

## **Intrapyloric Botulinum Toxin Injection for Refractory Gastroparesis May Offer Symptoms Improvement and Reduce Hospital Visits: A Single Center Experience**

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### **Abstract**

**Aim:** To evaluate the long-term outcomes of intrapyloric Botulinum toxin (BTX) injections in patients with well documented gastroparesis by gastric emptying test.

**Methods:** Retrospective chart review of patients diagnosed with gastroparesis who received BTX injections from January 2008 to July 2012 was performed. Demographics, comorbidities, diagnosis, past surgical history, the amount of BTX injected, procedural complications, medication use, emergency center and hospital visits were collected. A questionnaire with cardinal symptom index score and overall improvement scale was mailed to all patients. In cases with no mail response, patients were contacted by phone. Overall improvement after BTX injections, as well as adverse effects related to BTX injections, number of visits to emergency room (ER) and hospitalizations, need for gastric electrical stimulator placement were analyzed.

**Results:** Twenty five of thirty two patients [19 females (F), 6 males (M)] with gastroparesis responded to the questionnaire and were included in the study. The mean age was 46.1 years (range 21 - 71). Causes of gastroparesis were: idiopathic (IGP) 17 patients (13 females, 4 males); diabetic (DGP) 6 patients (4 females, 2 males); postsurgical (PGP) 2 females. The number of BTX injections per patient were: Single -15 patients (13F, 2M); Two - 5 patients (4F, 1M); Three - 3 patients (1F, 2M); Four-2 patients (1F, 1M). The mean follow-up was 31 months (range 13 - 42). Overall symptomatic improvement (by percentage) was: None (2F), 25% (5F), 50% (8F, 2M), 75% (3F, 4M), 100% (1F). Symptom improvement > 50% based on GP etiology was: 82% (14/17) patients with IGP, 67% (4/6) patients with DGP, 0% (0/2) patients with PGP. Reduced ER/hospital visits reported in 6 (24%) patients. Gastric electrical stimulator was implanted in 7 (28%) patients because of lack of long-term symptomatic improvement.

**Conclusions:** Approximately 72% of our GP patients noticed clinically significant (> 50%) symptomatic improvement after botox therapy. The subgroup of GP patients who benefited the most were males and patients with IGP. There may be still a role for BTX therapy in properly selected patients with refractory GP.

**Keywords:** *Gastroparesis; Endoscopy; Botulinum Toxin; Botox; Refractory Gastroparesis*

## Core Tip

Refractory gastroparesis (GP) constitutes a major therapeutic challenge. Drug therapy for GP is often ineffective long-term or associated with a high rate of adverse effects requiring its termination. While the use of endoscopic intrapyloric Botulinum toxin (BTX) injection for GP has been controversial, studies have suggested a limited but beneficial role of BTX in symptomatic improvement of patients with refractory gastroparesis. In this single center experience, we have found considerable symptomatic improvement in our patients after intrapyloric botox injection. We also noted a considerable decrease in ER visits and hospitalization post endoscopic botox therapy.

## Introduction

Gastroparesis is a chronic condition characterized by delayed gastric emptying in the absence of mechanical obstruction. Symptoms include early satiety, nausea, vomiting, bloating, postprandial fullness and upper abdominal pain [1]. GP is a relatively common condition encountered in the gastroenterology practice. Weight loss and malnutrition can be seen in refractory cases [1]. The age adjusted prevalence of GP has been estimated to be 9.6 for men and 37.8 for women per 100,000 by a community based study. GP is found to be 3 times more common in females when compared to males [2]. Major causes of gastroparesis include idiopathic, diabetes mellitus, and postsurgical. Other less common causes include connective tissue disease, neurological (including Parkinson's), ischemic, metabolic and endocrine conditions, and critical illness. In Parkinson disease and collagen vascular diseases, GP is usually secondary to autonomic neuropathy present in these conditions [3,4].

Goals of treatment in GP patients are symptom reduction and correction of malnutrition and electrolyte disturbances. Main treatments include dietary modifications, prokinetic medications, and antiemetics. Prokinetic agents are the mainstay of treatment in GP after diet failure [5]. However serious cardiac arrhythmias with cisapride, extrapyramidal and sedative side effects with metoclopramide, limited access to domperidone in the United States, low efficacy and tachyphylaxis to erythromycin have significantly limited the use of these drugs in GP patients [6-9]. The available treatment options depend on severity of GP. Botox (BTX) intrapyloric injections had been used successfully in the past, however BTX use has been reduced because of limited beneficial effects based on two small randomized trials [10,11]. Refractory gastroparesis embodies a major therapeutic challenge with limited and often ineffective drug treatment options. At times nutritional support is needed with jejunal feeding or parenteral nutrition. In severe cases gastric neurostimulation and surgery, such as pyloroplasty or gastrectomy, should be considered [12].

It has been suggested that a reduction of pyloric pressure by botulinum toxin-A (BTX) injection into pylorus may facilitate an improvement in gastric emptying and relieve symptoms associated with GP. This may be because of effects and altered antral activity and intubation of the pylorus and any spasm that may occur in this region of the stomach. The use of BTX for the treatment of GP have been advocated for many years but the lack of large population studies and negative results of two small negative randomized controlled trials discouraged its widespread use in GP.

## Objectives of the Study

The objectives of this study were to report on our single center experience with the use of intra-pyloric BTX for GP and describe the long-term outcomes in patient by assessing Gastroparesis Cardinal Symptoms Index (GCSI), overall improvement score, and emergency room (ER)/hospitalization visits.

## Materials and Methods

### Study Design and Population

After approval by institutional review board at Cleveland Clinic Florida, a retrospective chart review of patient records was performed to identify GP patients who underwent intrapyloric BTX injection between January 2008 and July 2012. All patients had a confirmed diagnosis of GP by gastric emptying scintigraphy.

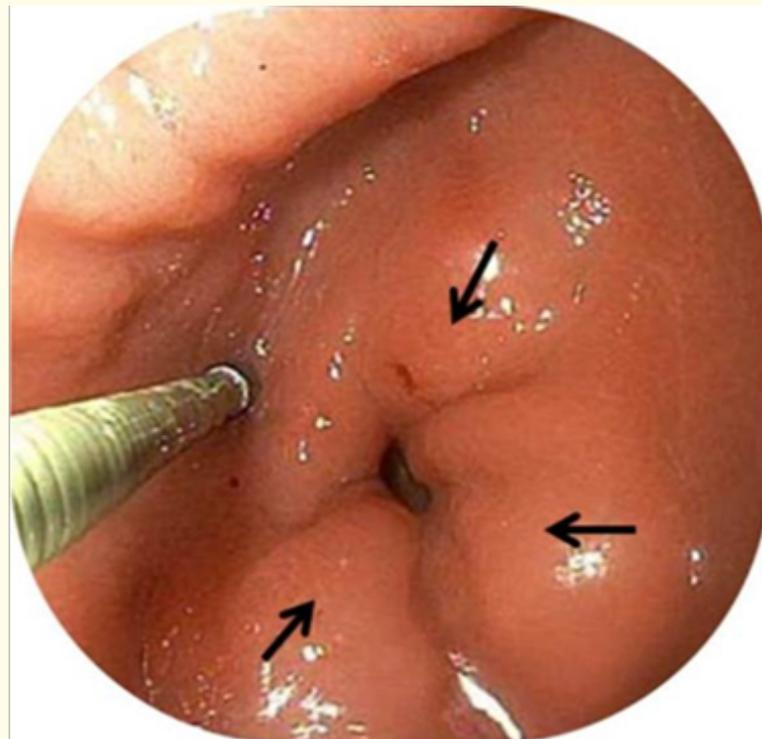
A survey was conducted to determine patient’s Gastroparesis Cardinal Symptoms Index (GCSI) scores and general overall improvement (percentage) post BTX injections to assess clinical response. Data regarding ER visits and hospitalizations was also collected [13]. Baseline symptoms scores were obtained from pre-procedural visit notes.

**Equipment and Procedure**

The procedures were performed using standard esophagogastroduodenoscopy (EGD) scopes (Pentax Medical, Ontvale, New Jersey, USA; or Fujinon, Fujifilm Corporation, Minato-ku, Tokyo, Japan). EGD with the Botulinum toxin injection was performed in a single session. Two attending physicians only performed all endoscopic procedures included in the study. Attending gastroenterologists were well familiar with Botox injections. The procedures were performed under nurse administered standard sedation with meperidine and midazolam, or under anesthesiology-provider administrated propofol (monitored anesthesia care). Endoscopy reports were generated by the physician with the details including dosage and sites of injection as mandatory fields.

**Technique of BTX Injection**

The commercial preparation of BTX-A (Botox; Allergan, Irvine, CA) in the United States was supplied in vials containing 50 or 100 Units (U) of the lyophilized powder. The powder was diluted in 5 mL of normal saline to yield a solution containing 20 - 25 U/mL. After diagnostic upper endoscopy, the pyloric sphincter area was identified, and a sclerotherapy needle (23 or 25 gauge) was introduced through the biopsy channel. Aliquots of 1 - 1.5 mL (20 - 25 U botulinum toxin/mL) were injected into each of four quadrants of the pylorus (See figure 1). A total dose injected ranged between 100 and 200 U. The dose was selected based on severity of delay in gastric emptying or prior response to Botox injection. Patients were discharged home after routine post-sedation criteria were met and they were allowed to eat light meal later on the same day.



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

**Data Collection**

Patient data including demographics, type of gastroparesis, gastric emptying test results, comorbidities, past surgical history, amount of Botulinum toxin injected and number of treatment sessions, intra-procedural complications, medications, follow up data post BTX injection, symptoms scores prior and after BTX injections were collected. A questionnaire was designed to assess the patient symptoms (bloating, abdominal distention, early satiety, nausea, vomiting) overall improvement, need for gastric electrical stimulator placement, BTX injections for GP outside of our institution, adverse effects related to BTX injections, and number of visits to ER/hospitalizations after BTX treatment. The questionnaire had a visual scale with marking of 0-25-50-75-100% for each symptom and overall improvement. The symptom improvement was graded as no improvement (0 to < 50%), partial (> 50% to < 100%) or complete improvement (100%) for individual symptom.

Data on future placement of gastric electrical neurostimulation was also recorded.

**Statistical Analysis**

Continuous demographic and clinical characteristics were described using means and ranges. Categorical characteristics were described using percentages. All symptomatic improvement percentages were calculated based on decrease in GCSI score. Taking the study sample size and heterogeneity of studied patients into consideration, only descriptive data analysis was performed.

**Results**

A total of 32 patients underwent botulinum toxin injections during the study period. Twenty five out of thirty two patients responded to the questionnaires and were included in the study. A majority of the patients were females (19). The mean age of the patients was 46.1 years (range 21 - 71 years). The baseline characteristics of the population are shown in table 1.

Variable	Patient population (N = 25)
Age (Range)	46.1 years (21 - 71)
Gender	19 females 6 males
<b>Etiology of gastroparesis</b>	17
Idiopathic	6
Diabetic	2
Post-Surgical	
<b>Number of botox injections</b>	
Single	15
Two	5
Three	3
Four	2
Follow up (Range)	31 months (13 - 42)

**Table 1:** Baseline characteristics of the GP population.

**Causes of gastroparesis:** Seventeen patients (13 females, 4 males) were diagnosed with idiopathic GP (IGP), six patients (4 females, 2 males) had diabetic GP (DGP) and two patients (females) had postsurgical GP (PGP) secondary to Nissen fundoplication.

**Symptom improvement:** Gastroparesis Cardinal Symptoms Index (GCSI) was used to assess the symptom severity before and after intervention [13]. Nine patients (all females) reported no improvement in bloating while 13 patients (9 females, 4 males) had partial improvement, and 3 patients (1 female, 2 males) reported complete improvement. Abdominal distention completely resolved in 4 patients (1 female, 3 males), partially improved in 11 patients (8 females, 3 males), with no improvement seen in 10 patients (all females). Five patients (2 females, 3 males) reported complete improvement in early satiety compared to 8 (6 females, 2 males) with partial improvement, and 12 patients (11 females, 1 male) had no improvement. Nausea did not improve in 7 patients (6 females, 1 male). 12 patients (10 females, 2 males) had partial improvement, and 5 (2 females, 3 males) reported complete improvement in nausea. In terms of vomiting, 8 patients (5 females, 3 males) had complete response, 12 (9 females, 3 males) had partial improvement, and 4 patients (all females) had no improvement after BTX injection (See table 2). In summary, 64% patients showed improvement in bloating, 60% patients had improvement in abdominal distension, and 52% patients had improvement in early satiety, while 71% patients had improvement in nausea and 84% patients had improvement in vomiting.

Response	Gender	Bloating	Abdominal distention	Early satiety	Nausea*	Vomiting*
No improvement (0 to < 50%)	Female	9	10	11	6	4
	Male	-	-	1	1	-
Partial Improvement (50 to < 100%)	Female	9	8	6	10	9
	Male	4	3	2	2	3
Complete improvement 100%	Female	1	1	2	2	5
	Male	2	3	3	3	3

**Table 2:** Symptom improvement with BTX injections (GCSI).

\* 1 patient had no nausea/vomiting

Percentage of overall improvement was also assessed by survey based on global symptom improvement (range 0, 25, 50, 75 and 100%). This scale was not validated previously. No improvement (0%) was reported by 2 patients (both females). Five patients (all females) reported only 25% improvement. 10 patients (8 females, 2 males) reported 50% improvement. Seven patients (3 females, 4 males) had 75% overall improvement and 1 patient (female) reported 100% improvement after BTX (See table 3). The symptomatic improvement (> 50%) based on etiology of GP was reported by 82% (14/17) patients from IGP category, and 67% (4/6) patients from DGP category. None of the post-surgical GP patients reported 50% symptomatic improvement.

Percentage improvement	Gender	0%	25%	50%	75%	100%
Number of patients	Female	2	5	8	3	1
	Male	-	-	2	4	-

**Table 3:** Overall symptom improvement by gender.

**Number of BTX injections and follow-up:** Fifteen (13 females, 2 males) had only one BTX injection. Five patients (4 females, 1 male) had BTX injections twice. Three patients (1 female, 2 males) had to undergo a third treatment, while 2 patients (1 female, 1 male) required four BTX injections. Mean follow up period was 31 months (range 13 - 42).

**Reduction in Emergency Room/hospital visits:** Twenty four percent (6/25) patients reported reduced number of visits to the ER/hospital after BTX injections in our study. Seven (28%) patients had gastric electrical stimulator placed later because of failure of all medical therapies.

## Discussion

Botulinum toxin has been used in the past with modest success in regards to symptomatic improvement in patients with refractory GP. In our study, 72% of our gastroparesis patients reported a clinically significant improvement (> 50%) in symptoms with BTX treatment. Most impressive improvement was seen in symptoms of nausea and vomiting when compared to symptoms of bloating, abdominal distention, and early satiety. Our goal was to analyze each symptom separately to identify symptoms for which botox injections may be more beneficial. However, overall improvement in symptoms may be more relevant. Our results are in accordance with previous studies, which have reported a symptom improvement post BTX ranging from 37.5 to 100% [4,10,11,14-19]. Although, the magnitude of symptomatic improvement suggested that BTX is an effective treatment option for patients who failed drug therapy, doubts were raised regarding its beneficial effect in two small randomized controlled trials [10,11]. Both trials showed an improvement in symptoms of GP in the BTX arm but it was not significantly different when compared to placebo arm. However, these studies were performed in small GP populations and the results should be analyzed with caution. Friedenber, *et al.* randomized 32 patients (16 - Botox injection, 16 - Saline injection) amongst which 7 patients in the BTX group and 10 patients in placebo group showed symptom improvement after 1 month [11]. Whereas, Arts., *et al.* in their cross-over trial randomized 23 patients to either botox or placebo and a crossover treatment 4 weeks after the first BTX injection. Although symptomatic improvement was seen in all the patients in the BTX group, it was not significantly different from the placebo group [10]. The results of these trials have been a reason for withdrawal of BTX therapy from armamentarium for refractory GP. The use of BTX has been not recommended by gastroenterological societies in the USA. However, because of limited options available especially in the USA, botox may be still an alternative in selected cases before more complex and costly surgical procedures.

In this small study, the response was particularly noted to be better in the patients with idiopathic and diabetic GP, as 82% patients (14) with IGP and 67% (4) with DGP reported > 50% symptomatic improvement. This data is in accordance with previously reported rates of symptom resolution after BTX injections. Arts., *et al.* evaluated almost exclusively (17/20) idiopathic GP patients and observed improvement in all the enrolled patients [19]. Similarly, Ezzeddine., *et al.* and Lacy., *et al.* noted symptomatic improvement in their diabetic population between 55 and 100% [14,15].

In our study, all male participants (6) were found to have at least 50% improvement in their symptoms as opposed to 12 of 19 females with similar outcomes. Bromer., *et al.* also showed greater improvement in males in their study. On the contrary, another larger retrospective study revealed better outcomes with BTX in females [4,16]. Most studies have had predominantly higher female population due to the fact that gastroparesis is much more common in females. Therefore, it might be possible that females also have worse outcomes when compared to males with botox therapy but larger studies are needed to test this hypothesis. With no definitive treatment available, primary treatment goal in patients with refractory GP should be also focused on improvement in quality of life (QOL). This can be partially assessed by the number of visits to the emergency room (ER) or frequency of hospitalizations. To our knowledge, no previous study has addressed these parameters. Twenty four percent (6) of our patients reported reduction in the number of visits to the emergency room and also in number of hospitalizations after BTX treatment. Although these numbers are relatively small and the results might not be an accurate depiction of the long term outcomes of a larger GP population, but this may prove to be vital information, as studies have shown almost 18 fold increase in hospitalization of gastroparesis patients over the past two decades [20]. These results are promising and must be considered for future research. In our study group, seven patients continued to be symptomatic despite BTX injections and drug therapy. All of these patients eventually received surgically placed permanent gastric electrical stimulator.

Our study has a few limitations. As previously mentioned, the study population was small and may not represent the overall outcomes in GP patients. However, our results are promising and worth consideration for a further exploration. Secondly, the lack of a comparison/control group makes it difficult to assess the effectiveness of BTX, which will require a clinical trial and randomization of patients to BTX versus placebo groups. Thirdly, the study was conducted in a survey format and the responses can be subject to a recall bias. Efforts were

made to decrease recall bias to a minimum by asking direct questions to patients and their charts were reviewed to correlate the acuity and severity of patient's symptoms. There is a need for a large multicenter trial to determine if botox injections are justified in patients with refractory gastroparesis. Botox therapy may be also used as an adjunct to drug therapy. Recent studies suggest that surgical or endoscopic pyloroplasty for GP patients with suspected pylorospasm is beneficial, which works on the similar mechanism as botox injection [21,22].

### **Conclusion**

In conclusion, the results of our study are encouraging and hold merit especially in terms of clinical improvement of symptoms. Seventy two percent of patients reported partial to complete improvement in symptoms of gastroparesis. Decreased number of ER visits and hospitalizations were reported in one-fourth of our patients. Therefore, our findings also strengthen the previously available literature on benefits of BTX in regards to symptom improvement. With increased incidence of gastroparesis and availability of endoscopic botox injections, there is a great need to conduct a large randomized multicenter trial in order to confirm the beneficial effects of BTX injections in GP and to clarify the role of BTX injections in the management algorithm of refractory GP.

### **Author's Contributions**

- Kanwarpreet Tandon, MD: Title Selection, Manuscript drafting, writing, editing and revision, and table formulation.
- Andrew Ukleja, MD: Topic selection, Title selection, manuscript drafting, writing, critical revision and editing.
- Amareshwar Podugu, MD: Manuscript drafting, writing and editing and table formulation.
- Baker Alkhairi, MD: Manuscript drafting, writing and editing and table formulation.
- Aleksandra Murawska, MD: Research design, data collection and analysis, and table formulation.
- Alison Schneider, MD: Manuscript drafting, writing, critical revision and editing.

### **Informed Consent Statement**

All study participants provided verbal informed consent. Waiver of Written consent was granted due to no more than minimal risk to the patients.

### **Conflict of Interest Statement**

All the authors declare no financial disclosure or conflict of interest.

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