

ORIGINAL ARTICLES

Functional GI Disorders

Botulinum Toxin A for the Treatment of Delayed Gastric Emptying

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BACKGROUND: Observational data suggest that intrapyloric injection of botulinum toxin A (BoTN/A) reduces symptoms and accelerates gastric emptying in idiopathic and diabetic gastroparesis. Our purpose was to determine whether botulinum toxin improves symptoms to a significantly greater extent than placebo. An additional objective was to determine whether there is an acceleration of gastric emptying after injection.

METHODS: A single-institution, randomized, double-blind, placebo-controlled trial* was done. Eligible patients had a Gastroparesis Cardinal Symptom Index score ≥ 27 with randomization to intrapyloric botulinum toxin, 200 U (units), or saline placebo. Reassessment of symptoms and repeat gastric emptying scan at 1-month follow-up were done.

RESULTS: Thirty-two patients were randomized to botulinum toxin (N = 16) and placebo (N = 16). At 1-month follow-up, 37.5% randomized to botulinum toxin and 56.3% randomized to placebo achieved improvement as defined by this study. There were no identifiable clinical predictors of response. The botulinum toxin group demonstrated improvement in gastric emptying; however, this was not superior to placebo. No serious adverse events were attributable to botulinum toxin.

CONCLUSIONS: Intrapyloric injection of botulinum toxin improves gastric emptying in patients with gastroparesis, although this benefit was not superior to placebo at 1 month. Also, in comparison to placebo, symptoms do not improve significantly by 1 month after injection. Overall, we are unable to recommend botulinum toxin therapy for widespread use in the treatment of delayed gastric emptying until more data are available.

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INTRODUCTION

Patients with gastroparesis, or delayed gastric emptying, may present with dyspeptic symptoms, including early satiety, postprandial bloating, nausea, vomiting, and abdominal pain (1). Gastric emptying is a highly regulated process that requires the integration of propulsive forces generated by proximal fundic tone and distal antral contractions with coordinated relaxation of the pyloric sphincter (2). Antral hypomotility as well as increased gastric outlet resistance due to pyloric dysfunction or pylorospasm are hypothesized to be important physiologic disturbances in gastroparesis (3–5). Prokinetic agents, the current treatment for gastroparesis, increase antral contractility and accelerate gastric emptying (6, 7). Promotility agents often have limited efficacy

and restricted usefulness due to side effects. These include cardiac arrhythmias with cisapride (Propulsid, Janssen, Titusville, NJ) and erythromycin, or extrapyramidal symptoms as in the case of metoclopramide (Reglan, Schwarz Pharma, Mequon, WI) (7, 8). Domperidone (Motilium, Janssen-Cilag, Sydney, Australia) may be effective for treating symptoms of gastroparesis; however, it is not marketed in the United States (9).

Botulinum toxin A (BoTN/A, Botox, Allergan, Irvine, CA) is an inhibitor of cholinergic neuromuscular transmission and has been used to treat spastic disorders of both striated and smooth muscles by local injection into the affected muscles (10). Observational data from case series have demonstrated that endoscopic injection of BoNT/A directly into the pylorus reduces symptoms and can accelerate gastric emptying in both idiopathic and diabetic gastroparesis (11–14). In a recent open-label study of 20 patients, a dose of 100 U (units)

*Clinicaltrials.gov: NCT00372970.

of BoNT/A was used and gastric emptying was measured at baseline and 1 month after injection. The $t_{1/2}$ for solid food emptying improved by approximately 40% and this was associated with an improvement in meal-related symptoms (15). In the largest open-label study to date, 63 patients with delayed gastric emptying were injected with either 100 or 200 U of BoNT/A (16). Overall, 43% of patients had a reduction in gastroparesis symptoms, defined as significant improvement in their predominant dyspeptic symptom or any two non-predominant dyspeptic symptoms, for a minimum of 4 wk after injection. Neither pyloric manometry nor repeat gastric emptying scintigraphy (GES) was performed after injection, thus the mechanism accounting for response was not clarified. The median duration of response was approximately 5 months and serious side effects were not reported. The duration of response was presumably limited by axonal regeneration of cholinergic neurons. Two unpublished randomized trials from one group have shown no improvement in gastroparesis symptoms after BoNT/A injection (17, 18). Unfortunately, despite the lack of controlled data, many gastroenterologists are now using pyloric BoNT/A injection outside the context of a clinical research study.

The primary objective of this study was to perform a double-blind, randomized trial to determine whether pyloric injection of BoNT/A can improve symptoms in patients with delayed gastric emptying to a significantly greater extent than injection with saline placebo. An additional objective was to determine whether there is an acceleration of gastric emptying 1 month after injection. Lastly, we sought to determine whether certain clinical variables could be identified that predict a beneficial response to BoNT/A.

MATERIALS AND METHODS

Eligibility Criteria

Patients referred to the Motility Section of Temple University Hospital with a diagnosis of, or symptoms consistent with, delayed gastric emptying were potentially eligible for the study. The manufacturer of BoNT/A had no role in the conduct or analysis of this manuscript. Figure 1 provides a flowchart of the study. Eligible patients were between 18 and 75 yr of age and were required to have delayed gastric emptying by scintigraphy performed at our institution within 3 months of study entry. We repeated the scans performed at other institutions. Patients were required to have a score of ≥ 27 on the Gastroparesis Cardinal Symptom Index (GCSI). The GCSI is a subscale of the Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM) and has been previously validated in a study group of patients with gastroparesis (Fig. 2)(19). Patients with gastroparesis secondary to diabetes were required to be under good metabolic control (fasting glucose < 140 mg/dL) for 1 month prior to study entry. For patients on a prokinetic drug providing partial effectiveness, we required that the daily dose remain stable for at least 4 wk prior to study entry. These patients were required to stay on their medication until the 1-month postinjection visit. However, the prokinetic was discontinued for

48 h prior to GES. If the patient was on an ineffective prokinetic drug, then it was discontinued 4 wk prior to study entry.

All patients were screened for other disorders that could mimic gastroparesis such as the peptic ulcer disease. Patients were excluded if pregnant or otherwise unfit to undergo upper endoscopy. Patients were also excluded if they had prior abdominal surgery except for hernia repair or appendectomy. Patients who had received prior BoNT/A and those with a known allergy to the protein were excluded. Finally, patients were excluded if unable to stop medications known to exacerbate delayed gastric emptying (*e.g.*, narcotic analgesics). All enrolled patients were required to sign informed consent approved by the Temple University institutional review board (IRB).

GES

A gastric emptying test was performed prior to treatment and at 1-month follow-up. After an overnight fast, the patient consumed a test meal consisting of an egg sandwich labeled with 500 μ Ci Technetium-99m sulfur colloid and 300 mL of water. Scintigraphic images were obtained for 240 min after meal ingestion (20). A region of interest was drawn around the entire stomach for all acquired images. The geometric mean of gastric counts was determined at each imaging time. After correction for radionuclide decay, geometric mean gastric counts at each imaging time were expressed as a percent of the maximal geometric mean counts at time zero. Normal solid-phase gastric emptying at our institution with this meal is $\leq 50\%$ retention at 2 h and $\leq 10\%$ at 4 h (20).

Symptom Score Determination

To quantify symptoms at baseline and after treatment, we used the GCSI. The GCSI evaluates nine symptoms using a scale from 0 (none) to 5 (very severe) and, therefore, the total maximum score is 45. A score of ≥ 27 was chosen to capture patients with moderate to severe symptoms. We also used the Gastroparesis Visual Analog Scale (GVAS), which provided an additional subjective measurement of symptom severity (21). The eight symptoms queried by the GVAS (all postprandial) include fullness, early satiety, bloating, epigastric discomfort (poorly localized ache), epigastric pain (a sharp, well-localized pain), nausea, belching, and vomiting. Symptom severity is scored on a 100-mm visual analog scale and, therefore, the maximal composite score is 800. We used a 5-point (0–4) Likert scale to assess the patient's baseline quality of life (QOL) as well to assess the impact that gastroparesis symptoms had on the ability to attend and function in work or school.

Randomization and Endoscopic Injection of Drug

After enrollment, patients were randomized to either sterile saline injection or treatment with BoNT/A. Randomization was performed using a randomization table and allocation was concealed. The randomization assignments were stored in an opaque envelope and were only accessed by the study coordinator. Study medication was stored in a locked refrigerator in the gastroenterology section. After an overnight

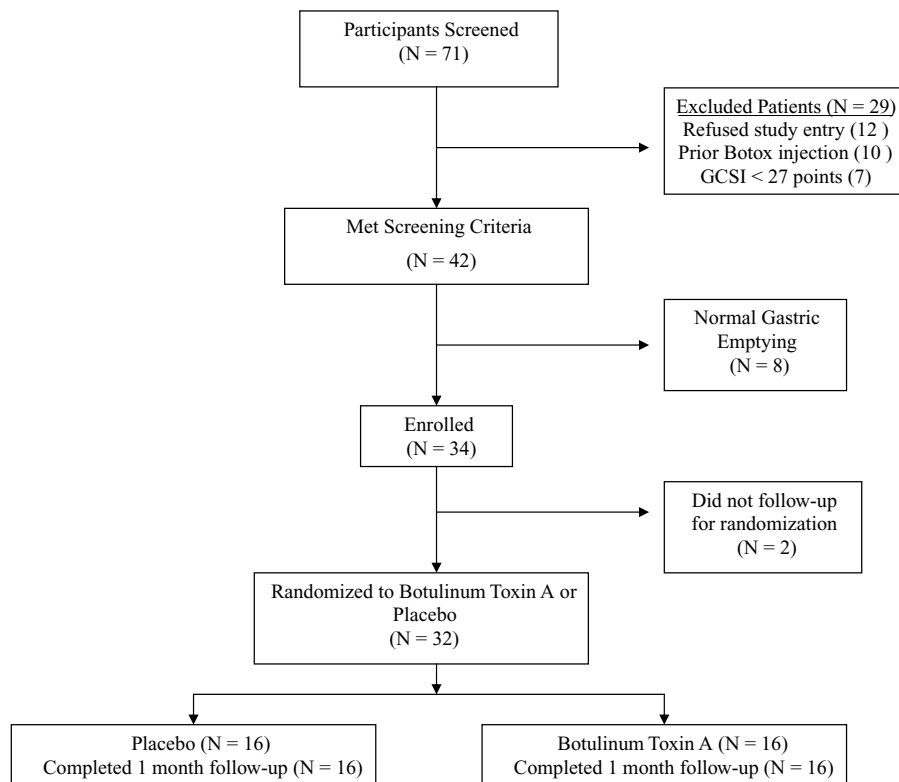


Figure 1. Study patient flowchart.

fast, patients underwent a standard upper endoscopy. During sedation, patients were monitored every 2.5 min for blood pressure and pulse, while oxygen saturation was monitored continuously. BoNT/A, in powder form, was reconstituted using a sterile, preservative-free diluent composed of 0.5 mg human albumin and 0.9 mg NaCl. The reconstituted preparation is clear and odorless and, thus, indistinguishable from saline. Study medication was loaded into a 5-mL syringe and connected to an injection catheter equipped with a 23-gauge, 6-mm retractable needle (Interject™, Boston Scientific, Natick, MA) outside the presence of the endoscopist and patient. Two hundred units of BoNT/A (total volume 5 mL) or an equal volume of sterile normal saline was then injected into the pylorus. One milliliter of study drug was injected at a time, circumferentially, into the pylorus after full air insufflation of the stomach. The tip of the injection catheter's needle was buried firmly into the pylorus before injection. The pyloric muscle was considered to be an area of defined muscular thickening surrounding the pyloric channel. Patients recovered until stable for discharge. The patient, the investigators injecting the study medication and administering the symptom questionnaire, and the physician reading the 1-month gastric emptying scan were blinded to the treatment assignment.

Follow-Up

Patients were evaluated 1 month after injection in our gastrointestinal (GI) research lab. The primary end point was the proportion of patients achieving a ≥ 9 -point reduction in the GCSI 1 month after injection. At the 1-month follow-up

visit, all patients underwent repeat GES. A secondary end point of the study was the improvement in gastric emptying 1 month after injection. We recorded whether any hospitalizations were required during the follow-up period. Patients were instructed not to start a new medication prior to the 1-month follow-up visits—any violation of this requirement was recorded.

Sample Size and Power Calculation

The percentage of patients in the active treatment group who were likely to achieve improvement 1 month after study drug injection was assumed to be 30% under the null hypothesis and 80% under the alternative hypothesis (11). Given a 2-sided alpha level of 0.05 and pooled variances, a sample size of 15 in the treatment group (BoNT/A) and 15 in the control group (saline) gave 81% power ($\beta = 0.19$) to detect a difference in symptom improvement (≥ 9 points on the GCSI) between the two groups of at least 50%. Very few dropouts were anticipated and 32 patients in total were recruited with an anticipated dropout rate of $\leq 5\%$.

Statistical Analysis

Continuous demographic and clinical characteristics are described using means and standard deviations, whereas categorical characteristics are described using frequencies and percentages. Demographic and baseline characteristics were compared between the treatment group and improvement (yes vs no) group using two-sample *t*-tests and χ^2 statistics for continuous and categorical measures, respectively.

The primary end point of ≥ 9 -point reduction in GCSI at 1 month was compared by treatment group using the χ^2 statistic. Changes in symptom scores and gastric retention from baseline were compared between treatment groups using two-sample *t*-tests. Pearson's correlation coefficients were used to estimate the degree to which the variance for change in the GCSI score could be accounted for by a change in gastric emptying from baseline to 1-month follow-up.

Statistical significance was taken at the 2-tailed 0.05 probability level. NCSS/PASS (Number Cruncher Statistical Systems, Kaysville, UT) was used to determine sample sizes, and SAS, version 9.1 (SAS Institute, Cary, NC) was used for statistical analysis.

RESULTS

In total 71 patients were screened for study inclusion (Fig. 1). Ultimately, 32 patients were randomized to receive BoNT/A (N = 16) or placebo (N = 16). Table 1 compares the characteristics of patients stratified by treatment allocation. The groups appeared to be well matched. At 1-month follow-up, 6 of 16 (37.5%) randomized to BoNT/A and 9 of 16 (56.3%) randomized to placebo achieved improvement as defined by our criteria. Table 2 demonstrates that both groups experienced a comparable reduction in both the GCSI and GVAS score at 1-month follow-up compared with baseline. The BoNT/A group demonstrated significant improvement in gastric emptying for both the 2- and 4-h measurements; however, the quantity of improvement from baseline was not

Table 1. Baseline Characteristics of Randomized Patients by Treatment Allocation

Variable	Botulinum Toxin (N = 16)	Placebo (N = 16)	P Value
Age (yr)	41.6 \pm 11.6	40.4 \pm 13.0	0.79
Gender (% male)	18.8	18.8	1.00
Gastroparesis etiology (N)			0.67
Idiopathic	6	7	
Diabetic	9	9	
Postsurgical	1	0	
Gastric retention (%)			
2 h	67 \pm 11.3	64 \pm 13.7	0.56
4 h	29 \pm 17.8	28 \pm 22.8	0.86
GCSI Score*	34.4 \pm 4.2	36.4 \pm 4.8	0.21
GVAS Score [†]	603 \pm 139	584 \pm 131	0.68
Ever hospitalized (N)	8	6	0.57
Previous therapy (N)			0.53
Metoclopramide	14	11	
Domperidone	3	2	
Erythromycin	2	3	
Tegaserod	2	2	
Proton pump inhibitor	8	9	0.77
QoL [‡]	3.4 \pm 0.6	3.4 \pm 0.8	0.88
Impact work/school score [§]	2.4 \pm 1.4	2.5 \pm 1.4	0.88

*Scored on a 0–45 scale; higher score, more severe symptoms.

[†]Scored on a 0–800 scale; higher score, more severe symptoms.

[‡]This was assessed for the prior 3 months; graded on a 0 (not at all) to 4 (very poor) scale.

[§]This was assessed for the prior 3 months; graded 0 (not at all) to 4 (severely).

statistically different from that seen in the placebo group. Table 3 provides individual data for all study participants. The change in gastric retention at either time point did not correlate with the change in the GCSI ($r = 0.01$ and $r = 0.13$ for the 2- and 4-h assessments, respectively).

As shown in Table 4, 15 of the 32 patients (46.9%) achieved symptomatic improvement (≥ 9 -point GCSI reduction), while 17 (53.1%) did not improve. Of the 15 patients who experienced improvement, 6 (40%) received BoNT/A, while 10 of 17 (58.8%) who failed to improve were randomized to this therapy ($P = 0.29$). In addition to treatment allocation, there were no other identifiable predictors of response. We sought to identify potential predictors of improvement with BoNT/A to determine whether a unique patient profile could be identified for which to recommend therapy. In fact, no unique predictor was found (Table 5).

Response by Gastroparesis Etiology

In the patients with diabetic gastroparesis, there was a reduction in the GCSI score by an average of 13.7 ± 16.3 points in those randomized to placebo and 11.4 ± 9.8 in the BoNT/A group ($P = 0.79$). In the nondiabetic subgroup, there was a reduction in the GCSI score by an average of 7.8 ± 10.1 points in the placebo group and 4.5 ± 8.5 in the BoNT/A group ($P = 0.45$). With respect to gastric emptying in the nondiabetic group, the 2-hr gastric retention decreased 11% with placebo and 17% with BoNT/A. Four-hour retention decreased 1% with placebo and 16% with BoNT/A. Despite the trends in favor of BoNT/A, neither of these relationships was statistically significant. In diabetics, differences in retention were less obvious. Two-hour retention decreased by 11% with placebo and 15% with BoNT/A. Four-hour changes were nearly identical (9% and 8%, respectively). Again, neither of these relationships was statistically significant.

Adverse Events

Adverse events included headache in both treatment groups (BoNT/A N = 6, placebo N = 3). Three patients in both groups complained of generalized fatigue. There were no acute allergic or neurological reactions. One patient in each group was hospitalized within 2 wk of injection for an exacerbation of symptoms of gastroparesis. One patient who received BoNT/A was admitted 48 h after treatment with a tachyarrhythmia and congestive heart failure. A similar episode occurred 8 months prior to randomization, and this was felt to be unrelated to medication. One patient randomized to placebo had a generalized tonic-clonic seizure 6 days later, and another receiving placebo had a severe motor vehicle accident resulting in traumatic brain injury. Both of these events were not felt to be related to the endoscopic procedure.

Therapeutic Changes

One patient who received placebo underwent implantation of a gastric electrical stimulator 3 wk after pyloric injection.

Table 2. Summary of the Effects of Placebo and Botulinum Toxin from Baseline to 1 Month After Injection

	Within Group				Between Group <i>P</i> Value
	Botulinum Toxin	<i>P</i> Value	Placebo	<i>P</i> Value	
Improved (%)*	37.5		56.3		0.29
GCSI Score	-6.8 ± 9.2	0.01	-10.1 ± 12.7	0.01	0.42
GVAS Score	-190 ± 228	0.01	-176 ± 256	0.02	0.88
% Gastric retention [†]					
2 h	-16.3 ± 22.9	0.02	-10.8 ± 20.6	0.08	0.52
4 h	-13.3 ± 18.0	0.01	-3.6 ± 25.5	0.62	0.27

*Improvement defined as a >9-point reduction in the score of the Gastroparesis Cardinal Symptom Index.

[†]Three patients randomized to placebo and one patient randomized to botulinum toxin did not complete a 1-month gastric emptying scan.

DISCUSSION

The treatment of delayed gastric emptying has remained a vexing problem for physicians. Dyspeptic symptoms such as nausea, early satiety, and bloating have a significant impact on QOL. Unfortunately, with the increasing prevalence of diabetes in the U.S. population, it is likely that more patients will develop this disorder in the future. The mainstay of treatment over the past 30 yr has remained prokinetic medication

alone or in combination with antiemetic therapy (22). These therapies are only marginally beneficial and have significant toxicities, which limit their attractiveness as long-term treatments. Also, tachyphylaxis frequently limits the long-term effectiveness of prokinetics (22). BoNT/A injection directly into the pylorus represents an attractive alternate treatment. The injection technique is simple and, theoretically, the neurolytic effects are local and long lasting (months). Preliminary results from uncontrolled trials have been exclusively

Table 3. Individual Response Data to Study Drug for Randomized Subjects

Patient Number	Randomization	GCSI Change*	Baseline GES (2 h) [†]	Baseline GES (4 h)	1-Month GES (2 h)	1-Month GES (4 h)
1	BoNT/A	5	0.70	0.42	0.67	0.29
2	Placebo	7	0.61	0.00	0.49	0.12
3	Placebo	0	0.50	0.10	N/A	N/A
4	Placebo	-15	0.66	0.13	0.49	0.09
5	BoNT/A	-1	0.59	0.09	0.53	0.00
6	BoNT/A	0	0.89	0.08	N/A	N/A
7	Placebo	-37	0.62	0.50	0.36	0.10
8	BoNT/A	-22	0.59	0.20	0.33	0.02
9	Placebo	-19	0.52	0.21	0.63	0.31
10	BoNT/A	-24	0.59	0.37	0.46	0.22
11	BoNT/A	0	0.67	0.46	0.77	0.54
12	Placebo	-15	0.88	0.61	0.84	0.58
13	BoNT/A	1	0.72	0.06	0.33	0.01
14	Placebo	-19	0.51	0.06	0.29	0.01
15	Placebo	-12	0.55	0.04	0.52	0.28
16	BoNT/A	-14	0.71	0.33	0.70	0.16
17	BoNT/A	-16	0.82	0.33	0.35	0.32
18	Placebo	-2	0.76	0.29	0.88	0.59
19	Placebo	-1	0.80	0.63	N/A	N/A
20	BoNT/A	-1	0.71	0.22	0.62	0.11
21	BoNT/A	4	0.80	0.67	0.06	0.01
22	BoNT/A	-14	0.51	0.13	0.58	.17
23	Placebo	-11	0.90	0.70	0.25	0.05
24	BoNT/A	-5	0.55	0.22	0.57	0.15
25	Placebo	4	0.65	0.30	0.68	0.38
26	BoNT/A	-3	0.77	0.56	0.48	0.20
27	Placebo	0	0.64	0.16	0.61	0.24
28	Placebo	-18	0.43	0.14	0.50	0.07
29	Placebo	-23	0.56	0.45	N/A	N/A
30	BoNT/A	-2	0.56	0.37	0.49	0.37
31	BoNT/A	-10	0.55	0.17	0.46	0.04
32	Placebo	9	0.72	0.16	0.50	0.01

*Represents 4-week score minus baseline score.

[†]Number represents fraction retained of egg meal at either 2 or 4 h after ingestion. Four patients did not complete a repeat gastric emptying test.

Table 4. Univariate Analysis of Predictors of Improvement at 1 Month

Variable	No Improvement		P Value
	Improved* (N = 15)	(N = 17)	
Received botulinum toxin A (%)	6 (40)	10 (58.8)	0.29
Age (yr)	37.9 ± 10.4	43.8 ± 13.2	0.17
Gender (m/f)	2/13	4/13	0.46
Baseline GCSI	35.9 ± 4.9	35.0 ± 4.4	0.60
Baseline GVAS	584 ± 123	603 ± 144	0.68
QoL	3.2 ± 0.8	3.5 ± 0.6	0.33
Ability to go to school/work	2.3 ± 1.4	2.6 ± 1.4	0.67
Gastroparesis etiology			0.51
Idiopathic	8	10	
Diabetic	7	6	
Postsurgical	0	1	
Baseline gastric retention (%)			
2 h	62.7 ± 14.2	68.5 ± 10.3	0.19
4 h	29.1 ± 20.1	28.2 ± 20.7	0.90

positive, and many gastroenterologists have incorporated this therapy into their practice. Our study represents the largest randomized, blinded study using BoNT/A for delayed gastric emptying.

Our primary end point was a reduction in gastroparesis symptoms 1 month after randomization. Our study demonstrated that BoNT/A accelerates gastric emptying, and this physiologic change did translate into a modest improvement in symptoms at 1 month (Table 2). However, very few patients achieved a meaningful improvement by our definition (a ≥9-point reduction in the GCSI score), and the benefit in gastric emptying and symptoms was no better with BoNT/A than with placebo.

There are potential reasons that the study was negative for the primary end point. First, it is possible that in patients with less severe disease (*i.e.*, a baseline GCSI <27) BoNT/A may have shown a benefit. Similarly, the threshold we chose for defining improvement may have been too

Table 5. Predictors of Improvement at 1 Month for the 16 Patients Randomized to Botulinum Toxin

Variable	No Improvement		P Value
	Improved* (N = 6)	(N = 10)	
Age (yr)	42.5 ± 7.6	41.1 ± 13.8	0.82
% male	16.7	20	0.87
Etiology of gastroparesis			0.42
Idiopathic	3	6	
Diabetic	3	3	
Postsurgical	0	1	
GCSI baseline	33.5 ± 4.6	34.9 ± 4.1	0.54
GVAS baseline	612 ± 94	599 ± 164	0.86
% Gastric retention 2 h	62.8 ± 11.5	69.6 ± 10.9	0.26
% Gastric retention 4 h	25.5 ± 10.0	31.5 ± 21.3	0.53
QOL	3.4 ± 0.5	3.4 ± 0.7	1.00
Ability to work/school	1.8 ± 1.7	2.8 ± 1.3	0.28

*Improvement defined as a >9-point reduction in the score of the Gastroparesis Cardinal Symptom Index.

Symptom*	None	Very Mild	Mild	Moderate	Severe	Very Severe
1. Nausea (feeling sick to your stomach as if you were going to vomit or throw up)	0	1	2	3	4	5
2. Retching (heaving as if to vomit, but nothing comes up)	0	1	2	3	4	5
3. Vomiting	0	1	2	3	4	5
4. Stomach fullness	0	1	2	3	4	5
5. Not able to finish a normal-sized meal	0	1	2	3	4	5
6. Feeling excessively full after meals	0	1	2	3	4	5
7. Loss of appetite	0	1	2	3	4	5
8. Bloating (feeling like you need to loosen your clothes)	0	1	2	3	4	5
9. Stomach or belly visibly larger	0	1	2	3	4	5

* For each symptom, the patient was asked to circle the number that best describes severity during the prior 2 weeks. If patient did not experience a symptom, asked to circle 0.

Figure 2. The Gastroparesis Cardinal Symptom Index. A score of ≥27 needed for study entry. Improvement defined as ≥9-point reduction at 1 month after study drug. (now included only in electronic format).

stringent. Second, several features of the injection process may have led to negative results. For instance, there are no data concerning the optimal depth and location of injection. Our method was adapted from the procedure used to inject the lower esophageal sphincter in patients with achalasia. (23, 24). It is possible that our method favors diffusion of toxin into the antral region, thereby hindering gastric emptying and favoring results toward the null. Technically challenging injections directed into the pyloric channel or proximal duodenal bulb may be more advantageous. Finally, it is possible, albeit unlikely, that higher doses may have been more effective. We chose a dose of BoNT/A (200 U), the highest used clinically, to induce sphincter relaxation in the GI tract. This maximized the potential to show an effect of active therapy. For achalasia, injection of 200 U into the lower esophageal sphincter is superior to 50 or 100 U for reducing symptoms (23).

Our study has several strengths. The study was blinded with concealed allocation. Both BoNT/A and saline placebo appear identical and, to the best of our knowledge, patients were unable to determine their assignment. All patients underwent GES using a standardized test meal in the same experienced nuclear laboratory. Care was taken to discontinue prokinetics in advance of the exam. Medical therapy remained unchanged until after the second gastric emptying study 1 month later. A potential weakness of our study was that our power calculation was based on an estimated response rate from BoNT/A of 80%. This estimate was based on the open-label results from Miller’s study, which had an approximately 70% response rate using either 100 or 200 U of BoNT/A (11). This

response rate estimate may have been too high, which would have an impact on sample size and power.

The results of our study (N = 32) are consistent with those of the previous two placebo-controlled randomized trials (N = 12 and N = 18, respectively) from the same institution despite several differences in the methodology (17, 18). Our study was a simple randomized trial, whereas one of their trials involved crossover methodology (17). Our study required a minimum GCSI score of 27 of 45, but both of their trials did not require a minimum GCSI and an *a priori* definition of improvement was not established. Our study used a total of 200 U of BoNT/A *versus* 100 U in their trials. We measured emptying over 4 h using a Tc-labeled egg meal, whereas they used a ¹⁴C-octanoate-labeled muffin meal. Despite these differences, one of their trials demonstrated an improvement in gastric emptying but not in symptoms relative to placebo (17), whereas the other, like ours, showed no benefit either in symptoms or in emptying rates over placebo (18).

Our study emphasizes the importance of a placebo-controlled study. If this had been another open-label study of BoNT/A, it would have been presented as showing a benefit of the therapy. However, this benefit was not superior to placebo. In fact, placebo not only improved symptoms, it improved gastric emptying as well. How can one account for these findings? Improvement in symptoms from placebo may be accounted for simply by enrollment in a clinical trial. Patients received considerably more attention and education about their disease by participating. They may have derived comfort from being seen at a tertiary care facility specializing in the treatment of gastroparesis. Improvement in gastric retention is more difficult to explain. Prokinetics were discontinued 48 h prior to gastric emptying both at baseline and at 1 month, but perhaps there was a residual effect. However, this effect should have influenced both studies, resulting in no net difference. A change in diet during the 1-month study period is not a plausible explanation either. We do not believe that saline injection, which should diffuse out of the gastric wall in a matter of minutes, improves gastric emptying. Future studies will be required to clarify the effects of saline placebo on gastric retention as seen in our study.

In conclusion, our study, consistent with the available controlled data, has demonstrated that intrapyloric injection of BoNT/A accelerates gastric emptying in patients with a delay, although this benefit was not superior to saline placebo. Also, in comparison to placebo, symptoms did not improve significantly. Therefore, in balance, we are unable to recommend BoNT/A therapy for widespread use in the treatment of delayed gastric emptying until more data are available.

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STUDY HIGHLIGHTS

What Is Current Knowledge

- Data on the use of intrapyloric botulinum toxin A (BoTN/A) have been primarily observational.
- Two small controlled trials did not demonstrate the efficacy of intrapyloric BoTN/A therapy.

What Is New Here

- In the largest randomized study to date, intrapyloric BoTN/A, at a dose of 200 U, was shown to reduce symptoms no greater than saline placebo.
- Intrapyloric BoTN/A accelerated gastric emptying of solids no greater than saline placebo.

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CONFLICT OF INTEREST

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