Dig Dis Sci (2009) 54:2634–2642
DOI 10.1007/s10620-008-0660-9

ORIGINAL ARTICLE

Factors Associated with Symptom Response to Pyloric Injection of Botulinum Toxin in a Large Series of Gastroparesis Patients

Radoslav Coleski · Michelle A. Anderson · William L. Hasler

Received: 22 October 2008 / Accepted: 28 November 2008 / Published online: 30 January 2009

Abstract Case series report symptom reductions after pyloric botulinum toxin injection in gastroparesis, but small controlled trials show no benefit. Factors that enhance response to therapy are undefined. A retrospective analysis of 179 gastroparetics undergoing pyloric botulinum toxin injection from 2001 to 2007 assessed responses relating to drug dosing, demographic factors, comorbidities, and gastric function. Overall, there was a decrease in gastroparetic symptoms 1–4 months after pyloric botulinum toxin injection in 92 patients (51.4%). Increasing the botulinum toxin dose significantly improved clinical responses of patients who provided information on symptoms after therapy (100 units: 54.2%; 200 units: 76.7%; $P = 0.02$). Other factors that improved response to botulinum toxin included female gender, age <50 years, and nondiabetic nonpostsurgical etiology (all $P < 0.05$). Eighty-seven patients received 307 follow-up injections. A clinical response to a second injection was observed in 73.4% of evaluable patients. In conclusion, responses to pyloric botulinum toxin depended on dose and were maintained on repeat injection. Subgroup analyses defined subgroups likely to benefit. These findings provide the foundation for large, controlled trials of high-dose botulinum toxin in selected gastroparesis subsets.

Keywords Gastroparesis · Gastric emptying · Botulinum toxin · Diabetes mellitus · Nausea and vomiting

R. Coleski · M. A. Anderson · W. L. Hasler (✉)
Division of Gastroenterology, Department of Internal Medicine, University of Michigan Health System, 3912 Taubman Center, 5362, Ann Arbor, MI 48109, USA
e-mail: whasler@umich.edu

Introduction

Most management protocols for gastroparesis rely on agents that correct delays in gastric emptying [1, 2]. Most such drugs relieve gastric retention by stimulating propulsive phasic antral pressure waves [3]. However, increases in pyloric tone and phasic contractions in subsets of gastroparesis patients have raised the possibility that a component of the delay in gastric emptying in this disorder stems from pylorospasm [4].

Botulinum toxin is a bacterial neurotoxin that binds to presynaptic cholinergic receptors and impairs neuronal acetylcholine release [5]. On manometric and scintigraphic testing, intrapyloric botulinum toxin injection reduces pyloric motor activity and accelerates gastric emptying in many gastroparesis patients [6–11]. Uncontrolled case series report symptom reductions after pyloric botulinum toxin injection in patients with refractory gastroparesis [7–15]. However, two small controlled trials have observed no benefits from this therapy compared with placebo [16, 17]. The ability of either controlled study to detect a treatment benefit may have been hampered by enrollment of heterogeneous gastroparesis patient populations that might have exhibited differential responsiveness to botulinum toxin therapy.

The primary aim of the present investigation was to delineate which clinical factors are associated with symptom reductions in gastroparesis patients treated with pyloric injection of botulinum toxin. A retrospective analysis was performed on all individuals with gastroparesis who underwent botulinum toxin treatment from October 2001 through May 2007 at a large tertiary medical center specializing in the care of gastrointestinal motility disorders. The patient population exhibited an expansive range of clinical characteristics and represents the largest

population from one institution reported to have received botulinum toxin therapy. Clinical responses, measured by decreased symptoms and changes in body weight 1–4 months after injection, were related to botulinum toxin dose to determine if higher doses produced greater benefits. Multivariate and subgroup analyses were performed relating botulinum toxin dose, demographic features (gender and age), clinical variables (etiology of gastroparesis and opiate use), and gastric functional parameters (rates of gastric emptying on scintigraphy and gastric food retention on endoscopy) to clinical response to assess if selected gastroparesis subsets might be more responsive to botulinum toxin therapy. A secondary aim of this investigation was to quantify responses to repeat botulinum toxin therapy to evaluate its long-term efficacy and development of tolerance. Through these analyses, we hoped to define factors which are associated with improved clinical response to pyloric botulinum toxin injection. Based on these findings, large, placebo-controlled trials could be designed to investigate the benefits of botulinum toxin therapy in selected gastroparesis subsets more likely to show improvement.

Methods

Patient Population

Patients undergoing pyloric botulinum toxin injection between October 25, 2001 and May 31, 2007 at the University of Michigan Hospital were identified by retrospective review of the CareWeb clinical care database and of the Medical Procedures Unit endoscopy database. In all patients, the diagnosis of gastroparesis was previously established by gastric emptying scintigraphy at the University of Michigan Hospital or referring medical centers. This investigation was approved by the University of Michigan Medical Center Institutional Review Board, which granted a waiver of informed consent to access the relevant databases.

Definition of Clinical Variables

Cases involving pyloric botulinum toxin injection were identified from the Medical Procedures Unit endoscopy database. Botulinum toxin doses and the presence of retained intragastric food were determined by review of endoscopy reports. Information regarding gender, age at time of first injection, opiate medication use at time of the outpatient visit preceding the injection, and rate of solid gastric emptying were obtained from the CareWeb clinical database. The etiology of gastroparesis was determined by the opinion of the referring outpatient gastroenterologist. Patients were considered to have diabetic gastroparesis if diabetes predated the onset of their gastrointestinal symptoms. Postsurgical gastroparesis was defined as disease developing after performance of an operation with intentional vagal sectioning (e.g., peptic ulcer surgery) or unintended vagal injury (e.g., fundoplication). All other cases were included in a nondiabetic nonsurgical group. Outpatient notes dictated between 1 and 4 months after injection were reviewed to determine response to therapy and to compare body weights pre and post treatment with botulinum toxin. A positive response was defined when the outpatient note specifically commented about reduced symptoms of gastroparesis that were attributed to the botulinum toxin injection. In most instances, nausea and/or vomiting were the symptoms that improved. In some individuals, botulinum toxin reduced bloating, early satiety, fullness, or discomfort. For this investigation, no distinction was made as to which symptoms specifically improved. A negative response was defined when the outpatient note specifically commented that botulinum toxin treatment produced no symptom reduction. An unknown response was defined when no mention was made of the response to pyloric injection therapy.

Continuous variables analyzed included age, gastric emptying at 2 h, and change in weight. Gastric emptying rates were compared only for individuals who had undergone scintigraphy after consuming a scrambled eggs meal and for which a value of emptying at 2 h was recorded. This was the primary emptying measure employed by the University of Michigan Department of Nuclear Medicine from 2001 to 2007. Variables with continuous ranges were further stratified to facilitate binary comparisons of the data. Age was stratified into those patients $\geq$50 and <50 years old. Patients were stratified into those with $\leq$20% and >20% gastric emptying at 2 h. Lastly, patients were stratified into those with weight loss, lack of weight loss, or unknown change in weight after pyloric injection therapy (usually secondary to lack of recorded measurement).

The final data analyses focused on repeat pyloric injections of botulinum toxin. Numbers of patients who underwent repeat injection were related to the initial botulinum toxin dose. Percentages of patients undergoing repeat injection who responded to the initial injection, did not respond, or who had an unknown response were compared. Response rates to repeat injections were compared for each botulinum toxin dose. Percentages of patients who received increased or decreased doses on repeat injection versus initial therapy were compared. Finally, loss of response to repeat botulinum toxin injection was assessed to determine the rate of development of tolerance to its therapeutic benefits. For this measure, persistence of responsiveness was recorded when clinical improvements were reported for two or more injections of

the same dose of botulinum toxin. Loss of response was defined when subjects with relief after initial injection therapy then reported no benefit from botulinum toxin dosing at the same or a higher dose of drug on subsequent treatment.

Statistical Analysis

Descriptive statistics are expressed as mean ± standard error of the mean (SEM). Two-tailed Student's *t*-testing or single-factor analysis of variance (ANOVA) was performed to compare results relating to variables with continuous values (age, gastric emptying rate, change in weight). The Tukey honestly significant differences (HSD) method was employed to test if absolute differences between any two sample means were significantly different. Differences in dose effects for botulinum toxin were determined by univariate analysis using chi-squared testing and by employing multivariate logistic regression controlling for age, gender, opiate use, etiology, gastric emptying rate, and retained food on endoscopy. Univariate analysis and multivariate logistic regression also was performed to determine the effects of predictive variables on symptom response to pyloric botulinum toxin injection. Subgroup analysis was performed to determine if response to dose varied among distinct groups. Univariate analysis and multivariate linear regression were used to examine which explanatory variables predicted changes in body weight following treatment. Statistical significance was defined by *P*-values of <0.05.

Results

Descriptions of Demographic Variables in Gastroparesis Patients

One hundred and seventy-nine gastroparesis patients underwent 486 pyloric botulinum toxin injections from October 25, 2001 through May 31, 2007. Eighty-two patients received an initial botulinum toxin dose of 100 units, while 43 received 150 units and 54 received 200 units. One hundred and thirty-two were women and 47 were men. Mean age was 44.2 ± 1.0 years; 71% of patients were <50 years old. Opiate use was noted for 55 patients, whereas 124 patients had no record of opiate use. Etiologies of gastroparesis were diabetic in 81 patients, postsurgical in 16 patients, and nondiabetic nonpostsurgical in 82 patients. Of this latter group, 76 individuals had no other systemic disease and likely had idiopathic gastroparesis. Systemic diseases in the other six individuals included systemic lupus erythematosus in one, sarcoidosis in one, multiple sclerosis in two, human immunodeficiency virus infection in one, and prior abdominal irradiation in one patient. Gastric emptying rates at 2 h were quantified for 90 patients. In these individuals, the mean emptying rate was 28.6 ± 2.1%, with 34 patients exhibiting severe gastroparesis (≤20% emptying at 2 h). Retained food on initial endoscopy was observed in 43 patients and was absent in 136 patients. Comparisons of patients receiving different botulinum toxin doses confirmed that the other clinical variables did not influence dose selection (Table 1).

Table 1 Comparisons of clinical variables among patients receiving different botulinum toxin doses

Variable		100 Units	150 Units	200 Units	*P*-Value
Continuous	Age (years)	44.4 ± 1.5	46.2 ± 2.3	42.3 ± 1.7	0.38
	Gastric emptying (% at 2 h)	25.7 ± 2.6	36.5 ± 5.2	27.1 ± 4.1	0.11
Categorical	Gender	Male, 24 (29%)	Male, 8 (19%)	Male, 16 (30%)	0.38
		Female, 58 (71%)	Female, 35 (82%)	Female, 38 (70%)	
	Age	≥50 years, 23 (28%)	≥50 years, 18 (42%)	≥50 years, 11 (20%)	0.07
		<50 years, 59 (72%)	<50 years, 25 (58%)	<50 years, 43 (80%)	
	Opiates	Yes, 26 (32%)	Yes, 13 (30%)	Yes, 16 (30%)	0.96
		No, 56 (68%)	No, 30 (70%)	No, 38 (70%)	
	Etiology	DM, 40 (49%)	DM, 15 (35%)	DM, 26 (48%)	0.26
		PS, 9 (11%)	PS, 2 (5%)	PS, 5 (9%)	
		Non-DM non-PS, 33 (40%)	Non-DM non-PS, 26 (60%)	Non-DM non-PS, 23 (43%)	
	Gastric emptying	≤20%, 20 (43%)	≤20%, 5 (24%)	≤20%, 9 (41%)	0.32
		>20%, 27 (57%)	>20%, 16 (76%)	>20%, 13 (59%)	
	Retained food	Yes, 20 (24%)	Yes, 10 (23%)	Yes, 13 (24%)	0.99
		No, 62 (76%)	No, 33 (77%)	No, 41 (76%)	

DM diabetic etiology, *PS* postsurgical etiology, *Non-DM non-PS* nondiabetic nonpostsurgical etiology

Factors Associated with Response to Initial Pyloric Botulinum Toxin Injection

A reduction in gastroparesis symptoms 1–4 months after initial injection was reported in 92 patients (51.4%), while 57 patients (31.8%) were reported no benefit from pyloric botulinum toxin therapy. No report of clinical outcome of therapy was recorded for 30 patients (16.8%). Weight gain after botulinum toxin injection was reported for 71 patients (39.7%), no change was recorded for 18 patients (10.1%), and weight loss was reported for 40 patients (22.3%). The status of weight change after botulinum toxin therapy was not recorded for 50 patients (27.9%).

Symptom responses were compared across the different botulinum toxin doses to determine if higher doses provided greater benefits than lower doses. On univariate logistic regression analysis, symptom reductions strongly correlated with dose ($P = 0.02$). For these analyses, only data on those individuals reporting either an improvement or no improvement in symptoms were included. Data relating to individuals for which no outcome of therapy was reported were not included. Responses to the 200 unit dose (33 of 43 evaluable patients, 76.7%) were superior to responses to the 100 unit dose (39 of 72 evaluable patients, 54.2%), with an odds ratio of 2.79 [95% confidence interval (CI) 1.20, 6.51] and showed a trend to greater responses compared with the 150 unit dose (20 of 34 evaluable patients, 58.8%), with an odds ratio of 2.31 (95% CI 0.86, 6.18) (Fig. 1). There were no differences in responses to the 150 and 100 unit doses (odds ratio 1.21, 95% CI 0.53, 2.76). On multivariate logistic regression including evaluation of other explanatory variables, patients receiving 200 units of botulinum toxin were more likely to report symptom reduction than those receiving 100 units, with an odds ratio of 3.05 (95% CI 1.16, 8.00) ($P = 0.02$). In contrast, the likelihoods of responses to 150 and 100 units were not statistically different (odds ratio 1.99, 95% CI 0.71, 5.53) ($P = 0.19$).

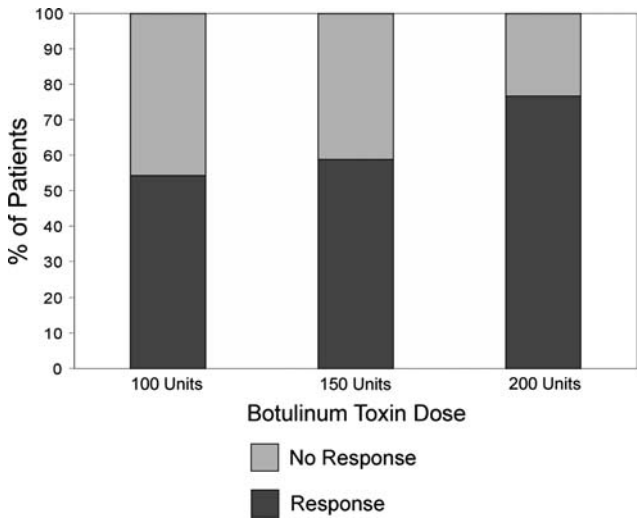

Fig. 1 Symptom response rates to the different botulinum toxin doses for individuals with a notation of clinical outcome upon review of clinic notes after pyloric therapy. Response rates strongly correlated with botulinum toxin dose ($P = 0.02$). The 200 unit dose produced significantly greater responses compared with the 100 unit dose and showed a trend to greater response over the 150 unit dose

Subgroup analysis was performed to determine if response to different botulinum toxin doses varied among distinct patient subsets (Table 2). Better responses to 200 units of botulinum toxin versus other doses were observed for women ($P = 0.02$) but not men ($P = 0.13$). Women who received 200 units were more likely to respond than those who received 100 units, with an odds ratio of 3.54 (95% CI 1.23, 10.17). Enhanced response to increasing botulinum toxin doses were noted for those with nondiabetic nonpostsurgical gastroparesis ($P = 0.01$) but not those with diabetic ($P = 0.78$) or postsurgical ($P = 0.24$) gastroparesis. The likelihood of response to 200 units of botulinum toxin among those with nondiabetic nonpostsurgical gastroparesis was greater than that to 100 units, with an odds ratio of 7.89 (95% CI 1.52, 41.02). Women with nondiabetic nonpostsurgical gastroparesis exhibited trends to greater responses to increasing treatment doses ($P = 0.06$), whereas nondiabetic nonpostsurgical gastroparetic men showed no dose-dependent responsiveness ($P = 0.15$). Age <50 years was strongly associated with greater responses to the 200 unit versus the 100 unit dose, with an odds ratio of 4.00 (95% CI 1.41, 11.33) ($P = 0.009$) (Table 3). Trends to dose-dependent responses were observed for absence of retained food on initial endoscopy ($P = 0.051$), lack of opiate use ($P = 0.08$), and severe delays in gastric emptying ($P = 0.09$). Factors not relating to the increase in response with greater botulinum toxin dose included age ≥50 years ($P = 0.98$), mild delays in gastric emptying ($P = 0.40$), retained food on endoscopy ($P = 0.62$), and opiate use ($P = 0.43$).

Symptom responses were compared across other explanatory variables to characterize the range of factors

Table 2 Subgroups exhibiting dose-dependent responses to botulinum toxin

Patient subgroup	Odds ratio of dose-dependent response (200 units versus 100 units)	95% Confidence interval	*P*-Value
Female gender	3.54	1.23–10.17	0.02
Age <50 years	4.00	1.41–11.33	0.009
Nondiabetic nonpostsurgical etiology	7.89	1.51–41.02	0.01

Table 3 Associations of demographic and gastric functional factors with symptom reductions

	Symptom reduction			
Demographic factors	Yes	No	Unknown	*P*-Value
Gender	Male, 28 (30%)	Male, 13 (23%)	Male, 6 (20%)	0.41
	Female, 64 (70%)	Female, 44 (77%)	Female, 24 (80%)	
Age	≥50 years, 27 (33%)	≥50 years, 19 (33%)	≥50 years, 6 (20%)	0.43
	<50 years, 65 (67%)	<58 years, 38 (67%)	<50 years, 24 (80%)	
Opiate use	Yes, 32 (35%)	Yes, 15 (26%)	Yes, 8 (27%)	0.48
	No, 60 (65%)	No, 42 (74%)	No, 22 (73%)	
Etiology	DM, 42 (46%)	DM, 26 (46%)	DM, 13 (43%)	0.67
	PS, 8 (9%)	PS, 7 (12%)	PS, 1 (3%)	
	Non-DM non-PS, 42 (46%)	Non-DM non-PS, 24 (42%)	Non-DM non-PS, 16 (53%)	
Gastric emptying at 2 h	≤20%, 19 (39%)	≤20%, 13 (45%)	≤20%, 2 (17%)	0.23
	>20%, 30 (61%)	>20%, 16 (55%)	>20%, 10 (83%)	
Retained food on endoscopy	Yes, 20 (22%)	Yes, 16 (28%)	Yes, 7 (23%)	0.68
	No, 72 (78%)	No, 41 (72%)	No, 23 (77%)	

DM diabetic etiology, *PS* postsurgical etiology, *Non-DM non-PS* nondiabetic nonpostsurgical etiology

that relate to the benefits of botulinum toxin therapy. Mean weight increases in those who responded to therapy were 2.2 ± 0.7 pounds, whereas weight increases were 0.4 ± 0.9 pounds in those with no symptom benefit, a difference that did not reach statistical significance ($P = 0.12$). Likewise, weight increases were not statistically different for 100 unit (1.00 ± 0.73 pounds), 150 unit (1.68 ± 1.27 pounds), or 200 unit (2.95 ± 1.39 pounds) botulinum toxin dosing ($P = 0.39$). On univariate analysis, symptom reductions did not relate to gender, age, opiate use, etiology, rates of gastric emptying, or retained food on endoscopy (Table 3). On multivariate logistic regression analysis, treatment response did not relate to gender, opiate use, etiology, gastric emptying rate, or retained food. On multivariate analysis, a minor effect was observed for age, with superior responses to botulinum toxin therapy relating to younger age with an odds ratio of 1.06 (95% CI 1.00, 1.11) ($P = 0.04$) even when controlling for botulinum toxin dose. On univariate and multivariate analysis, change in weight did not relate to gender, age, opiate use, etiology, gastric emptying rate, or retained food.

Responses to Repeat Pyloric Botulinum Toxin Injection

Eighty-seven patients underwent 307 repeat botulinum toxin injections. Second injections were performed 39–1,288 days after initial therapy. Forty-one of 82 patients (50.0%) receiving an initial dose of 100 units underwent repeat injection, whereas 20 of 43 patients (46.5%) initially receiving 150 units and 26 of 54 patients (48.1%) initially receiving 200 units underwent repeat therapy ($P = 0.93$) (Table 4). Repeat injection doses were 100 units in 19 instances, 150 units in 102 cases, and 200 units in 186 endoscopies. Sixty-four of 92 patients (69.6%) with an initial response to botulinum toxin underwent repeat injection, while 18 of 58 patients (31.0%) with no response underwent additional therapy ($P < 0.001$). Response rates to the each of the initial botulinum toxin doses were not different in individuals who received repeat injections ($P = 0.65$) (Table 4). Five individuals with an unknown response to therapy underwent repeat pyloric injection. Response rates to the second botulinum toxin dose trended higher in those who responded to the initial treatment (39 of 50 evaluable patients, 78.0%) versus those who did not respond to initial injection (7 of 12 evaluable patients, 58.3%), but this difference was not statistically significant ($P = 0.16$).

Thirty-nine of 41 patients (95.1%) receiving an initial dose of 100 units received higher doses with subsequent injections, whereas 11 of 26 patients (42.3%) receiving an initial dose of 150 units received escalating doses on repeat therapy. Dose reduction was performed in four instances. Symptom responses to repeat dosing at 150 units (30 of 43 evaluable patients, 69.8%) and 200 units (58 of 79 evaluable patients, 73.4%) were similar to initial responses ($P = 0.32$ and $P = 0.69$), whereas responses to repeat dosing at 100 units (six of six evaluable patients, 100%) were greater than initial responses to that dose ($P = 0.03$) (Table 4). Responses to repeat dosing at each of the three doses were not different ($P = 0.29$). Clinical responses to repeat injection at higher than initial doses (23 of 33 evaluable patients initially receiving either 100 or

Table 4 Data on repeat botulinum toxin injections

Demographic factors	Botulinum toxin dose			
	100 Units	150 Units	200 Units	*P*-Value
Patients undergoing repeat injection	Yes, 41 (50%)	Yes, 20 (43%)	Yes, 26 (48%)	0.93
	No, 41 (50%)	No, 23 (57%)	No, 28 (52%)	
Response to initial injection	Yes, 28 (68%)	Yes, 14 (70%)	Yes, 22 (85%)	0.65
	No, 10 (24%)	No, 5 (25%)	No, 3 (12%)	
	Unknown, 3 (7%)	Unknown, 1 (5%)	Unknown, 1 (4%)	
Response to repeat injection	Yes, 6 (100%)	Yes, 30 (70%)	Yes, 58 (73%)	0.29
	No, 0 (0%)	No, 13 (30%)	No, 21 (27%)	
Loss of response to repeat injection	Yes, 5 (23%)	Yes, 2 (20%)	Yes, 6 (33%)	0.67
	No, 17 (73%)	No, 8 (80%)	No, 12 (67%)	

150 units, 69.7%) were similar to responses to repeat injections at the same dose as the first treatment (8 of 10 evaluable patients initially receiving either 100 or 150 units, 80.0%) ($P = 0.52$). However, responses to repeat injections were frequently not recorded in outpatient notes (13 injections of 100 units, 59 injections of 150 units, and 107 injections of 200 units).

Loss of response to botulinum toxin was observed in 13 of 50 patients (26%) exhibiting a response to initial dosing and was similar in those receiving an initial dose of 100 units (5 of 22 evaluable patients, 23%), 150 units (2 of 10 patients, 20%), and 200 units (6 of 18 patients, 33.3%) ($P = 0.67$) (Table 4). Responses were not recorded for 14 patients undergoing repeat injection after initial response to botulinum toxin. Loss of response for those who underwent $\geq$2 successful injections was observed in 2 of 21 patients (9.5%); responses for this group were not recorded for 10 patients.

Discussion

Pyloric injection of botulinum toxin has been promoted as therapy to reverse the exaggerated motor activity in the pylorus in gastroparesis. Manometric studies demonstrate prolonged elevations in pyloric tone (>10 mmHg for >3 min) with associated increases in phasic contractions in a subset of gastroparesis patients [4]. In a study of type I diabetics with gastroparesis, isolated exaggerated pyloric pressure waves were documented for up to 11 h after eating [6]. Botulinum toxin impairs neural acetylcholine release, reduces pyloric substance P immunoreactivity, and disrupts pyloric myoelectric activity [18, 19]. In a diabetic patient, pyloric botulinum toxin injection reduced isolated pyloric contractions and improved antroduodenal coordination [6]. In series of gastroparesis patients, botulinum toxin accelerated solid gastric emptying, suggesting potential efficacy as a prokinetic therapy [7–11].

Botulinum toxin injections have been reported to reduce symptoms of gastroparesis in uncontrolled case series. Improved nausea, fullness, bloating, and eructation have been observed in patients with idiopathic gastroparesis as well as disease due to diabetes, Nissen fundoplication, esophagectomy, and pancreatic transplantation [7–15, 20]. Additional benefits include weight gain and improved quality of life [10]. Most series have been too small to provide insight into which factors are associated with symptom responses to pyloric botulinum toxin. In the largest published investigation of 63 patients, male gender was related to improved symptoms while vomiting was associated with a lack of response [13]. However, women exhibited longer duration of response (4.9 months) than men (3.5 months). These time courses correlate with studies that have observed recovery of neuronal function 2–6 months after botulinum toxin exposure [21]. Another study observed a correlation of accelerated gastric emptying after botulinum toxin therapy with reductions in symptoms, with an *R*-value of 0.56 [8].

Two placebo-controlled trials have failed to show benefits of botulinum toxin therapy in gastroparesis [16, 17]. In one study, 23 gastroparesis patients (19 idiopathic) received 100 units of botulinum toxin versus placebo in crossover fashion. Symptom responses and changes in rates of gastric emptying were similar after botulinum toxin and placebo [17]. However, it is difficult to envision how results from a crossover study might be analyzed as the effects of botulinum toxin can persist for more than 6 months in some cases. In the second study, 32 gastroparesis patients (13 idiopathic, 18 diabetic, and 1 postsurgical) were randomized to pyloric botulinum toxin versus placebo [16]. Symptom reductions were observed in both groups 1 month after injection but were not different in those who received active drug compared with placebo. Gastric emptying was accelerated by botulinum toxin but not placebo. Both investigations enrolled very small numbers of patients that exhibited heterogeneous clinical

characteristics and may not have targeted patient subsets most likely to respond; for example, if botulinum toxin therapy produces a 15% greater response rate than placebo, a sample size of 173 patients would be needed in each treatment arm to achieve a *P*-value of 0.05 with a power of 80% to detect a true difference in response—a significantly larger sample size than employed in either published controlled trial. Given such assumptions, the sample sizes of the two trials provided <25% power to detect a positive effect of botulinum toxin therapy.

The primary aim of the present investigation was to delineate which factors are associated with improved symptoms in gastroparesis patients treated with pyloric injection of botulinum toxin. Most importantly, the analysis aimed to ascertain if responses to therapy were greater with higher botulinum toxin doses. Other demographic, clinical, and gastric functional variables were assessed to determine if specific gastroparesis subsets might show selective benefits from pyloric injection treatments. To address this aim, a retrospective analysis was performed on a case series of gastroparesis patients nearly threefold larger than any other in the literature with diversity unmatched in other series. The most significant finding of this study was that symptom reductions related most strongly to the dose of botulinum toxin delivered into the pylorus. On subgroup analysis, demographic factors associated with dose-dependent responses included female gender and age <50 years, with trends to dose-dependent symptom reductions with a lack of opiate use. This contrasts with prior reports of superior responses in men [13]. Although there was a trend to a difference in age distribution for the different botulinum toxin doses in Table 1, there were no differences in age distributions for the 100 and 200 unit doses. Thus, dose-dependent responses in younger individuals did not relate to differences in age distribution for the different doses. Even among factors unrelated to botulinum toxin dose, an effect of younger age (<50 years) relating to superior response was significant on multivariate analysis. Those with nondiabetic nonpostsurgical gastroparesis exhibited better symptom benefits from higher doses of botulinum toxin, whereas no relation was observed with the other two etiologies. Finally, those without retained food on initial endoscopy and those with severely delayed emptying showed trends to superior responses with greater botulinum toxin doses. None of the other clinical functional factors correlated with symptom reductions after injection therapy. The findings of this analysis suggest that younger women with idiopathic gastroparesis receiving high-dose botulinum toxin may derive the greatest benefit from injection therapy and should be the focus of future controlled trials. However, because of smaller sample sizes, this study may not have had adequate power to detect dose-dependent responses to botulinum toxin in men, those over age 50 years, and individuals with retained food on endoscopy or on opiates.

The response rates to high-dose botulinum toxin in the present investigation are higher than those of some case series and of both controlled trials. This raises the possibility that a significant component of the response rate stems from a placebo effect. However, the current study employed a higher botulinum toxin dose than one controlled trial and followed symptom responses for a longer period of time than the other controlled study. These could provide partial explanations for the enhanced response rates in this investigation. Furthermore, the observation that symptom reductions exhibited significant dose dependency to botulinum toxin therapy is more consistent with a true drug effect. Even though most patients exhibited a response to botulinum toxin in this study, a substantial number of individuals derived no benefit. This observation is consistent with studies that have characterized other potential pathogenic factors in symptom production in gastroparesis including impaired relaxation of the gastric fundus, alterations in perception of gastric distention, and abnormal burst contractile patterns in the small intestine [22–25].

This investigation also observed no dose-dependent effects of botulinum toxin on body weight. It might be presumed that individuals with a chronic condition such as gastroparesis that causes nausea, vomiting, and other upper gastrointestinal symptoms might lose weight. However, a recent study reported that only 5% of gastroparetic patients are underweight and that nearly two-thirds are overweight or obese [26]. This observation provides a possible explanation for the discordance in improved symptoms and changes in body weight after botulinum toxin injection in the present investigation.

To date, only one small case series has addressed responses of gastroparesis patients to repeated botulinum toxin injections [8]. In that investigation, four of five patients receiving additional botulinum toxin therapy experienced continued symptom relief. This issue is important because of the chronic nature of gastroparesis and the limited duration of action of botulinum toxin. A secondary aim of the current study was to quantify responses to repeat injection therapy in this large and diverse patient database to assess for development of tolerance to its actions. Half of the patients in this series underwent one or more additional injections after initial pyloric dosing. Not unexpectedly, repeat dosing was more often performed in individuals with an initial symptom response to therapy. However, many individuals without an initial response exhibited beneficial responses to subsequent dosing. In many cases, such repeat treatments were performed at higher doses, although the sample size was too small to determine if the higher doses themselves were

responsible for responses to repeat injections in initial nonresponders. Responses for repeat injections did not show a dose dependency as with the initial treatments, possibly due to exclusion of initial nonresponders from additional therapy. Symptom reductions were maintained in nearly three-quarters of patients undergoing repeat injection, suggesting that tolerance may develop only after a large number of injections. However, dose escalation with additional injections was common, raising the possibility that some degree of impaired responsiveness to the benefits of botulinum toxin therapy occurred. This phenomenon has been observed with use of this agent in skeletal muscle disorders [27]. Many repeat botulinum toxin treatments were performed in open-access fashion without regular outpatient clinic visits between endoscopy sessions, thus much data on the benefits of repeat dosing are missing. Thus, conclusions about the benefits of repeat dosing must await prospective investigation. Nevertheless, it is unlikely that patients would continue to ask for or be offered repeat botulinum toxin injections if there were no continuing benefits from therapy.

In conclusion, pyloric botulinum toxin injection reduced symptoms in most patients in a large case series of gastroparesis patients. Responses depended on toxin dose. Subgroup analyses suggested that individuals most likely to respond to increasing botulinum toxin doses included women, those under 50 years old, patients with nondiabetic nonpostsurgical gastroparesis, and possibly individuals without retained food or opiate use or with severely delayed gastric emptying. Symptom benefits were maintained in nearly three-quarters of patients undergoing repeated injections. The rigorous analyses in this study provide the foundation for large, placebo-controlled trials of high-dose botulinum toxin in selected gastroparesis patient subsets.

Acknowledgments Dr. Hasler receives grant funding from the NIH (1 U01 DK073985-01) to support his research in gastroparesis.

References

1. Parkman HP, Hasler WL, Fisher RS. American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. *Gastroenterology*. 2004;127:1592–1622. doi:10.1053/j.gastro.2004.09.055.
2. Soykan I, Sivri B, Saroseik 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. doi:10.1023/A:1026665728213.
3. Annese V, Janssens J, Vantrappen G, et al. Erythromycin accelerates gastric emptying by inducing antral contractions and improved gastroduodenal coordination. *Gastroenterology*. 1992;102:823–828.
4. Mearin F, Camilleri M, Malagelada JR. Pyloric dysfunction in diabetics with recurrent nausea and vomiting. *Gastroenterology*. 1986;90:1919–1925.
5. Montecucco C, Schiavo G. Mechanism of action of tetanus and botulinum neurotoxins. *Mol Microbiol*. 1994;13:1–8. doi:10.1111/j.1365-2958.1994.tb00396.x.
6. Gupta P, Rao SS. Attenuation of isolated pyloric pressure waves in gastroparesis in response to botulinum toxin injection: a case report. *Gastrointest Endosc*. 2002;56:770–772. doi:10.1016/S0016-5107(02)70140-5.
7. 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. doi:10.1067/mge.2002.124739.
8. Miller LS, Szych GA, Kantor SB, et al. Treatment of idiopathic gastroparesis with injection of botulinum toxin into the pyloric sphincter muscle. *Am J Gastroenterol*. 2002;97:1653–1660. doi:10.1111/j.1572-0241.2002.05823.x.
9. Lacy BE, Zayat EN, Crowell MD, Schuster MM. Botulinum toxin for the treatment of gastroparesis: a preliminary report. *Am J Gastroenterol*. 2002;97:1548–1552. doi:10.1111/j.1572-0241.2002.05741.x.
10. 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. doi:10.2337/diacare.27.10.2341.
11. Arts J, Van Gool S, Caenepeel P, Verbeke K, Janssens J, Tack J. Influence of intrapyloric botulinum toxin injection of gastric emptying and meal-related symptoms in gastroparesis patients. *Aliment Pharmacol Ther*. 2006;24:661–667. doi:10.1111/j.1365-2036.2006.03019.x.
12. Wiesel PH, Schneider R, Dorta G, Blum AL, Gillet M, Michetti P. Botulinum toxin for refractory postoperative pyloric spasm. *Endoscopy*. 1997;29:132. doi:10.1055/s-2007-1004091.
13. Bromer MQ, Friedenberg 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. doi:10.1016/S0016-5107(05)00328-7.
14. Ben-Youssef R, Baron PW, Franco E, Walter MH, Lewis T, Ojogho O. Intrapyloric injection of botulinum toxin A for the treatment of persistent gastroparesis following successful pancreatic transplantation. *Am J Transplant*. 2006;6:214–218. doi:10.1111/j.1600-6143.2005.01153.x.
15. Kent MS, Pennathur A, Fabian T, et al. A pilot study of botulinum toxin injection for the treatment of delayed gastric emptying following esophagectomy. *Surg Endosc*. 2007;21:754–757. doi:10.1007/s00464-007-9225-9.
16. Friedenberg 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. doi:10.1111/j.1572-0241.2007.01676.x.
17. Arts J, Holvoet L, Caenepeel P, et al. Clinical trial: a randomized-controlled crossover study of intrapyloric injection of botulinum toxin in gastroparesis. *Aliment Pharmacol Ther*. 2007;26:1251–1258.
18. Schiavo G, Shone CC, Rossetto O, Alexander FC, Montecucco C. Botulinum neurotoxin serotype F is a zinc endopeptidase specific for VAMP/synaptobrevin. *J Biol Chem*. 1993;268:11516–11519.
19. Hou YP, Zhang YP, Song YF, Zhu CM, Wang YC, Xie GL. Botulinum toxin type A inhibits rat pyloric myoelectrical activity and substance P release in vivo. *Can J Physiol Pharmacol*. 2007;85:209–214. doi:10.1139/Y07-018.
20. De Looze DA, Verdievel HG, Peeters TL, De Vos MM. The pyloric sphincter is back in town. *Gastroenterology*. 2000;118:A468. abstract.

21. Harris CP, Alderson K, Nebeker J, Holds JB, Anderson RL. Histologic features of human orbicularis oculi treated with botulinum A toxin. *Arch Ophthalmol*. 1991;109:393–395.
22. Bredenoord AJ, Chial HJ, Camilleri M, Mullan BP, Murray JA. Gastric accommodation and emptying in evaluation of patients with upper gastrointestinal symptoms. *Clin Gastroenterol Hepatol*. 2003;1:264–272. doi:10.1016/S1542-3565(03)00130-7.
23. Samsom M, Salet GA, Roelofs JM, Akkermans LM, Van Berge Henegouwen GP, Smout AJ. Compliance of the proximal stomach and dyspeptic symptoms in patients with type I diabetes mellitus. *Dig Dis Sci*. 1995;40:2037–2042. doi:10.1007/BF02208676.
24. Samsom M, Roelofs JM, Akkermans LM, Van Berge Henegouwen GP, Smout AJ. Proximal gastric motor activity in response to a liquid meal in type I diabetes mellitus with autonomic neuropathy. *Dig Dis Sci*. 1998;43:491–496. doi:10.1023/A:1018894520557.
25. Camilleri M, Malagelada JR. Abnormal intestinal motility in diabetics with the gastroparesis syndrome. *Eur J Clin Invest*. 1984;14:420–427. doi:10.1111/j.1365-2362.1984.tb01206.x.
26. Bizer E, Harrell S, Koopman J, Hatfield C, Cacchione R, Wo JM. Obesity is common in gastroparesis despite nausea, vomiting, and early satiety. *Gastroenterology*. 2005;128:M1895. abstract.
27. Jankovic J. Botulinum toxin in movement disorders. *Curr Opin Neurol*. 1994;7:358–366.