The Treatment of Diabetic Gastroparesis With Botulinum Toxin Injection of the Pylorus

BRIAN E. LACY, PHD, MD
MICHAEL D. CROWELL, PHD
ANN SCHEITTLER-DUNCAN, RN
CAROLE MATHIS, PHD
PANKAJ J. PASRICA, MD

OBJECTIVE — Gastroparesis is a disorder of delayed gastric emptying that is often chronic in nature. Up to 50% of type 1 diabetic subjects have symptoms of gastroparesis, which include nausea, vomiting, and early satiety. Elevated pyloric pressures may be responsible for delayed gastric emptying in diabetic subjects. Botulinum toxin inhibits the release of acetylcholine and produces transient paralysis when injected into smooth muscle. The aim of this study was to determine whether injection of the pylorus with botulinum toxin in patients with diabetic gastroparesis improves symptoms of gastroparesis, alters gastric emptying scan time, and/or changes weight and insulin use.

RESEARCH DESIGN AND METHODS — This was an open-label trial with age- and sex-matched control subjects from a tertiary care referral center for patients with gastroparesis. Eight type 1 diabetic subjects (six women and two men; mean age 41 years; mean years with diabetes 25.3) who had failed standard therapy were enrolled. Intervention consisted of injection of the pylorus with 200 units of botulinum toxin during upper endoscopy. Symptoms, antropyloric manometry, gastric emptying scan times, weight, and insulin use were all recorded before intervention and during a 12-week follow-up period.

RESULTS — Seven of the eight patients completed the full 12-week follow-up period. No complications were noted. Mean symptom scores declined from 27 to 12.1 (P < 0.01), whereas the SF-36 physical functioning domain also improved (P < 0.05). Four patients noted an increase in insulin use of >5 units/day. Six of the seven patients gained weight (P = 0.05). Gastric emptying scan time improved in four patients.

CONCLUSIONS — Botulinum toxin injection of the pylorus is safe and improves symptoms in patients with diabetic gastroparesis. These results warrant further investigation with a large, double-blind, placebo-controlled trial.

Diabetes Care 27:2341–2347, 2004

Gastroparesis is a disorder of gastrointestinal motility defined as a delay in gastric emptying in the absence of mechanical obstruction. Common symptoms include early satiety, nausea, vomiting, anorexia, weight loss, and episodic gastroparesis is a disorder of delayed gastric emptying that is often chronic in nature. Up to 50% of type 1 diabetic subjects have symptoms of gastroparesis, which include nausea, vomiting, and early satiety. Elevated pyloric pressures may be responsible for delayed gastric emptying in diabetic subjects. Botulinum toxin inhibits the release of acetylcholine and produces transient paralysis when injected into smooth muscle. The aim of this study was to determine whether injection of the pylorus with botulinum toxin in patients with diabetic gastroparesis improves symptoms of gastroparesis, alters gastric emptying scan time, and/or changes weight and insulin use.

RESEARCH DESIGN AND METHODS — This was an open-label trial with age- and sex-matched control subjects from a tertiary care referral center for patients with gastroparesis. Eight type 1 diabetic subjects (six women and two men; mean age 41 years; mean years with diabetes 25.3) who had failed standard therapy were enrolled. Intervention consisted of injection of the pylorus with 200 units of botulinum toxin during upper endoscopy. Symptoms, antropyloric manometry, gastric emptying scan times, weight, and insulin use were all recorded before intervention and during a 12-week follow-up period.

RESULTS — Seven of the eight patients completed the full 12-week follow-up period. No complications were noted. Mean symptom scores declined from 27 to 12.1 (P < 0.01), whereas the SF-36 physical functioning domain also improved (P < 0.05). Four patients noted an increase in insulin use of >5 units/day. Six of the seven patients gained weight (P = 0.05). Gastric emptying scan time improved in four patients.

CONCLUSIONS — Botulinum toxin injection of the pylorus is safe and improves symptoms in patients with diabetic gastroparesis. These results warrant further investigation with a large, double-blind, placebo-controlled trial.
Botulinum toxin for diabetic gastroparesis

and pelvis). A solid-phase gastric emptying scan was delayed in all eight patients.

The control group consisted of age- and sex-matched control subjects without diabetes and without any complaints referable to the gastrointestinal system. Exclusion criteria for both groups were as follows: pregnancy; known allergy to eggs, botulinum toxin, or lidocaine; previous surgery to the stomach, pylorus, or small bowel; previous Nissen fundoplication or other antireflux surgery; known pyloric stricture; previous stroke, transient ischemic attack, or chronic diseases involving the central nervous system; concurrent use of opiates or anticholinergics. Women of child-bearing age had both urine and serum human chorionic gonadotropin checked to ensure that they were not pregnant before testing and treatment. Prokinetic and antiemetic agents were continued during the trial; however, new medications were not initiated during the trial. All patients stayed on a gastroparesis diet (small frequent meals low in both fat and fiber). This protocol was approved by the Institutional Review Board of Johns Hopkins Bayview Medical Center.

Gastric emptying scans
Gastric emptying scans were performed in an identical manner both before and 1 week after botulinum toxin injection to objectively measure changes in gastric emptying. After an overnight fast, patients were given a standard meal consisting of two scrambled eggs mixed with one mCi-99 technetium sulfur colloid (15), two slices of white bread, and 300 ml of water (total of 270 kcal; 23% protein, 37% carbohydrate, 40% fat). Images were taken every minute for a minimum of 120 min using a gamma camera (Adak Company, Militas, CA), and the t1/2 for gastric emptying was calculated (mean for normal patients in the Nuclear Medicine Department is 90 ± 15 min). Radiologists who read the study were blinded to the study protocol.

Antropyloric manometry
Antral and pyloric intraluminal pressures were recorded using a manometric assembly (optical density 8 mm), which incorporated a 6-cm sleeve sensor and five side holes (Dentsleeve, Wayville, Australia). The 6-cm sleeve sensor was positioned across the pylorus and recorded both pyloric tone and phasic activity. Four side holes located at 0, 3, 6, and 9 cm above the oral end of the sleeve recorded pressure events in the terminal and proximal antrum, respectively. The remaining side hole was located 1 cm distal to the aboral end of the sleeve and recorded duodenal pressure events. The manometry assembly was perfused with distilled water using a low-compliance pneumohydraulic pump (MUI Scientific, Ontario, Canada) with a flow rate of 0.8 ml/min. After preamplification and low pass filtration (PC Polgraf HR; Syntec Medical, Stockholm, Sweden), pressure events were digitized at 16 Hz on a microcomputer (Polygram Upper GI Edition; Syntec Medical).

After topical anesthesia (2% lidocaine HCl, AstraZeneca, Wilmington, DE) to the nose, the catheter assembly was positioned across the pylorus using fluoroscopic guidance. Accommodation time of ~1 h occurred before obtaining 3 h of recordings in a fasting state. The patient was then fed a standard liquid meal (Pulmocare; Ross Products, Columbus, OH) (837 ml; 355 kcal; 16.7% protein, 28.2% fat, 55.1% carbohydrate), and recordings were continued for another 2 h. To minimize exacerbation of gastroparesis (2), blood glucose was monitored during the test, and insulin or glucose was provided to maintain serum glucose between 80 and 150 mg/dl. Antropyloric manometry was performed in an identical manner in the week before and 1 week after injection of the pylorus with botulinum toxin. This portion of the study provided an objective measure of the response to botulinum toxin injection.

Analysis of antropyloric manometry
Pyloric pressure activity was classified into one of three groups, according to the description by Mearin et al. (9). Baseline elevation of the pyloric pressure wave >3 mmHg for >1 min was defined as a tonic pattern; antral-type phasic pressure activity mixed with duodenal phasic activity was categorized as a phasic pattern; and a phasic pattern superimposed on tonic activity was categorized as a combined tonic-phasic pattern. Pylorospasm was defined as prolonged (>3 min) or intense (>10 mmHg) contractions above baseline. Each 15 min of pyloric recording was subjected to area under the curve analysis to assess response to botulinum toxin injection.

Symptom questionnaires and weights
Each patient filled out a symptom questionnaire (see APPENDIX). Each question asked the patient to rate symptoms from none (0 points) to severe (3 points); the maximum score was 36. Patients completed two standardized questionnaires, SF-36 and SCL-90, at the initiation and completion of the study. Questionnaires were included in this study because the U.S. Food and Drug Administration now recommends that subjective measures be included as either primary or secondary end points in studies of gastrointestinal disorders. Patients were asked to record daily insulin use and to monitor the need for additional insulin. Weights were measured at the initiation of the protocol and at routine follow-up after treatment.

Laboratory studies
A complete blood count, blood urea nitrogen, creatinine, fasting glucose, HbA1c, albumin, and urinalysis were checked before enrollment and again at 8 weeks after injection.

Injection of the pylorus
After informed consent, patients underwent esophagogastroduodenoscopy to rule out mechanical obstruction. All procedures were performed by one physician (B.E.L.). Two hundred units of botulinum toxin A (Botox; Allergan, Irvine, CA) were dissolved in 4 ml of sterile normal saline and injected into the pylorus using a standard sclerotherapy 25-gauge, 4-mm needle (Ballard, Draper, UT) (50 units of Botulinum toxin A into each quadrant). The patient was observed for 1–2 h in the recovery area and then discharged home. Telephone follow-up occurred at 24 h to look for immediate side effects or complications. Patients were seen in follow-up at 1, 2, 4, 6, 8, and 12 weeks after the injection therapy.

Statistics
Data were analyzed using the statistical software SPSS. Pre- and postinjection weights, gastric emptying scan times, symptom scores, SF-36, and SCL-90 data were compared using a paired sample Student’s t test. Pyloric manometry was analyzed by comparing the area under the curve in the pre- and postinjection period using a paired sample Student’s t test.
RESULTS

Symptoms
The mean symptom score of all eight patients before treatment was 27.0. Mean symptom scores at weeks 1, 4, 6, and 8 were 14.5, 11.4, 12.1, and 12.2, respectively, for all eight patients (Fig. 1). One patient (C.F.) developed severe nausea and vomiting at week 9 and underwent repeat endoscopy with a second injection (200 units) of botulinum toxin without any complications. Symptoms of nausea and vomiting completely resolved after the second injection. This patient’s symptom scores are included for follow-up weeks 1–8 but not week 12. Symptom scores of the seven patients who completed all 12 weeks of follow-up after only one injection of botulinum toxin were not significantly different from the scores listed above for all eight patients and were all significantly reduced compared with baseline ($P < 0.01$ at all visits).

SF-36 scores and SCL-90 scores were measured both before and after botulinum toxin injection of the pylorus. Two patients did not completely fill out both sets of forms and thus were excluded from analysis. In the six patients who completely filled out both pre- and postinjection SF-36 questionnaires, total scores did not change significantly. However, subscores for the physical functioning domain did improve ($P < 0.05$). No significant differences were noted in SCL-90 scores over the 12-week follow-up period.

Gastric emptying scans
Mean solid-phase gastric emptying scan time ($t_{1/2}$) before injection was 339.1 min (range 74–999). Gastric emptying time was reduced by one-third 1 week after injection to a mean of 227.3 min (range 74–906; $P = 0.11$). One patient had a normalization of gastric emptying scan time after injection ($t_{1/2}$ of 142 min compared with 82 min). Three patients had significant improvement in their gastric emptying scan half-times, although they did not normalize (182–108 min; 351–148 min; 800–278 min). Three patients did not have any significant change in their gastric emptying scan half-times, whereas one patient had an increase in gastric emptying scan half-time (78–146 min). These latter four patients all noted an objective improvement in their symptoms on the questionnaire.

Antropyloric manometry
In eight healthy volunteers, there was no evidence of pylorospasm during antropyloric manometry. Pylorospasm was noted in all eight diabetic patients, which confirms the findings of Mearin et al. (9). Data were available for complete analysis from only five patients. Data were excluded from two patients because the catheter migrated during portions of the preinjection period and because of persistent vomiting in one patient. After botulinum toxin injection, area under the curve analysis revealed that pylorospasm was significantly reduced compared with baseline.

Figure 1—Symptom scores of patients at baseline (prebotox) and over the 12-week trial period. Symptom scores reflect all eight patients for baseline and 1-, 2-, 4-, and 8-week follow-up visits. Symptom scores for the week 12 follow-up visit reflect seven patients. Maximum symptom score was 36. The x-axis reflects time, and the y-axis reflects symptom score.

![Symptom scores graph](image-url)
**Botulinum toxin for diabetic gastroparesis**

\( P = 0.04 \). A reduction in tonic pyloric pressures was also noted, although this was not significantly different compared with the preinjection state \( P = 0.06 \) (Fig. 2).

**Laboratory tests**

Values for the complete blood count, blood urea nitrogen, creatinine, fasting glucose, HbA1c, albumin, and urinalysis obtained at the 8-week follow-up visit were not significantly different from baseline.

**Insulin use**

No changes were noted in either regular or NPH insulin use in any of the patients at the 1-, 2-, and 4-week follow-up appointments. At the 8-week follow-up visit, four patients noted an increase in NPH insulin requirements of \( \geq \)5 units each day, whereas the remaining four patients did not require an increase in NPH insulin use. At the 12-week follow-up visit, three of the four patients still required at least 5 units more of NPH insulin use per day, whereas the other four patients did not have a change in their NPH insulin use compared with baseline. No differences were noted for regular insulin use at either the 8- or 12-week follow-up appointments.

**Complications**

Patients were questioned about possible side effects during the telephone interview 24 h after botulinum toxin injection and again at the 1-, 2-, 4-, 8-, and 12-week follow-up appointments. No complications were reported as a result of the upper endoscopy or botulinum toxin injection of the pylorus.

**CONCLUSIONS** — Several research studies have shown that achalasia, a disorder of esophageal motility characterized by dysphagia and poor emptying of the esophagus, can be effectively treated with botulinum toxin (16–18). Injection of the lower esophageal sphincter (LES) with botulinum toxin relaxes the LES, improves esophageal emptying, and improves complaints of dysphagia with minimal side effects.

Investigations in our laboratory led us to believe that diabetic gastroparesis is similar to achalasia. Both conditions involve smooth muscle sphincters that fail to relax appropriately and have elevated tone. Elevated sphincter tone can prevent normal emptying of either the esophagus or the stomach. Modeling the therapeutic success in achalasia, two patients with severe diabetic gastroparesis had a dramatic improvement in symptoms after botulinum toxin injection of the pylorus (10). These preliminary results led us to initiate the current study involving eight patients with long-standing diabetes and mean insulin use of 24.4 years. All patients had failed standard medical therapy (erythromycin, metoclopramide, cisapride, domperidone) without improvement in symptoms. When asked to objectively measure their symptoms of nausea, vomiting, and abdominal pain, mean pretreatment scores were 27 of a maximum of 36. Subjectively, all eight patients stated that their symptoms greatly reduced their quality of life on a daily basis. Botulinum toxin injection of the pylorus was easily accomplished during routine endoscopy in all eight patients without any immediate or delayed side effects.

Individually, all eight patients noted an improvement in symptom scores over the 12-week study period. Collectively, symptom scores decreased significantly at all follow-up visits when compared with baseline \( P < 0.01 \). The greatest decrease occurred in the first week after botulinum toxin injection, with a smaller drop during the second week. Individually, the greatest decline in symptom scores occurred in nausea and vomiting. Total SF-36 scores did not significantly improve in the six patients who completely filled out both pre- and postinjection questionnaires, although the physical functioning score did improve \( P < 0.05 \). This may reflect an increased ability to function due to fewer episodes of nausea and vomiting.

Gastric emptying scan times were found to improve or normalize in four of eight subjects. This confirms the findings by Ezzeddine et al. (14). Although the sample size is small, this improvement is remarkable, as these patients had previously failed all other standard therapy. In addition, nearly all previously published studies that evaluated the efficacy of prokinetic agents failed to demonstrate an improvement in gastric emptying scan times. Three patients did not have an improvement in gastric emptying scan time, although all noted an improvement in their symptoms. Interestingly, one patient’s gastric emptying scan time increased somewhat, although, subjectively, the patient felt better, and objectively, her symptom scores declined. This discordance might reflect a delayed response to botulinum toxin, transient worsening of pylorospasm, or day-to-day variation in gastric emptying.

Several patients were surprised that, after injection therapy, they were able to gain weight and reverse a gradual trend of weight loss secondary to chronic nausea and vomiting. Three patients gained \( \geq 10 \) pounds each, and all three of these patients required at least \( \geq 5 \) units of NPH insulin each day over the course of the study period. A reduction in early satiety, epigastric pain, nausea, and vomiting in these patients may all have contributed to an increased ability to eat.

This study confirms the previous report by Mearin et al. (9), which showed that patients with diabetic gastroparesis have pylorospasm. In the current study, pylorospasm was reduced in all five patients who completed both antropyloric manometries. This confirms and extends the findings published in a recent case report (13). Symptom scores decreased in all five patients, whereas gastric emptying scan times improved in three patients.

In contrast to current medical therapy, botulinum toxin injection of the pylorus has the unique advantage of treating a specific site within the stomach (the pylorus).
Figure 2—Antropyloric manometry using a Dentsleeve catheter. A and B: The first two panels reflect activity in the antrum (proximal and distal), the third panels reflect pyloric activity, and the last panels reflect duodenal activity. A: Baseline (preinjection). Area under the curve for the pylorus in this patient is 30,449.90 s. B: Postbotulinum toxin injection of the pylorus. In the same patient, a reduction in phasic activity in the pylorus can be visualized. Tonic-phasic activity, as measured by the area under the curve, decreased to 14,976.90 s.
Botulinum toxin for diabetic gastroparesis

Table 1—Symptom questionnaire

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper abdominal discomfort</td>
<td>None Mild Moderate Severe</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>None Mild Moderate Severe</td>
</tr>
<tr>
<td>Bloating</td>
<td>None Mild Moderate Severe</td>
</tr>
<tr>
<td>Heartburn</td>
<td>None Mild Moderate Severe</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>None Mild Moderate Severe</td>
</tr>
<tr>
<td>Nausea (# days per week ____)</td>
<td>None Mild Moderate Severe</td>
</tr>
<tr>
<td>Vomiting (# times per week ____ )</td>
<td>None Mild Moderate Severe</td>
</tr>
<tr>
<td>Abdominal pain after eating</td>
<td>None Mild Moderate Severe</td>
</tr>
<tr>
<td>Abdominal pain between meals</td>
<td>None Mild Moderate Severe</td>
</tr>
<tr>
<td>Abdominal pain after drinking liquids</td>
<td>None Mild Moderate Severe</td>
</tr>
<tr>
<td>Early satiety (filling up very quickly)</td>
<td>None Mild Moderate Severe</td>
</tr>
<tr>
<td>Burning sensation in chest/upper abdomen</td>
<td>None Mild Moderate Severe</td>
</tr>
</tbody>
</table>

Symptom score = ___.

(notes, references, and discussion)

With intractable nausea and vomiting who cannot tolerate oral medications and in those with persistent symptoms despite maximal medical therapy. Although our study demonstrated that patients noted an improvement in both nausea and vomiting, it is not likely that this therapy will replace the use of traditional antiemetic agents for gastroparetic patients with only mild nausea, given the expense of botulinum toxin and the need for endoscopy. Future trials will need to evaluate the long-term safety, efficacy, and cost of botulinum toxin therapy compared with balloon dilation of the pylorus, pyloromyotomy, and gastric electrical stimulation.

Summary

In this study, botulinum toxin injection of the pylorus in eight patients with severe diabetic gastroparesis was found to be safe and to improve symptoms of nausea, vomiting, and abdominal pain. Pyloric tone and pressure was reduced after intraspincteric injection with botulinum toxin. Gastric emptying scan half-times improved in some, but not all, patients, whereas some patients gained weight and required higher doses of daily insulin.

Before botulinum toxin injection of the pylorus is adopted in clinical practice for the routine treatment of diabetic gastroparesis, we recommend that endoscopists interested in using this technique consider pooling both resources and patients to conduct a blinded, placebo-controlled trial to confirm the efficacy of this treatment. Funding agencies such as the National Institutes of Health or the American Diabetes Association should strongly consider support of such research, which has the potential to bring relief to diabetic patients suffering from gastroparesis.

Acknowledgments — This study was funded by donations to the Marvin M. Schuster Center for Digestive and Motility Disorders and by unrestricted educational grants (to B.E.L. [CERT grant from Johns Hopkins and Allergan]).

APPENDIX

Please rate any symptoms that you currently have. If the symptoms were given as numbers, then no symptoms would equal 0, mild symptoms would equal 1, etc.
References


moderate symptoms would equal 2, and severe symptoms would equal 3 (Table 1).