooth muscle of gastrointestinal tract. However, the benefits of BT injections in GP have been unclear. Several retrospective and open label studies have shown clinical advantages of intrapyloric Botulinum toxin type A injections, while two small randomized trials did not show positive results. Therefore, the available published studies yielded conflicting results leading to fading out of botox therapy for GP. We recognize possible clinical benefit of BT injections without any disadvantages of this treatment. We are calling for revisiting the endoscopy guided botox therapy in refractory GP. In this review we discuss important features of these studies pointing out differences in results among them. Differences in patient selection, doses and method of administration of botox toxin in the prior studies may be the cause of conflicting results. The mechanism of action, indications, efficacy and side-effects of BT are reviewed. Finally, we recognize limited evidence to recommend BT in GP and calling attention for future research in this field since no advances in drug management had been made in the last two decades.

Key words: Gastroparesis; Delayed gastric emptying; Botox; Botulinum toxin; Refractory gastroparesis

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Core tip: Refractory gastroparesis (GP) has been identified as a chronic debilitating disease. After failure of diet and prokinetic drugs for treatment of refractory GP only surgical options are left. Because of the limited available treatment options and frequent failure of medical therapy, botulinum toxin (BT) injection in the pylorus might offer clinical value in GP. Currently available evidence is not strong enough to support the recommendation of this procedure in all patients with

refractory GP; but promising results have been seen as most patients have noticed symptomatic improvement. Although BT injections were successful in some GP patients, the role of BT remains undetermined. We addressed the position of botulinum toxin in the spectrum of available treatments for refractory GP. Continuing other treatment modalities after BT may improve the results.

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INTRODUCTION

Refractory gastroparesis (GP) constitutes a major therapeutic challenge. Drug therapies are often found to be ineffective for a long term treatment. We found in our practice that some GP patients noticed significant improvement in symptoms and quality of life after botulinum toxin (BT) injections. Therefore, we question if there is a role for intrapyloric BT-A injections for treatment of GP. In this review article, the latest available literature (using Medline) and our own data on this topic will be summarized.

Epidemiology and types of GP

GP has been defined as a chronic disorder of impaired gastric motility in the absence of any mechanical obstruction of the upper gastrointestinal tract. Characteristic symptoms include early satiety, nausea, vomiting, bloating, postprandial fullness and upper abdominal pain^[1]. The age adjusted prevalence of GP has been estimated to be 9.6 for men and 37.8 for women per 100000 by a community based study^[2]. Most cases of GP have been found to be idiopathic or secondary to autonomic neuropathy associated with diabetes mellitus, surgery, Parkinson disease and collagen vascular diseases^[3,4].

Idiopathic GP (IGP), the most common type of GP, is a result of viral or bacterial infection^[5]. The underlying etiology of IGP is degeneration of myenteric plexus combined with loss of interstitial cells of Cajal^[6]. In diabetic GP (DGP), many mechanisms are responsible for delayed gastric emptying (GE) including neuropathy which affects vagal nerve, reduction in the numbers of intrinsic inhibitory neurons responsible for motor coordination, and reduction in number of pacemaker cells. Acute hyperglycemia with serum glucose levels > 288 mg/dL significantly delays GE in diabetic patients when compared to euglycemia^[7]. Post-surgical GP is less common type seen after surgery for peptic ulcer, fundoplication and bariatric surgery, pylorus-sparing pancreaticoduodenectomy and heart and lung transplantation^[8-10].

Pathophysiology and diagnosis of GP

Delayed GE as the major pathophysiological mechanism of GP is multifactorial, which includes impaired fundal tone, antral hypomotility, antroduodenal discoordination, gastric pacemaker dysrhythmias and excessive inhibitory feedback from the small bowel to the stomach^[11]. It has been suggested that increased tone of the pylorus (pylorospasm) may contribute to delayed gastric emptying^[12]. Therefore, reduction of pyloric pressure may facilitate improved GE and this can be achieved by botulinum toxin-A (BT-A) injection.

Diagnosis of GP is established based on the presence of clinical symptoms of GP, absence of gastric outlet obstruction or ulceration, and delay in gastric emptying. It is also recommended to document delayed gastric emptying before starting drug therapy of gastroparesis^[13].

Treatment of GP

Treatment options for GP include dietary changes, prokinetic drugs, antiemetics, correction of malnutrition and electrolyte disturbances, jejunal feeding, parenteral nutrition, gastric neurostimulation therapy and surgery. In refractory cases of GP, a total gastrectomy has been suggested^[14]. Prokinetic agents are the mainstay of treatment in GP after diet failure. However, the side effects and lack of effectiveness limits the long-term use of prokinetics in GP. Because of limited medical options, botulinum toxin-A intrapyloric injections have been offered as a salvage therapy in cases of refractory GP.

Botulinum toxin: Mechanism of action and clinical uses

Botulinum toxin, a bacterial neurotoxin, is one of the most potent paralytic agents of skeletal muscle. In two (2) *in-vivo* studies on piglets evaluating effects of BT-A on smooth muscle, the basal sphincter of Oddi pressure decreased by 50%, and lower esophageal sphincter pressure decreased by 60% with BT-A injection when compared to saline injection^[15,16]. An *in vitro* study done on pyloric muscle strips showed that BT-A injection was able to decrease contractions induced by acetylcholine (Ach), substance P and electric field stimulation^[17]. Two underlying mechanisms have been proposed for the action of BT-A. At low doses, BT-A inhibits the calcium dependent release of acetylcholine from cholinergic nerve terminals, and at higher doses direct inhibition of smooth muscle contraction has been observed^[17]. The effects of BT-A are time and concentration dependent as axonal sprouting and accumulation of extrajunctional Ach lead to slow reversal of denervation^[18,19].

BT-A has been found to be effective in the treatment of spastic disorders of smooth muscle in the upper and lower gastrointestinal tract. Case reports and prospective trials have shown positive results with BT-A administration in treatment of diffuse esophageal spasm^[20], achalasia^[21], oropharyngeal dysphagia^[22], anismus^[23], anal fissures^[24] and anterior rectocele^[25]. Administration of BT-A has a very low rate of adverse reactions and complications. Several case reports and



Figure 1 Endoscopic technique for botox injection in the pylorus (4 quadrants - see arrows).

trials of the effects of intrapyloric BT-A injection in GP have been published. Two small prospective studies suggested a limited value of endoscopic intrapyloric BT-A injections in GP^[26,27].

There is conflicting data whether BT-A can effectively relieve the symptoms, improve quality of life and improve the rate of gastric emptying in GP patients.

Suggested technique of BT-A injection

The commercial preparation of BT-A in the United States is supplied in vials containing a 50 or 100 U of the lyophilized powder. The powder is diluted in 5 mL of normal saline to yield a solution containing 20-25 U/mL. After diagnostic upper endoscopy, the pyloric sphincter area is identified, and a sclerotherapy needle (23 or 25 gauge) is introduced through the biopsy channel. Aliquots of 1-1.5 mL (20-25 U botulinum toxin/mL) are injected into each of four quadrants of the pylorus, for a total of 100 U (See Figure 1). A total dose between 100 to 200 U can be injected. Patients go home after routine post-sedation criteria are met and they are allowed to eat light meal later on the same day.

CLINICAL STUDIES OF BT-A FOR TREATMENT OF GP

The first data on the intrapyloric application of botulinum toxin in patients with GP was published by Ezzeddine *et al.*^[28] in 2002. An open label trial included 6 males with diabetic GP, documented by solid phase gastric emptying study, and a mean age of 62 years. All patients had 100 U of botulinum toxin injected in the pyloric sphincter. A solid phase gastric emptying study was done before the BT-A injection, and then repeated at 48 h and 6 wk after the procedure. The mean solid phase gastric emptying at 90 min improved from 27.8% before BT-A injection to 44.4% at 2 wk, and 49% at 6 wk. Baseline clinical symptoms were recorded and the symptoms were reassessed at 2 wk and 6 wk interval after the BT-A injection to document improvement. A mean improvement of 55% was noticed at both 2 and 6 wk. No complications were seen after BT-A therapy.

This study was very limited in terms of population and control group but it certainly demonstrated some clinical efficacy and immediate improvement in gastric emptying rate.

In an open label trial^[29], eight patients (including 6 women) with type 1 diabetes and GP were studied. Mean age was 41 years. A control group consisted of asymptomatic non-diabetic patients matched for age and gender. A higher dose of BT-A 200 U was used. Clinical symptoms, antro-pyloric manometry, gastric emptying, weight and insulin use were measured at baseline and at 12 wk with follow up completed in 7 patients. Prokinetic drugs were not discontinued during the trial. Significant improvement in symptoms after the BT-A injection was reported in all the patients with the average symptom score reduction to 12 from 27.4 patients had improvement in the solid phase gastric emptying post therapy including 1 case of normal GE study. Three patients had no improvement in GE, and 1 patient had a worse gastric emptying rate when compared to the pre-procedural values. Radiologists reading the gastric emptying study were blinded to the trial protocol. Pylorospasm was demonstrated on antro-pyloric manometry in all patients with GP, but it was not seen in any of the controls. Significant reduction in pylorospasm was found after BT-A when compared to baseline. Insulin requirement was increased in 4 patients at 8 wk and remained increased in 3 of them at 12 wk follow up. Weight gain was noticed in all patients except one. Prokinetic drug use was reduced in 50% of the patients.

A retrospective study by Bromer *et al.*^[30] included 63 patients (53 women; 10 men) with average age 42 years. Most of the patients (44) received a dose of BT-A 200 U and 13 patients received 100 U. No dose was recorded for 6 cases. The outcomes in this study were assessed on the basis of improvement in major GP symptoms. Forty-three percent patients reported improvement in symptoms, and men had better response to BT-A therapy than women. The mean duration of response to BT-A therapy was 5.1 mo. Treatment with BT-A was repeated based on recurrence of symptoms. Apart from the small study population, the absence of any quantitative measure of improvement and no standardized scale of symptomatic relief limited the quality of this study.

A small retrospective analysis of 21 patients (15 females) with refractory GP was recently published from the United Kingdom^[31]. The mean age of patients was 47.8 years and 81% of cases were secondary to DGP. A dose of 200 U of BT-A was used in all the patients. The mean follow up was 2 years. Sixty-two percent patients reported response to treatment compared to 19% non-responders. The mean response duration was 4.2 mo. Weight gain and increased insulin requirement was observed in the diabetic group. Greater effectiveness of BT-A therapy was found in the diabetic population compared to idiopathic GP cases.

In an open label trial^[32] of 10 female patients with

IGP, a mean duration of symptoms of 4 years and prokinetics failure, BT-A in doses 80-100 U was used. Response was assessed on the basis of upper GI symptom improvement and 4-h solid phase gastric emptying study at 4 wk after the treatment compared to the baseline. Nine out of 10 patients reported improvement in symptom scores. An improvement in the gastric emptying rate was found in 7 of the 10 patients (70%), while 2 patients had no change and 1 case had worsening of gastric emptying rate. The patients were followed up for at least 6 mo. In 5 out of 10 patients repeat BT-A injections were required due to recurrent symptoms. All the patients reported improvement after the second BT-A injection. This study showed effectiveness of repeat BT-A injection but at the same time raised a question regarding long term outcomes of the procedure.

In another open label study^[33], 20 patients with GP (17 women; 17 IGP) received 100 U of BT-A injections in the pylorus. An assessment of solid and liquid gastric emptying, and improvement in intensity of cardinal GP symptoms was performed at 4 wk. Significant improvement was found in solid phase gastric emptying and the symptom score compared to pre procedural numbers, but no improvement in liquid phase emptying was seen. No correlation was found between symptomatic improvement and the change in gastric emptying rate. This study had only a short follow up. The study raised an important question pertaining to the methods of measurement of improvement in GP patients. If we should assess the objective improvement based on the diagnostic test (GE study), a measurable standard, or the subjective improvement should be determined on the basis of their symptom scores as outcome measures.

Those promising results from the open label trials and observational studies prompted researchers to conduct randomized control trials. Two randomized, placebo controlled double blinded studies were published. In a trial by Friedenber *et al*^[26], a total of 32 patients were divided into two groups of 16, and randomized to receive either 200 U of botulinum toxin or saline injection in the pylorus. Each group contained 9 patients with diabetic GP. All patients had a symptom score ≥ 27 . A decrease of 9 points or more in the symptom score at 1-mo follow up was considered as the primary endpoint. Only 6 patients in the botox group showed improvement compared to 9 patients in the saline injection group. Gastric emptying rate improved markedly in the BT-A group, but did not reach statistical significance when compared to the placebo group. Out of the 32 patients, 17 had no symptom improvement including 10 from the BT-A group. The study was based on an assumption of an efficacy of 80% for the BT-A injection which was relatively high and had a small population size and low statistical power. The second randomized controlled study by Arts *et al*^[27] included 23 patients with GP (18 women, and 19 IGP). The mean age of the patients was 45 years. The

study was double-blinded and patients received either BT-A injection at a dose of 100 U or saline injection in a cross-over pattern. Baseline gastric emptying and GP cardinal symptom index (GCSI) were recorded. In the first session, 12 patients received BT-A injections and 11 had saline injections. Both groups showed considerable improvement in the solid phase gastric emptying after the first injection. But no subsequent improvement was seen in either group after the second injection (cross-over). No statistically significant difference was seen when pooled data was compared from both groups after the two procedures. Both groups showed similar improvement in GCSI. Even though the pooled data analysis showed considerable improvement of post-prandial fullness and bloating in the BT-A group, it was not statistically different from the placebo group.

The largest study published up to date was a retrospective trial of 179 patients including 81 with DGP and 76 IGP cases^[4]. The response was measured in terms of symptom improvement and change in body weight within 1 to 4 mo after BT-A injection. Almost 51% patients reported benefit and 32% of them had no benefit from the BT-A therapy. No record was available for the rest of the patients. BT-A was injected in doses ranging between 100-200 U. Patients who received higher doses reported better symptom control. Many patients (87) underwent repeat BT-A injections and received doses of 150 U or 200 U. Similar results were observed on repeat injections among first time responders and non-responders. This study results suggested a better response in women, younger patients (< 50 years old) and those with idiopathic GP.

Recently a case series^[34] of 3 patients with diabetic GP and islet cell transplant between ages 42-55 years was published. They were treated with intrapyloric BT-A injections (2 patients received 200 U and one received 150 U). Symptomatic improvement was noticed in all the patients. The response lasted 6-8 wk in 2 patients who had BT-A 200 U injections and 8 mo in the patient who received lower dose 150 U. This result raised a question of the most effective dose to use for intrapyloric BT-A injections in GP.

The data on the use of BT-A in pediatric population with GP is even more scant. Only 1 study^[35] has been published on BT-A in refractory GP. A retrospective review of 47 children including 23 girls was conducted with follow up available for 45 of them. The mean age of the patients was 9.8 years and mean follow up was 18 mo. The majority of the patients (66%) had idiopathic GP. Botulinum toxin was injected at a dose of 6 U/kg up to a maximum total dose of 100 U. The outcome was measured based on symptoms index as no response, mild, moderate or complete resolution of symptoms. At least mild improvement in symptoms was seen in 66.7% patients, with only 1 patient reporting worsening of symptoms. Repeat BT-A injections were required in 18 patients, out of which 8 showed response and 7 did not benefit from repeat treatment. Median duration of response to BT-A was 3 mo. The children older than 12

Table 1 Summary of the literature on use of botulinum toxin injection for gastroparesis in adults

Ref.	Number of patients	Study design	Botox dose (units)	Results (% of patients with symptomatic improvement)
Ezzeddine <i>et al</i> ^[28]	6	Prospective non-controlled	100	55
Lacy <i>et al</i> ^[29]	8	Prospective non-controlled	200	100
Bromer <i>et al</i> ^[30]	63	Retrospective	100 (<i>n</i> = 13) 200 (<i>n</i> = 44) Unknown (<i>n</i> = 6)	43
Rameshshanker <i>et al</i> ^[31]	21	Retrospective	200	62
Miller <i>et al</i> ^[32]	10	Prospective non-controlled	80-100	100
Arts <i>et al</i> ^[33]	20	Prospective non-controlled	100	100
Friedenberg <i>et al</i> ^[26]	32	RCT	200	37.5
Arts <i>et al</i> ^[27]	23	RCT	100	100 ¹
Coleski <i>et al</i> ^[4]	179	Retrospective	100-200	51

¹100% improvement was seen on botulinum toxin as well as normal saline so botox was not proved to be better than placebo. RCT: Randomized-controlled trial; n: Number of patients.

years showed better response when compared to those of < 12 years old. This study was important by showing that efficacy rates, duration of response and safety of botox in children were comparable to the results seen in adult population.

In a recent meta-analysis^[36] of 15 studies, including single case reports of GP, almost all open label and retrospective studies showed a beneficial effect of BT-A treatment for GP, while 2 randomized control trials have shown no superiority of BT-A in comparison to placebo. Based on the meta-analysis, it has been suggested that the current evidence did not justify the use of BT-A in GP patients, but the analysis consisted of only a small population (186 patients). Across these studies, the 2 randomized control trials included in the meta-analysis were found to be significantly heterogeneous. Because of these limitations, the meta-analysis failed to add any useful knowledge for practical purposes in therapy of GP (Table 1).

DISCUSSION

Botulinum toxin has been widely used in the past as a treatment option for patients with refractory GP with clinically beneficial effects, mainly symptomatic improvement. All the open label trials have reported the intrapyloric BT-A injection to be useful therapy in GP^[28-35]. However, two small prospective randomized control trials (RCT)^[26,27] did not show positive response to botox injection in regards to symptomatic improvement and rate of gastric emptying. Both studies in different subgroups (DGP vs IGP) of patients have not proven BT-A to be superior to normal saline injection, and cast some doubts over its effectiveness. Based on results of those RCTs some GI societies do not recommend routine use of botox injections as a treatment option in GP.

Limitations of therapy for gastroparesis

It has been a major concern that currently available drug therapy for severe GP is very limited. Traditionally prokinetics, metoclopramide, domperidone and cisapride, have been widely used in the treatment of functional dyspepsia and GP^[37]. These prokinetic agents work by increasing antral contractility and accelerating gastric emptying^[38]. In a systematic analysis, prokinetics have been shown to be more effective than placebo in GP by improving the symptoms of postprandial fullness, nausea and vomiting^[39-42]. However, available prokinetic drugs only modestly enhance gastric emptying and the evidence that their symptomatic improvement in GP is related to enhancement of gastric emptying is actually lacking. Serious side effects such as cardiac arrhythmias (QT prolongation) seen with cisapride (Propulsid; Janssen Pharmaceutica, Titusville, NJ) led to withdrawal of the drug from United States market in 2000^[43]. Cisapride was also banned in India and Philippines in 2011, and its use in Europe has also been quite limited. Metoclopramide (Reglan; A. H. Robins, Richmond, Va) is the most commonly used drug for the treatment of GP. However, extrapyramidal symptoms and sedative effects of metoclopramide limited its usage in GP. Metoclopramide significantly increases the risk of tardive dyskinesia, drug-induced Parkinsonism, and subjective akathisia^[44]. The severity of tardive dyskinesia was greater in diabetics when compared to non-diabetics^[44]. A dramatic reduction in prescribing of metoclopramide by clinicians for GP has been seen after a black box warning was placed for the risk of tardive dyskinesia when used for prolonged period^[45]. Side effects are a common reason for discontinuation of metoclopramide therapy. Erythromycin is the only other Food and Drug Administration (FDA) approved drug for use in GP. Studies have shown symptom improvement in only 43% of the patients taking

erythromycin^[46]. The use of erythromycin is often limited by development of tachyphylaxis as a result of down regulation of motilin receptors, which develops days after initiating the treatment^[47]. Other side effects of erythromycin such as nausea, vomiting, and abdominal pain seen more often with higher doses can result in discontinuation of therapy^[48,49]. Domperidone (Motilium; Janssen) appears to be effective for treating symptoms of GP. However, it is not available for sale in the United States. Domperidone has not been approved by the FDA because of concerns regarding its cardiotoxicity, mainly QT prolongation seen especially in hypokalemic patients^[50]. The hurdles in obtaining the drug have discouraged the physicians in United States regarding its applications in GP. Currently, domperidone can be prescribed in United States for GP patients 12 years of age and older through an expanded access investigational new drug application and local institutional review board (IRB) approval^[51].

Hence, there is a clear need for new therapeutic approaches for the treatment of GP. Gastric electric stimulator (GES) has been shown in clinical studies to be effective to control nausea and vomiting in GP patients. Even though patients with refractory symptoms have embraced the availability of this device, the special status and certain requirements used by some third party insurance carriers may deny coverage. The GES device has a humanitarian device status. Therefore, the gastric electrical stimulator cannot be implanted at any center unless its placement has been approved by the local IRB. Candidates for this therapy are patients with diabetes and IGP with relentless nausea and vomiting, who have failed medical therapy. Conversely, patients without nausea and vomiting but with other manifestations such as fullness, early satiety, anorexia, and abdominal pain have not been shown to predictably respond to gastric stimulation^[52].

General concerns regarding studies on botox in GP

Most published studies looked only at a total symptom score (GCSI) rather than selected symptoms of nausea and vomiting. From clinical standpoint improvement in symptoms appears to be the most important outcome when treating patients with GP. The most troublesome symptoms for patients are nausea and vomiting, which tremendously limit oral intake and may lead to progressive weight loss and malnutrition. Abdominal pain associated with GP is the most challenging symptom to treat since patients often request pain medications, especially narcotics, and those drugs can lead to further delay in gastric emptying and diffuse GI tract dysmotility. Chronic dependence on narcotics has to be recognized in patients with both IGP and DGP. Those patients are taking opioids for different reasons including abdominal pain, but often not related to GP. Narcotics use makes this condition more difficult to treat. For some patients discontinuation of pain medications is not a viable option because of their quality of life.

In patients with refractory GP, even a partial clinical

response may provide significant improvement in quality of life and possibly reduce number of hospitalizations. On the other hand, improvement in GE has not been shown to correlate with symptom improvement in this patient population. Therefore assessing response to BT-A based on GE study only has its own limitations.

Patients with severe refractory GP often require frequent visits to emergency center (ER) and hospitalizations, which is also associated with higher cost of medical care. Because of above limitations and high prevalence of GP, other therapeutic options are needed to improve symptoms and quality of life in GP patients. With the limited availability of medical treatment options, side effects and drug failure, we believe that physicians may need to reconsider botox as a trial therapy before directing patient with refractory GP for more aggressive treatment such as surgical interventions including placement of jejunostomy tube or GES and gastrectomy.

Our limited experience with Botox therapy in GP

In our small retrospective unpublished study of patients with GP (confirmed by solid phase gastric emptying study) treated with intrapyloric BT-A injection, a survey was performed to assess symptoms, the overall improvement after procedure, and the number of visits to ER and hospitalizations^[53]. Twenty-five patients (19 females; 6 males) were included in the analysis. The causes of GP were idiopathic 17, diabetes 6, and postsurgical 2. Mean follow up was 31 mo. Seventy-two percent of our patients noticed significant (> 50%) symptom improvement. The patients who benefited the most from BT-A injection were males and those with IGP. Twenty-eight percent of patients (7/25), non-responders to botox therapy underwent laparoscopic GES placement. Reduction in number of ER visits and hospitalizations was reported by 24% of patients.

Role of botox in treatment of GP

The results of available literature are quite controversial to determine the clinical effects of botox therapy in GP. Some patients clearly reported symptomatic improvement with botox therapy. In refractory GP cases it is quite difficult to reject this therapeutic option especially as it is very safe.

For example, there is also controversy on effectiveness of botox in patients with anismus, but it has been often used since no other therapies offer benefits in this condition. We have solid data available on use of botox in achalasia, including safety and need for repeat injections. Despite more effective and permanent solutions available including Heller myotomy and peroral endoscopic myotomy, BT-A injections are still in the armamentarium for achalasia^[54,55].

Several questions need to be further addressed regarding botox application in refractory GP. First, it is unclear, which patients with GP benefit the most from botox therapy. Some studies have suggested better results in patients with IGP including our own data^[4,53].

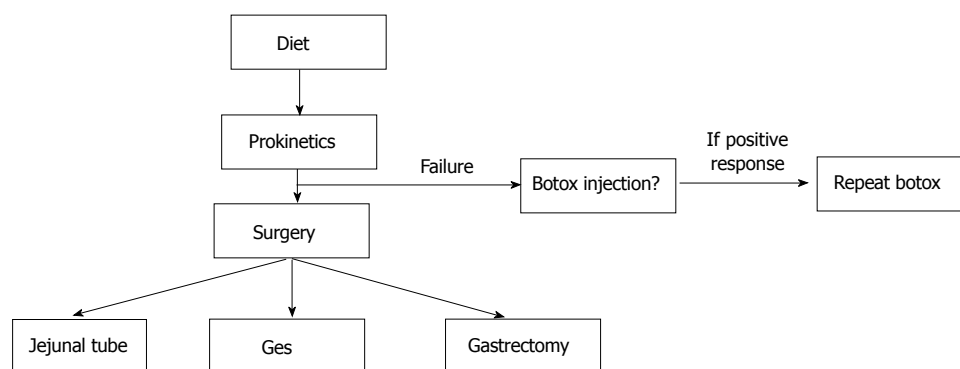


Figure 2 Summary of therapeutic options for gastroparesis. GES: Gastric electric stimulation.

There may be also a sex difference in response to BT-A injections. In a one retrospective study men had superior response^[30], while the other large study showed the opposite results^[4]. The effects of patient age on outcomes also need to be evaluated further. In pediatric population, older children appeared to have better results to BT-A injection^[35]. There is a concern regarding safety of multiple BT-A injections into pylorus which could lead to local scarring as documented for comparison in achalasia patients^[56,57].

Another issue that requires further study is to evaluate if the effect of botox injection may be dose dependent? Is a higher dose of botox more beneficial in GP? There is no clear answer to this question. In the RCTs botox was mainly used in two different dosages of 100 U or 200 U, and both showed negative outcomes^[26,27]. Question has been raised about the effectiveness of higher dose of botox and the length of the response^[34]. For example, in achalasia, no data exist to support that higher dose of botox is more effective and has longer lasting beneficial effect. One of the concerns is rather a short lasting effect of BT-A injections in GP. Based on the available studies the beneficial effects of Botox lasted between 3-8 mo^[32,34]. Therefore, patients may require additional BT-A injections. The results on the duration of response to BT-A injection appear to be similar to published data in patients with achalasia. Often retreatment may be needed.

When to repeat BT-A injection? Should botox be used if there is no prior response or only if previously there was a good response to it? Should a higher dose of botox be injected next time if no response is found to the first treatment? Should the dose of botox be selected based on the severity of delayed gastric emptying?

Based on the prior studies, patients who had a positive response to the first dose continued to respond to repeat BT-A injections^[4,32]. The studies do not provide an answer in which setting to use repeat botox. In our practice we use a standard dose of 100 U in each case. From personal experience we repeat BT-A injection only if there is an initial symptomatic improvement after first injection. The BT-A injections are repeated based on duration of response typically every 6 mo if needed. In patients with IGP spontaneous improvement in

symptoms over time can be expected. Therefore botox injection may be used as a bridging therapy during a period of severe symptoms before the condition can be managed by diet and prokinetic drugs only.

To our knowledge no studies evaluated quality of life in patients with GP after BT-A injections. This issue may also be evaluated in further studies. If lower number of ER visits or hospitalizations can be documented with Botox therapy this could have an impact on cost of care in GP patients. Finally, we recognize that patients after BT-A injection need to continue to follow the diet and drug therapy. Diet and prokinetics adjustments should be done gradually as patients report symptomatic improvement. In only one study a reduction in prokinetic medication use has been addressed as an outcome measure^[29].

There may still be a role for Botox use when patients fail diet modification, prokinetics or when the promotility drugs are not available. (See our proposed algorithm (Figure 2). At present there is no clear answer which patients benefit the most from botox injection. In general, patients have no contraindications for BT-A injection unless they face major cardiopulmonary issues not allowing for a safe endoscopy. Studies suggest that GP patients with pylorospasm have the best response to BT-A injections. However, in clinical practice, no easy access to gastroduodenal motility testing is available. Therefore, a decision to use botox has to be individualized in GP. Botox injections should not be used routinely in all GP cases.

CONCLUSION

Pyloric injection with botulinum toxin is an easy to perform procedure with minimal risk and negligible side effects compared to other available treatments for refractory GP. Although, the lack of convincing evidence has limited the use of botox in clinical practice, most uncontrolled studies have shown symptomatic improvement in the GP patients. Other concern regarding botox use is that, the dose and most effective site of BT-A injection for optimal response has not been standardized. Misplaced injections and skills of the endoscopist should also be taken into account

when determining the effectiveness of treatment with botox injection. If botox therapy is effective, the results of this treatment have not been long lasting and repeat procedures may be necessary. The long-term effects with repeat procedures have not been well studied. Further large population randomized studies are required to justify the use of botox for refractory GP. There may be a role for BT-A therapy in properly selected GP patients. With limited treatment options, we believe that botox injections can still be considered as treatment option for refractory GP when drug therapy failed.

REFERENCES

- 1 Camilleri M, Bharucha AE, Farrugia G. Epidemiology, mechanisms, and management of diabetic gastroparesis. *Clin Gastroenterol Hepatol* 2011; **9**: 5-12; quiz e7 [PMID: 20951838 DOI: 10.1016/j.cgh.2010.09.022]
- 2 Jung HK, Choung RS, Locke GR, Schleck CD, Zinsmeister AR, Szarka LA, Mullan B, Talley NJ. The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006. *Gastroenterology* 2009; **136**: 1225-1233 [PMID: 19249393 DOI: 10.1053/j.gastro.2008.12.047]
- 3 Soykan I, Sivri B, Sarosiek I, Kiernan B, McCallum RW. Demography, clinical characteristics, psychological and abuse profiles, treatment, and long-term follow-up of patients with gastroparesis. *Dig Dis Sci* 1998; **43**: 2398-2404 [PMID: 9824125]
- 4 Coleski R, Anderson MA, Hasler WL. Factors associated with symptom response to pyloric injection of botulinum toxin in a large series of gastroparesis patients. *Dig Dis Sci* 2009; **54**: 2634-2642 [PMID: 19184429 DOI: 10.1007/s10620-008-0660-9]
- 5 Bityutskiy LP, Soykan I, McCallum RW. Viral gastroparesis: a subgroup of idiopathic gastroparesis--clinical characteristics and long-term outcomes. *Am J Gastroenterol* 1997; **92**: 1501-1504 [PMID: 9317072]
- 6 Zárate N, Mearin F, Wang XY, Hewlett B, Huizinga JD, Malagelada JR. Severe idiopathic gastroparesis due to neuronal and interstitial cells of Cajal degeneration: pathological findings and management. *Gut* 2003; **52**: 966-970 [PMID: 12801952 DOI: 10.1136/gut.52.7.966]
- 7 Abell TL, Camilleri M, Donohoe K, Hasler WL, Lin HC, Maurer AH, McCallum RW, Nowak T, Nusynowitz ML, Parkman HP, Shreve P, Szarka LA, Snape WJ, Ziessman HA. Consensus recommendations for gastric emptying scintigraphy: a joint report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. *Am J Gastroenterol* 2008; **103**: 753-763 [PMID: 18028513 DOI: 10.1111/j.1572-0241.2007.01636.x]
- 8 Fich A, Neri M, Camilleri M, Kelly KA, Phillips SF. Stasis syndromes following gastric surgery: clinical and motility features of 60 symptomatic patients. *J Clin Gastroenterol* 1990; **12**: 505-512 [PMID: 2229993]
- 9 Dong K, Yu XJ, Li B, Wen EG, Xiong W, Guan QL. Advances in mechanisms of postsurgical gastroparesis syndrome and its diagnosis and treatment. *Chin J Dig Dis* 2006; **7**: 76-82 [PMID: 16643334 DOI: 10.1111/j.1443-9573.2006.00255.x]
- 10 Berkowitz N, Schulman LL, McGregor C, Markowitz D. Gastroparesis after lung transplantation. Potential role in postoperative respiratory complications. *Chest* 1995; **108**: 1602-1607 [PMID: 7497768 DOI: 10.1378/chest.108.6.1602]
- 11 Lacy BE, Weiser K. Gastric motility, gastroparesis, and gastric stimulation. *Surg Clin North Am* 2005; **85**: 967-987, vi-vii [PMID: 16139031]
- 12 Mearin F, Camilleri M, Malagelada JR. Pyloric dysfunction in diabetics with recurrent nausea and vomiting. *Gastroenterology* 1986; **90**: 1919-1925 [PMID: 3699409]
- 13 Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L. Clinical guideline: management of gastroparesis. *Am J Gastroenterol* 2013; **108**: 18-37; quiz 38 [PMID: 23147521 DOI: 10.1038/ajg.2012.373]
- 14 Jones MP, Maganti K. A systematic review of surgical therapy for gastroparesis. *Am J Gastroenterol* 2003; **98**: 2122-2129 [PMID: 14572555 DOI: 10.1111/j.1572-0241.2003.07721.x]
- 15 Sand J, Nordback I, Arvola P, Pörsti I, Kalloo A, Pasricha P. Effects of botulinum toxin A on the sphincter of Oddi: an in vivo and in vitro study. *Gut* 1998; **42**: 507-510 [PMID: 9616312 DOI: 10.1136/gut.42.4.507]
- 16 Pasricha PJ, Ravich WJ, Kalloo AN. Effects of intrasphincteric botulinum toxin on the lower esophageal sphincter in piglets. *Gastroenterology* 1993; **105**: 1045-1049 [PMID: 8405847]
- 17 James AN, Ryan JP, Parkman HP. Inhibitory effects of botulinum toxin on pyloric and antral smooth muscle. *Am J Physiol Gastrointest Liver Physiol* 2003; **285**: G291-G297 [PMID: 12660140 DOI: 10.1152/ajpgi.00296.2002]
- 18 Nakov R, Habermann E, Hertting G, Wurster S, Allgaier C. Effects of botulinum A toxin on presynaptic modulation of evoked transmitter release. *Eur J Pharmacol* 1989; **164**: 45-53 [PMID: 2568939 DOI: 10.1016/0014-2999(89)90229-X]
- 19 Arnon SS, Schechter R, Inglesby TV, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Fine AD, Hauer J, Layton M, Lillibridge S, Osterholm MT, O'Toole T, Parker G, Perl TM, Russell PK, Swerdlow DL, Tonat K. Botulinum toxin as a biological weapon: medical and public health management. *JAMA* 2001; **285**: 1059-1070 [PMID: 11209178 DOI: 10.1001/jama.285.8.1097]
- 20 Storr M, Allescher HD, Rösch T, Born P, Weigert N, Classen M. Treatment of symptomatic diffuse esophageal spasm by endoscopic injections of botulinum toxin: a prospective study with long-term follow-up. *Gastrointest Endosc* 2001; **54**: 754-759 [PMID: 11726856 DOI: 10.1067/mge.2001.119256]
- 21 Kolbasnik J, Waterfall WE, Fachnie B, Chen Y, Tougas G. Long-term efficacy of Botulinum toxin in classical achalasia: a prospective study. *Am J Gastroenterol* 1999; **94**: 3434-3439 [PMID: 10606299 DOI: 10.1111/j.1572-0241.1999.01605.x]
- 22 Zaninotto G, Marchese Ragona R, Briani C, Costantini M, Rizzetto C, Portale G, Zanetti L, Masiero S, Costantino M, Nicoletti L, Polidoro A, Feltrin G, Angelini C, Ancona E, Guidolin D, Parenti AR. The role of botulinum toxin injection and upper esophageal sphincter myotomy in treating oropharyngeal dysphagia. *J Gastrointest Surg* 2004; **8**: 997-1006 [PMID: 15585387 DOI: 10.1016/j.gassur.2004.09.037]
- 23 Ron Y, Avni Y, Lukovetski A, Wardi J, Geva D, Birkenfeld S, Halpern Z. Botulinum toxin type-A in therapy of patients with anismus. *Dis Colon Rectum* 2001; **44**: 1821-1826 [PMID: 11742168 DOI: 10.1007/BF02234461]
- 24 Maria G, Casseta E, Gui D, Brisinda G, Bentivoglio AR, Albanese A. A comparison of botulinum toxin and saline for the treatment of chronic anal fissure. *N Engl J Med* 1998; **338**: 217-220 [PMID: 9435326 DOI: 10.1056/NEJM199801223380402]
- 25 Brisinda G, Cadeddu F, Brandara F, Maria G. Management of defecation disorders with botulinum neurotoxin. *Aliment Pharmacol Ther* 2004; **19**: 1131-1133; author reply 1135-1136 [PMID: 15142203 DOI: 10.1111/j.1365-2036.2004.01951.x]
- 26 Friedenbergh FK, Palit A, Parkman HP, Hanlon A, Nelson DB. Botulinum toxin A for the treatment of delayed gastric emptying. *Am J Gastroenterol* 2008; **103**: 416-423 [PMID: 18070232 DOI: 10.1111/j.1572-0241.2007.01676.x]
- 27 Arts J, Holvoet L, Caenepeel P, Bisschops R, Sifrim D, Verbeke K, Janssens J, Tack J. Clinical trial: a randomized-controlled crossover study of intrapyloric injection of botulinum toxin in gastroparesis. *Aliment Pharmacol Ther* 2007; **26**: 1251-1258 [PMID: 17944739 DOI: 10.1111/j.1365-2036.2007.03467.x]
- 28 Ezzeddine D, Jit R, Katz N, Gopalswamy N, Bhutani MS. Pyloric injection of botulinum toxin for treatment of diabetic gastroparesis. *Gastrointest Endosc* 2002; **55**: 920-923 [PMID: 12024156 DOI: 10.1067/mge.2002.124739]
- 29 Lacy BE, Crowell MD, Schettler-Duncan A, Mathis C, Pasricha PJ. The treatment of diabetic gastroparesis with botulinum toxin injection of the pylorus. *Diabetes Care* 2004; **27**: 2341-2347 [PMID: 15344442 DOI: 10.2337/27.12.2341]

- 15451898 DOI: 10.2337/diacare.27.10.2341]
- 30 **Bromer MQ**, Friedenber F, Miller LS, Fisher RS, Swartz K, Parkman HP. Endoscopic pyloric injection of botulinum toxin A for the treatment of refractory gastroparesis. *Gastrointest Endosc* 2005; **61**: 833-839 [PMID: 15933684 DOI: 10.1016/S0016-5107(05)00328-7]
- 31 **Rameshshanker R**, Smith L, Southern P, Whitelaw D, Beckett C. Gastroparesis and botulinum toxin. *Gut* 2011; **60** (Suppl 1): A105-A106
- 32 **Miller LS**, Szych GA, Kantor SB, Bromer MQ, Knight LC, Maurer AH, Fisher RS, Parkman HP. Treatment of idiopathic gastroparesis with injection of botulinum toxin into the pyloric sphincter muscle. *Am J Gastroenterol* 2002; **97**: 1653-1660 [PMID: 12135014 DOI: 10.1111/j.1572-0241.2002.05823.x]
- 33 **Arts J**, van Gool S, Caenepeel P, Verbeke K, Janssens J, Tack J. Influence of intrapyloric botulinum toxin injection on gastric emptying and meal-related symptoms in gastroparesis patients. *Aliment Pharmacol Ther* 2006; **24**: 661-667 [PMID: 16907899 DOI: 10.1111/j.1365-2036.2006.03019.x]
- 34 **Thomas MP**, Wilson CH, Nayar M, Manus DM, Walker M, Shaw J, White SA. Endoscopic botulinum toxin injection for the treatment of diabetic gastropathy in pancreas and islet-cell transplant patients. *Exp Clin Transplant* 2012; **10**: 168-171 [PMID: 22432763]
- 35 **Rodriguez L**, Rosen R, Manfredi M, Nurko S. Endoscopic intrapyloric injection of botulinum toxin A in the treatment of children with gastroparesis: a retrospective, open-label study. *Gastrointest Endosc* 2012; **75**: 302-309 [PMID: 22248598 DOI: 10.1016/j.gie.2011.09.042]
- 36 **Bai Y**, Xu MJ, Yang X, Xu C, Gao J, Zou DW, Li ZS. A systematic review on intrapyloric botulinum toxin injection for gastroparesis. *Digestion* 2010; **81**: 27-34 [PMID: 20029206 DOI: 10.1159/000235917]
- 37 **Holtmann G**, Talley NJ. Functional dyspepsia. Current treatment recommendations. *Drugs* 1993; **45**: 918-930 [PMID: 7691499]
- 38 **Soo S**, Moayyedi P, Deeks J, Delaney B, Innes M, Forman D. Pharmacological interventions for non-ulcer dyspepsia. *Cochrane Database Syst Rev* 2000; **(2)**: CD001960 [PMID: 10796840 DOI: 10.1002/14651858.CD001960]
- 39 **Finney JS**, Kinnersley N, Hughes M, O'Bryan-Tear CG, Lothian J. Meta-analysis of antisecretory and gastrokinetic compounds in functional dyspepsia. *J Clin Gastroenterol* 1998; **26**: 312-320 [PMID: 9649020]
- 40 **Stanghellini V**, Tosetti C, Paternico A, Barbara G, Morselli-Labate AM, Monetti N, Marengo M, Corinaldesi R. Risk indicators of delayed gastric emptying of solids in patients with functional dyspepsia. *Gastroenterology* 1996; **110**: 1036-1042 [PMID: 8612991 DOI: 10.1053/gast.1996.v110.pm8612991]
- 41 **Perri F**, Clemente R, Festa V, Annese V, Quitadamo M, Rutgeerts P, Andriulli A. Patterns of symptoms in functional dyspepsia: role of *Helicobacter pylori* infection and delayed gastric emptying. *Am J Gastroenterol* 1998; **93**: 2082-2088 [PMID: 9820377 DOI: 10.1111/j.1572-0241.1998.00597.x]
- 42 **Sarnelli G**, Caenepeel P, Geypens B, Janssens J, Tack J. Symptoms associated with impaired gastric emptying of solids and liquids in functional dyspepsia. *Am J Gastroenterol* 2003; **98**: 783-788 [PMID: 12738456 DOI: 10.1111/j.1572-0241.2003.07389.x]
- 43 **Veldhuyzen van Zanten SJ**, Jones MJ, Verlinden M, Talley NJ. Efficacy of cisapride and domperidone in functional (nonulcer) dyspepsia: a meta-analysis. *Am J Gastroenterol* 2001; **96**: 689-696 [PMID: 11280535 DOI: 10.1111/j.1572-0241.2001.03521.x]
- 44 **Ganzini L**, Casey DE, Hoffman WF, McCall AL. The prevalence of metoclopramide-induced tardive dyskinesia and acute extrapyramidal movement disorders. *Arch Intern Med* 1993; **153**: 1469-1475 [PMID: 8512437 DOI: 10.1001/archinte.1993.00410120051007]
- 45 **Ehrenpreis ED**, Deepak P, Sifuentes H, Devi R, Du H, Leikin JB. The metoclopramide black box warning for tardive dyskinesia: effect on clinical practice, adverse event reporting, and prescription drug lawsuits. *Am J Gastroenterol* 2013; **108**: 866-872 [PMID: 23735907 DOI: 10.1038/ajg.2012.300]
- 46 **Maganti K**, Onyemere K, Jones MP. Oral erythromycin and symptomatic relief of gastroparesis: a systematic review. *Am J Gastroenterol* 2003; **98**: 259-263 [PMID: 12591038 DOI: 10.1111/j.1572-0241.2003.07167.x]
- 47 **Richards RD**, Davenport K, McCallum RW. The treatment of idiopathic and diabetic gastroparesis with acute intravenous and chronic oral erythromycin. *Am J Gastroenterol* 1993; **88**: 203-207 [PMID: 8424421]
- 48 **Ray WA**, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM. Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med* 2004; **351**: 1089-1096 [PMID: 15356306 DOI: 10.1056/NEJMoa040582]
- 49 **Erbas T**, Varoglu E, Erbas B, Tastekin G, Akalin S. Comparison of metoclopramide and erythromycin in the treatment of diabetic gastroparesis. *Diabetes Care* 1993; **16**: 1511-1514 [PMID: 8299441 DOI: 10.2337/diacare.16.11.1511]
- 50 **Reddymasu SC**, Soykan I, McCallum RW. Domperidone: review of pharmacology and clinical applications in gastroenterology. *Am J Gastroenterol* 2007; **102**: 2036-2045 [PMID: 17488253 DOI: 10.1111/j.1572-0241.2007.01255.x]
- 51 **Ahmad N**, Keith-Ferris J, Gooden E, Abell T. Making a case for domperidone in the treatment of gastrointestinal motility disorders. *Curr Opin Pharmacol* 2006; **6**: 571-576 [PMID: 16997628 DOI: 10.1016/j.coph.2006.07.004]
- 52 **Abell TL**, Bernstein RK, Cutts T, Farrugia G, Forster J, Hasler WL, McCallum RW, Olden KW, Parkman HP, Parrish CR, Pasricha PJ, Prather CM, Soffer EE, Twillman R, Vinik AI. Treatment of gastroparesis: a multidisciplinary clinical review. *Neurogastroenterol Motil* 2006; **18**: 263-283 [PMID: 16553582 DOI: 10.1111/j.1365-2982.2006.00760.x]
- 53 **Murawska A**, Ukleja A, Schneider A. Outcomes of intrapyloric botulinum toxin injection for refractory gastroparesis - A single center experience. United European Gastroenterology week. Berlin: United European Gastroenterology Journal, 2013
- 54 **Inoue H**, Minami H, Kobayashi Y, Sato Y, Kaga M, Suzuki M, Satodate H, Odaka N, Itoh H, Kudo S. Peroral endoscopic myotomy (POEM) for esophageal achalasia. *Endoscopy* 2010; **42**: 265-271 [PMID: 20354937 DOI: 10.1055/s-0029-1244080]
- 55 **Rosemurgy A**, Villadolid D, Thometz D, Kalipersad C, Rakita S, Albrink M, Johnson M, Boyce W. Laparoscopic Heller myotomy provides durable relief from achalasia and salvages failures after botox or dilation. *Ann Surg* 2005; **241**: 725-733; discussion 733-735 [PMID: 15849508 DOI: 10.1097/01.sla.0000160702.31452.d5]
- 56 **Richardson WS**, Willis GW, Smith JW. Evaluation of scar formation after botulinum toxin injection or forced balloon dilation to the lower esophageal sphincter. *Surg Endosc* 2003; **17**: 696-698 [PMID: 12616390 DOI: 10.1007/s00464-002-8628-x]
- 57 **Horgan S**, Hudda K, Eubanks T, McAllister J, Pellegrini CA. Does botulinum toxin injection make esophagomyotomy a more difficult operation? *Surg Endosc* 1999; **13**: 576-579 [PMID: 10347294 DOI: 10.1007/s004649901044]

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