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ORIGINAL ARTICLE

Botulinum Toxin A Improves Symptoms of Gastroparesis

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Abstract

Background and Aims Pyloric injections of botulinum toxin A (BoNT/A) have shown benefit in open-label studies for patients with gastroparesis but not in randomized trials. We sought to examine the effectiveness of BoNT/A injections in a prospective open-label trial of patients with gastroparesis to assess specific symptom improvements over the course of 6 months. We also wanted to determine if specific biochemical measures including creatinine kinase, lactate dehydrogenase, aldolase, and C-reactive protein suggesting muscular injection could be used to predict successful response to pyloric injections of BoNT/A.

Methods Patients with gastroparesis undergoing pyloric BoNT/A injections for the treatment of symptomatic gastroparesis were enrolled. The patients completed the Gastroparesis Cardinal Symptom Index (GCSI) at the initial encounter and at 1, 3, and 6 months. Blood samples were collected before and 1 h after BoNT/A therapy.

Results We enrolled 34 patients for serum analysis of which 25 patients were available for symptom follow-up. Sixty-four percent of patients had an improvement in symptoms at 1 month. Patients with improved GCSI total score at 1 month had an improvement in most individual symptoms evaluated. For patients that improved at 1 month, this improvement often extended up to 6 months ($p = 0.04$). Serum measures studied did not correlate with clinical outcomes.

Conclusions BoNT/A therapy to the pylorus provided symptomatic improvement at 1 month in 64% of patients. For those patients initially responding, the improvement can last out to 6 months. The biochemical markers did not serve to predict the outcome of injections.

Keywords Gastroparesis · Botulinum toxin · Nausea · Vomiting · Abdominal pain · Gastrointestinal muscle injection

Introduction

Gastroparesis (GP) is a syndrome defined by delayed gastric emptying in the absence of gastric outlet obstruction or ulceration. Patients frequently present with a constellation of symptoms associated with an impaired quality of life, including nausea, vomiting, early satiety, postprandial fullness, bloating, and upper abdominal pain. Gastroparesis is more common than once thought. The age-adjusted prevalence of confirmed gastroparesis per 100,000 persons was

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37.8 for women and 9.6 for men in 2007 [1]. The syndrome is strongly associated with diabetes, with a prevalence of about 5% among type 1 diabetics and 1% among type 2 diabetics, compared with 0.2% among non-diabetic individuals [2]. However, the majority of cases may be idiopathic with no clear etiology for delayed gastric emptying [3]. The presence of gastroparesis symptoms in combination with objectively delayed gastric emptying makes the diagnosis of gastroparesis. The number of hospitalizations attributed to gastroparesis has increased [4]. As the cost of care and the incidence of diabetes, as well as gastroparesis, continue to rise in accordance with increasing rates of obesity, improvement in therapeutic strategies will become increasingly important.

First-line therapy for the management of gastroparesis includes replenishing electrolytes, nutritional support, dietary modifications, and improved glycemic control in diabetic patients [5–7]. Medical management typically involves a combination of prokinetic agents such as dopamine (D_2)-receptor antagonists (metoclopramide and domperidone) and antiemetic agents [5, 6]. However, the side effects of these medications, including extrapyramidal symptoms and potential QT interval prolongation, limit their long-term use [8, 9]. For refractory symptoms, one considers more invasive treatments such as gastric electric stimulation and/or pyloromyotomy. In more severe cases, enteral feeding via jejunostomy tube or dual jejunostomy and gastrostomy tubes has been shown to help symptoms and reduce hospitalizations [5]. Even with these options, many patients have refractory symptoms.

Endoscopic pyloric injection of botulinum toxin A (BoNT/A), an inhibitor of cholinergic neuromuscular transmission, is thought to decrease pylorospasm, improve gastric emptying, and to provide improvement in symptoms [10, 11]. Previous studies regarding the use of BoNT/A have had mixed results. Most open-label studies have found positive benefits with patients reporting a reduction in symptoms [12–14]. In one study that showed clinical improvement in 179 patients, increasing doses of BoNT/A (to 200 IU), patients under the age of 50, non-diabetic gastroparesis, and female patients were the most likely to respond [15]. However, two randomized control trials showed no benefit to BoNT/A over placebo [16, 17].

Although pyloric BoNT/A injection remains in use for patients with refractory gastroparesis, further research into the efficacy of BoNT/A injection is needed. There is currently no accepted parameter or marker to indicate a successful pyloric muscle injection of BoNT/A. Having such a marker may improve technique and lead to better patient response or at least notify physicians of an unsuccessful injection and the need for more immediate reinjection.

The goal of a successful intramuscular—rather than submucosal—injection of BoNT/A is to cause smooth muscle inhibition and pyloric relaxation. Creatine kinase (CK), C-reactive protein (CRP), lactate dehydrogenase (LDH), aldolase, myoglobin, troponin, and aspartate aminotransferase (AST) are the most useful serum markers of muscle injury [18–20]. We hypothesized that an increase in serum levels of CK, CRP, LDH, and/or aldolase would indicate a successful pyloric injection, defined as symptomatic improvement in gastroparesis with a decrease in their Gastroparesis Cardinal Symptom Index (GCSI) score.

The goal of this study was twofold. The first was to assess patients' response to BoNT/A injection over the course of 6 months in patients with diagnosed and confirmed gastroparesis. In particular, we focused on the change in symptoms in the first month post-procedure and then determined the duration of a successful response. No placebo group was utilized as this had been done previously and our focus was to examine the duration of effect that a patient may experience. Secondly, we set out to determine whether the release of muscle enzymes and inflammatory markers into the bloodstream following pyloric BoNT/A injection could be used as a measure of the procedure's success and correlate with symptom scores.

Materials and Methods

Patients undergoing BoNT/A therapy for gastroparesis were enrolled prospectively from February 2016 until February 2018 at Temple University Hospital, a tertiary care center for gastrointestinal disorders. Patients were symptomatic with refractory gastroparesis despite medical treatment. Delayed gastric emptying was typically demonstrated by scintigraphy revealing > 10% gastric retention of a solid-phase meal at 4 h [21]. As patients had confirmed gastroparesis by scintigraphy and symptoms, we sought to examine this group of patients and did not include patients with functional dyspepsia in the study. Medical therapy outside of the BoNT/A injections was left to the discretion of the referring physician, and no limitations on motility agents, including prokinetic agents, were imposed for inclusion.

Injection of BoNT/A to the pylorus was carried out with standard endoscopic procedures generally with propofol sedation. Physicians chose among Interject (Boston Scientific) or Carr-Locke (US Endoscopy) needles. All needles were 23 gauge and used to inject 200 IU of BoNT/A to the pylorus in five 40 IU aliquots circumferentially. The study was IRB-approved and met guidelines and regulations for the inclusion of human subjects. It was conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Blood was drawn before and 1 h after the procedure to evaluate for levels of CK, LDH, aldolase, and CRP. Serum

enzyme levels were analyzed in our clinical laboratory by standard methods. CK, LDH, and aldolase were measured by photometric assays of enzymatic activity, while CRP was determined by ELISA.

At the initial blood draw prior to the upper endoscopy and BoNT/A injection, patients completed the Gastroparesis Cardinal Symptom Index (GCSI), a validated questionnaire that quantifies the severity of nine gastroparesis symptoms over three symptom categories [22]. Patients were contacted by phone to again complete the survey at 1, 3, and 6 months. Only three researchers conducted phone interviews and followed an established script to reduce the potential for recall bias and ensure homogeneity in the collection of data. No patients received placebo treatment as this had previously been studied and was not the aim of our research at hand.

Results were reported as Mean ± SEM. The mean total GCSI ± SEM was calculated for all patients. Each individual symptom on the GCSI was also analyzed in the same manner as total scores and reported as the Mean ± SEM over the course of 6 months. To examine a correlation between serum levels and clinical response, patients were divided into either Improvement (lower GCSI score with a decrease of ≥ 1 point on the GCSI) or No Improvement (higher or no change in GCSI score) based on the GCSI total score at 1 month. As described in Pasricha 2015, a decrease of ≥ 1 point on the GCSI correlated with improvement [23]. In the rare instance where a patient could not be reached at 1 month, or his 1-month score matched his initial score, the 3-month score was used to see if the injections provided a delayed effect.

Total mean GCSI scores as well as individual symptoms scores over the course of 6 months were compared with one-way ANOVA with Bonferroni correction. Specific symptoms were compared between the initial survey and 1 month and compared with a Student's paired *t* test. Mean enzyme levels pre- and post-injection were calculated and compared with a Student's paired *t* test. For all statistical comparisons, significance was set to $p < 0.05$.

Results

Patient Characteristics

Thirty-four patients were enrolled for survey and blood analysis prior to the procedure. Of the 34 patients enrolled for blood analysis, 25 patients (21 female, 4 male) were able to be reached for symptomatic survey follow-up. Of the 25 patients enrolled, 12 had gastroparesis secondary to diabetes, while the remaining 13 had idiopathic gastroparesis. The average age of respondents was 43.4 ± 3.3 years. In accordance with our approved IRB and institutional policy, a monitoring program for adverse events was established. No adverse events were reported during the course of the study, and no peri-procedural complications were recorded.

Symptom Severity After BoNT/A Injections

Initial mean GCSI for all patients was 31.0 ± 1.7; this improved to 26.3 ± 2.2 ($p = 0.30$) at 1 month after pyloric injection of BoNT/A (Table 1 and Fig. 1). BoNT/A injections provided improvement in symptoms in 16 of 25 patients (64%) at 1 month as evidenced by a decrease in their GCSI

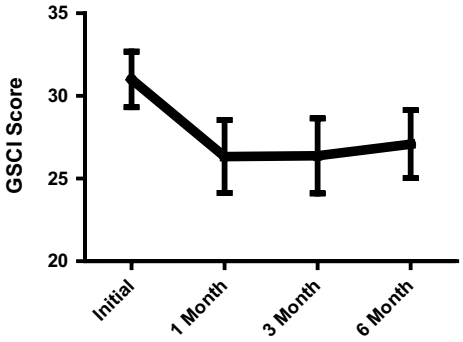

Fig. 1 Gastroparesis Cardinal Symptom Index for all patients over the course of the study. Data are reported as mean GCSI ± SEM. *$p < 0.05$

Table 1 Patient demographics and Gastroparesis Cardinal Symptom Index

	Age	Initial	1 month	3 month	6 month	*p*
All comers	43.4 ± 3.3	31.0 ± 1.7	26.3 ± 2.2	26.4 ± 2.3	27.1 ± 2.1	*0.30*
(21F, 4M)	(21F, 4M)	(21F, 4M)	(17F, 4M)	(20F, 4M)	(19F, 4M)	
Improvement	42.9 ± 4.2	32.9 ± 1.9	25.0 ± 2.9	23.8 ± 2.7	25.5 ± 2.1	*0.04**
(13F, 3M)	(13F, 3M)	(13F, 3M)	(11F, 3M)	(13F, 3M)	(13F, 3M)	
No Improvement	44.1 ± 5.8	27.6 ± 3.1	29.0 ± 3.4	31.5 ± 3.6	30.7 ± 4.8	*0.86*
(8F, 1M)	(8F, 1M)	(8F, 1M)	(6F, 1M)	(7F, 1M)	(6F, 1M)	

All *p* values are given in italics

Patient demographics and Gastroparesis Cardinal Symptom Index scores for the duration of the study

*Indicates significance ($p < 0.05$)

score ($p = 0.04$). Nine of 16 (56%) patients with improvement in our study were diabetic, and 11 of 16 (69%) were younger than 50 years old. The response rate in the diabetic group was 69% compared to 58% in the idiopathic group (9/13 vs. 7/12, respectively). The response in the < 50-year-old group was 69% compared to 56% in those ≥ 50 years. The response in the females was 62%, whereas it was 75% in males although the study only contained four men in total.

Individual symptoms were compared from initial scores to 1 month (Table 2). Of the 25 patients available for follow-up, a statistically significant reduction in the following symptoms was observed at 1 month (Table 2): retching ($p = 0.02$), stomach fullness ($p = 0.05$), feeling excessively full ($p = 0.03$), bloating ($p = 0.01$), and stomach visibly larger ($p = 0.01$).

In general, patients experienced a decrease in symptoms lasting 3 months, and, in many of these patients, until 6 months, although this did not reach statistical significance for all comers ($p = 0.30$). At 3 and 6 months, the mean GCSI for all patients was 26.4 ± 2.3 and 27.1 ± 2.1, respectively (Table 1 and Fig. 1 ($p = 0.30$)). While patients tended to improve over the course of the study and for a longer duration than expected, this improvement did not reach statistical significance for the entire treated patient group.

Subjects were grouped into either "Improvement" or "No Improvement" based on the clinical score at 1 month (or at 3 months in the rare situation where 1-month data were not available or equivocal as above) (Table 1 and Fig. 1). For patients with Improvement, the initial mean GCSI was 32.2 ± 1.8 and at 1 month improved to 24.1 ± 2.6. At 1 month, this group had improvement in nearly all symptoms: nausea ($p < 0.01$), retching ($p < 0.01$), vomiting ($p < 0.01$), stomach fullness ($p < 0.01$), feeling excessively full ($p < 0.01$), bloating ($p < 0.01$), and stomach visibly larger ($p = 0.01$). No relief or statistically significant change was seen for the symptoms of loss of appetite and inability to finish a meal. In contrast, patients who reported No Improvement had a mean initial GCSI of 27.1 ± 3.4 that rose to a mean of 28.7 ± 4.0 at 1 month. At 1 month, these patients also had a statistically significant reduction in nausea ($p < 0.01$) and feeling excessively full ($p = 0.03$).

Patients with Improvement at 1 month showed a statistically significant improvement over the course of the 6 months ($p = 0.04$) with the GCSI being 23.8 ± 2.7 at 3 months and 25.5 ± 2.1 at 6 months. Individual symptom scores were also tracked over this period and reported in Table 3. Over the course of 6 months, for patients in the Improvement group, there was a statistically significant reduction in nausea ($p = 0.02$). In contrast, patients who reported No Improvement at 1 month had a mean GCSI of 31.5 ± 3.6 at 3 months and finally at 6 months it was 30.7 ± 4.8. Among the nine patients with No Improvement, there was no statistically significant difference over the 6 months ($p = 0.86$).

Biochemical Measures

Thirty-four patients were enrolled for analysis of blood serum levels (Table 4 and Fig. 2). The mean age was 42.6 ± 2.8 years. For all patients, mean serum levels pre- and post-procedure are reported in Table 4. None of the evaluated changes in serum markers pre- and post-procedure were statistically significant among the 34 patients receiving Botox. When the 25 patients with outcome data available were sorted by clinical response, Improvement versus No Improvement, there was no difference in the laboratory measures either.

Table 2 Individual symptoms of GCSI from initial to 1 month

Symptom from GCSI survey	All comers			Improvement			No Improvement		
	Initial	1 month	*p*	Initial	1 month	*p*	Initial	1 month	*p*
Nausea	3.8 ± 0.2	3.1 ± 0.3	*0.14*	4.3 ± 0.2	2.8 ± 0.4	*< 0.01**	2.9 ± 0.5	3.9 ± 0.6	*< 0.01**
Retching	2.4 ± 0.4	2.0 ± 0.4	*0.02**	2.8 ± 0.4	1.8 ± 0.5	*< 0.01**	1.8 ± 0.6	2.4 ± 0.8	*0.46*
Vomiting	2.2 ± 0.4	1.3 ± 0.4	*0.07*	2.2 ± 0.5	1.0 ± 0.4	*< 0.01**	2.1 ± 0.7	2.0 ± 0.9	*1.00*
Stomach fullness	4.2 ± 0.2	3.7 ± 0.3	*0.05**	4.4 ± 0.3	3.5 ± 0.4	*< 0.01**	3.8 ± 0.3	4.0 ± 0.4	*0.17*
Not able to finish a meal	3.9 ± 0.2	3.7 ± 0.3	*0.23*	4.1 ± 0.3	3.6 ± 0.5	*0.05*	3.7 ± 0.3	3.9 ± 0.5	*0.20*
Feeling excessively full after meals	4.3 ± 0.2	3.6 ± 0.3	*0.03**	4.5 ± 0.3	3.3 ± 0.4	*< 0.01**	3.9 ± 0.3	4.3 ± 0.5	*0.03**
Loss of appetite	3.2 ± 0.3	2.9 ± 0.4	*0.22*	3.6 ± 0.4	3.1 ± 0.5	*0.07*	2.7 ± 0.6	2.3 ± 0.6	*0.88*
Bloating	3.8 ± 0.3	3.2 ± 0.4	*0.01**	4.0 ± 0.4	3.1 ± 0.4	*< 0.01**	3.3 ± 0.5	3.3 ± 0.7	*0.65*
Stomach visibly larger	3.5 ± 0.3	2.9 ± 0.3	*0.01**	3.5 ± 0.5	2.8 ± 0.4	*0.01**	3.4 ± 0.4	3.0 ± 0.6	*0.51*

All *p* values are given in italics

Individual symptom scores for each aspect of the Gastroparesis Cardinal Symptom Index from initial to 1 month

*Indicates significance ($p < 0.05$)

Table 3 Individual symptoms from GCSI

Symptom from GCSI survey	All comers					Improvement					No Improvement				
	Initial $n=25$	1 month $n=21$	3 months $n=24$	6 months $n=23$	p	Initial $n=16$	1 month $n=14$	3 months $n=16$	6 months $n=16$	p	Initial $n=9$	1 month $n=7$	3 months $n=8$	6 months $n=7$	p
Nausea	3.8 ± 0.2	3.1 ± 0.3	3.3 ± 0.3	3.3 ± 0.3	*0.56*	4.3 ± 0.2	2.8 ± 0.4	3.1 ± 0.4	3.1 ± 0.4	*0.02**	2.9 ± 0.5	3.9 ± 0.6	3.8 ± 0.4	3.9 ± 0.7	*0.47*
Retching	2.4 ± 0.2	2.0 ± 0.4	1.7 ± 0.4	2.0 ± 0.4	*0.97*	2.8 ± 0.4	1.8 ± 0.5	1.2 ± 0.4	1.7 ± 0.4	*0.07*	1.8 ± 0.6	2.4 ± 0.8	2.6 ± 0.7	2.9 ± 0.7	*0.69*
Vomiting	2.2 ± 0.4	1.3 ± 0.4	2.1 ± 0.4	1.7 ± 0.4	*0.93*	2.2 ± 0.5	1.0 ± 0.4	1.9 ± 0.5	1.2 ± 0.4	*0.22*	2.1 ± 0.7	2.0 ± 2.9	2.5 ± 0.8	2.9 ± 0.7	*0.96*
Stomach fullness	4.2 ± 0.2	3.7 ± 0.3	3.6 ± 0.3	3.7 ± 0.3	*0.75*	4.4 ± 0.3	3.5 ± 0.4	3.4 ± 0.4	3.7 ± 0.3	*0.15*	3.8 ± 0.3	4.0 ± 0.4	4.1 ± 0.4	3.7 ± 0.6	*0.89*
Not able to finish a meal	3.9 ± 0.2	3.7 ± 0.3	3.4 ± 0.3	3.4 ± 0.3	*0.23*	4.1 ± 0.3	3.6 ± 0.5	3.0 ± 0.4	3.3 ± 0.4	*0.24*	3.7 ± 0.3	3.9 ± 0.5	4.1 ± 0.3	3.7 ± 0.5	*0.82*
Feeling excessively full after meals	4.3 ± 0.2	3.6 ± 0.3	3.8 ± 0.3	3.8 ± 0.3	*0.76*	4.5 ± 0.3	3.3 ± 0.4	3.4 ± 0.4	3.8 ± 0.3	*0.11*	3.9 ± 0.3	4.3 ± 0.5	4.4 ± 0.3	3.9 ± 0.5	*0.69*
Loss of appetite	3.2 ± 0.3	2.9 ± 0.4	2.7 ± 0.3	2.7 ± 0.3	*0.81*	3.6 ± 0.4	3.1 ± 0.5	2.6 ± 0.4	2.6 ± 0.4	*0.28*	2.7 ± 0.6	2.3 ± 0.6	2.9 ± 0.4	3.0 ± 0.5	*0.82*
Bloating	3.8 ± 0.3	3.2 ± 0.4	3.1 ± 0.3	3.3 ± 0.4	*0.87*	4.0 ± 0.4	3.1 ± 0.4	2.9 ± 0.4	3.1 ± 0.5	*0.28*	3.3 ± 0.5	3.3 ± 0.7	3.5 ± 0.4	3.6 ± 0.5	*0.98*
Stomach visibly larger	3.5 ± 0.3	2.9 ± 0.3	2.8 ± 0.4	3.0 ± 0.4	*0.88*	3.5 ± 0.5	2.8 ± 0.4	2.4 ± 0.5	2.9 ± 0.4	*0.38*	3.4 ± 0.4	3.0 ± 0.6	3.6 ± 0.5	3.3 ± 0.7	*0.88*

All p values are given in italics

Individual symptoms from the Gastroparesis Cardinal Symptom Index are tracked over the course of 6 months

*Indicates significance ($p < 0.05$)

Table 4 Biochemical measures

	Age	Pre-CK (U/L)	Post-CK (U/L)	*p*	Pre-LDH (U/L)	Post-LDH (U/L)	*p*	Pre-aldolase (U/L)	Post-aldolase (U/L)	*p*	Pre-CRP (mg/L)	Post-CRP (mg/L)	*p*
All comers ($n=29$–34)	42.6 ± 2.8	104.6 ± 10.9	100.7 ± 10.3	*0.68*	214.2 ± 16.0	217.3 ± 21.0	*0.92*	8.8 ± 1.0	8.2 ± 0.9	*0.51*	1.6 ± 0.6	1.7 ± 0.7	*0.57*
Improvement ($n=13$–16)	42.9 ± 4.2	100.0 ± 14.5	88.3 ± 10.7	*0.38*	247.9 ± 30.9	218.0 ± 29.8	*0.43*	10.3 ± 1.7	9.3 ± 1.6	*0.55*	1.1 ± 0.4	1.1 ± 0.4	*0.58*
No Improvement ($n=8$–9)	44.1 ± 5.8	105.4 ± 17.2	99.2 ± 13.7	*0.59*	209.8 ± 16.2	216.0 ± 39.2	*0.88*	8.3 ± 1.0	7.1 ± 0.9	*0.36*	0.8 ± 0.2	0.6 ± 0.2	*0.15*

All *p* values are given in italics

Measures of CK, LDH, aldolase, and CRP before and 1 h after injection of BoNT/A to the pylorus

*Indicates significance ($p<0.05$)

Discussion

This open-label study of botulinum toxin injection into the pylorus provides valuable information for gastroparesis patients being considered for this treatment. Our study found a positive symptomatic response to the BoNT/A injections with 64% of patients with gastroparesis in our study reporting a reduction in symptoms as determined by the Gastroparesis Cardinal Symptom Index (GCSI). In line with mathematical modeling outlined in previous studies, a decrease of ≥ 1 point on the GCSI was considered symptomatic improvement [23]. Overall, patients showed a 15% reduction in symptoms at both 1 and 3 months and a 13% reduction at 6 months. Many individual symptoms including retching, stomach fullness, feeling excessively full, bloating, and stomach visibly larger had improvement. Importantly, if one responds to Botox injection initially at 1 month, many patients continue with this improvement over a 3–6-month period. We did not compare the findings with a placebo group as this had been done previously and was not the intent of our study [17].

When the patients were segregated by response, those with improved symptoms had a 24% reduction in symptoms at 1 month. This trend was also seen through 6 months with the most improved clinical score being found at the 3-month mark (28% reduction; $p=0.04$). Patients who did not demonstrate improvement had a 14% increase in symptoms at 3 months ($p=0.86$). Of note, the patients who did not have clinical improvement had a lower GCSI initial score than those who did show response to BoNT/A injections, 27.6 ± 3.1 compared to 32.9 ± 1.9 ($p=0.13$).

Two previous open-label studies of equal or greater patient enrollment had a less positive response than our trial. Bromer et al. reported that 42.9% of 63 patients had improved symptoms, and Arts showed a 45% response rate in 20 patients [12, 13]. Arts et al. administered 100 IU of BoNT/A, while Bromer et al. used both 100 and 200 IU [12, 13]. Our findings were similar to the retrospective study by Coleski et al. that showed improvement in 51.4% of patients, with an increase to 76.7% in patients that received 200 IU of BoNT/A [15]. As in the Coleski et al. study, our study also showed better results for diabetic patients and patients under 50 years old. Nine of 16 (56%) patients with improvement in our study were diabetic, and 11 of 16 (69%) were younger than 50 years old. Overall, 69% of diabetic patients responded to therapy as did 69% of patients < 50 years old.

In regard to individual symptoms, of the 25 patients available for follow-up, a statistically significant reduction in the following symptoms was observed at 1 month (Table 2): retching, stomach fullness, feeling excessively

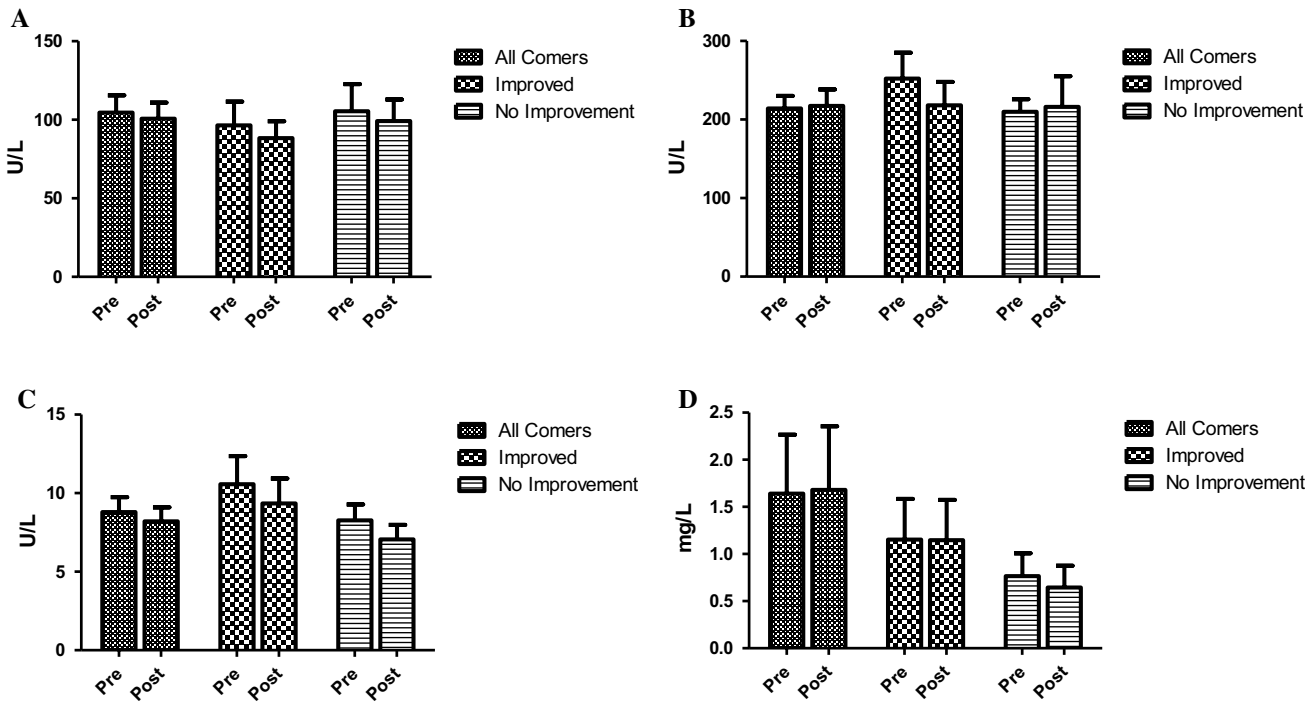

Fig. 2 Biochemical measures before and 1 h after injection of BoNT/A. **a** CK, **b** LDH, **c** aldolase, **d** CRP. Data are reported as mean ± SEM. $^{*}p < 0.05$

full, bloating, and stomach visibly larger. Patients sorted into the Improvement category also saw a statistically significant reduction in these symptoms as well as nausea and vomiting. No relief or statistically significant change was seen for the symptoms of loss of appetite and inability to finish a meal. Our study agrees with earlier investigations that showed that stomach fullness and bloating were significantly improved with BoNT/A injections [8, 13, 16]. However, it is difficult to draw direct comparisons to these previous studies because each study used a different assessment of symptoms.

The duration of clinical improvement for some patients lasted longer than expected, in some, up to 6 months. Prior consensus in the field was that the duration of BoNT/A's effect on the pylorus lasted about 3 months [12, 13]. Four studies have followed patients beyond 4 months but contain only 13 patients totally [24–27]. Our study suggests that clinical improvement may last as long as 6 months in those that have an initial favorable response. To date, our study is the largest in terms of number of patients to follow outcomes for so long after pyloric BoNT/A injection.

We sought to find an indicator of good pyloric injection that could help predict a clinical response. Successful intrapyloric injection can be complicated by the variable size of the pylorus, peristalsis, respirations, and variations in the endoscopic technique. Further, there are no data guiding practitioners as to the target depth or location of the injection [17]. Recently, it was shown that EndoFlip could be utilized to assess the pylorus for cross-sectional area, diameter, and distensibility [28]. Decreases in these measures correlated with higher scores on the GCSI [28]. The effects of BoNT/A injection are not immediate, and a measure to predict successful injection during or right after the procedure would be beneficial. We selected biochemical measures of muscle injury including CK, LDH, aldolase, and CRP. We had laboratory data from 34 patients that had been enrolled in the study. For all patients, and those with and without clinical improvement, there was no change in measures of any of the enzymes after BoNT/A injection. Many circumstances could account for the lack of change in biochemical markers including the small gauge of the needle as well as the timing of the second blood test as it may have occurred too soon after injection to detect muscle injury. Lastly, our laboratory assays may not be sensitive enough to detect small changes in marker levels.

Our study is not without limitations. We enrolled 34 patients for blood analysis, but only 25 were available for follow-up. Increasing the sample size might yield more significant results. It would be interesting to delay the second blood draw to see if a rise in enzymes could be captured later. We did not obtain follow-up gastric emptying tests after treatment to see if improved gastric emptying was associated with improved symptoms. Ideally, a randomized control trial with a placebo group would provide the strongest

evidence to evaluate the efficacy of BoNT/A injections. However, despite the limitations of our study, it is one of the few studies to look at both idiopathic and diabetic gastroparesis in one cohort and the largest study to follow patient outcomes to 6 months.

In conclusion, our study examined 25 patients for 6 months after BoNT/A injection for the treatment of gastroparesis. We found a surprisingly high rate of response to the BoNT/A injections at 64% with a trend for improvement in symptoms for as long as 6 months. Levels of CK, LDH, aldolase, and CRP were not found to be useful measures of successful symptomatic response. Given the procedure's low-risk profile and the promising results of our study, we suggest a larger trial of BoNT/A injections for patients that have not been helped by other modalities. Further research into gastroparesis and treatments remains important given the rise in both diagnosis and related hospitalizations.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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