

Endoscopic Botulinum Toxin Injection for the Treatment of Diabetic Gastropathy in Pancreas and Islet-cell Transplant Patients

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Abstract

Objectives: Gastroparesis is a well-recognized, long-term complication of diabetes. Prokinetic drugs are often not effective, prompting the development of alternative therapies. We report our experience of using one such alternative, endoscopic botulinum toxin injection, to ameliorate diabetic gastropathy in association with pancreas and islet-cell transplant patients.

Materials and Methods: Three male diabetic patients aged 42 to 55 years had been treated with botulinum toxin in our center. Two patients were both after-simultaneous pancreas-kidney transplant and 1 was awaiting islet-cell transplant after pancreatectomy. Mechanical gastric outlet obstruction was first excluded by radiological and endoscopic studies. Between 100 and 200 IU of toxin were then injected in the prepyloric region using an endoscopic technique. A subjective scoring scale was used to assess symptoms before and after botulinum therapy.

Results: Improvement in subjective symptom severity scoring was seen in all patients, with a posttreatment improvement from 55% to 91%. Such improvement was temporary in 2 patients and long-lasting in 1 patient.

Conclusions: The time for improvement of gastric autonomic function after pancreas or islet-cell transplantation remains unclear. Some patients may continue to be symptomatic, leading to

increasing morbidity. However, endoscopic botulinum injections may provide short-term relief while waiting for improvement and spare patients the morbidity associated with more-invasive therapies.

Key words: *Gastroparesis, Neurotoxin, Transplant*

Introduction

Delayed gastric emptying (DGE), otherwise known as gastroparesis, is characterized by delayed emptying of food in the absence of any mechanical gastrointestinal obstruction.¹ Long-standing diabetic neuromyopathy can lead to DGE via a combination of poorly coordinated gastric contractions in both the antrum and pylorus (ie, pylorospasm).^{1,2}

Upper gastrointestinal symptoms (eg, pain, distension, early satiety, nausea, and vomiting) have been reported by up to 19% of diabetic patients, and of these, 48% to 65% have been shown to have DGE.³ Current treatment of diabetic gastroparesis involves tight control of blood glucose levels and optimization of insulin regimens, as hyperglycemia has been shown to exacerbate symptoms.⁴ Dietary modifications also have been advocated, along with the use of prokinetic agents such as metoclopramide, domperidone and erythromycin, which work via an increase in antral contractility. The use of prokinetics can cause complications in posttransplant patients. For example, improvement in gastric motility can facilitate the absorption of immunosuppressants, such as tacrolimus, which in theory, could subsequently increase its bioavailability and result in toxicity requiring a dose reduction.⁵

In refractory cases when dietary and medical therapy are unsuccessful, endoscopic and surgical procedures are available, such as the insertion of a

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feeding jejunostomy tube,^{6, 7} the use of implantable gastric electrical stimulator devices,^{8, 9} or major surgical resection, such as partial or total gastrectomy.¹⁰ We report the use of endoscopic botulinum toxin (Botox, Allergan, Inc., Irvine, CA, USA) injection in patients with symptomatic DGE secondary to diabetic gastroparesis, specifically in patients who have undergone or are awaiting either pancreas or islet-cell transplantation.

Materials and Methods

We treated 3 patients with endoscopic injection of botulinum A toxin in our center since February 2010. Mechanical gastrointestinal obstruction was first excluded as a cause for their symptoms after radiological contrast studies and a gastroscopy. One patient (case 1) also underwent formal gastric emptying studies. Each patient then underwent endoscopic injection of botulinum toxin. Gastroscopy was performed by a single endoscopist (MN) using conscious sedation consisting of benzodiazepines and opiates. Hyoscine butylbromide (Buscopan, Boehringer Ingelheim, Germany) was given as an antispasmodic agent to aid accurate visualization of the prepyloric region for ease of toxin injection. Botulinum toxin was then injected into the prepyloric area in a quadrant fashion at the 12-, 3-, 6-, and 9-o'clock positions. The therapeutic procedure lasted approximately 5 minutes. Subsequent response to botulinum treatment was assessed using a subjective 11-point symptom severity rating scale, from 0 to 10, assessing 5 upper gastrointestinal symptoms. This scale has been used previously to assess the response to botulinum toxin injection.¹¹

Results

Patient 1

A 42-year-old man underwent a simultaneous pancreas and kidney transplant (SPK). Before botulinum treatment, he had been taking 3 different prokinetic agents. A total of 200 IU of toxin was injected during his first treatment and he had 2 additional injections later. Symptom severity scores before and after botulinum toxin therapy are shown in Table 1. The improvement in symptom severity persisted for 6 to 8 weeks, and he has since been referred for consideration of an implantable gastric stimulator device for ongoing symptom management.

Table 1. Pre-Botox and post-Botox subjective symptom scoring, by patient.

Treatment used before Botox	Patient 1	Patient 2	Patient 3
Sucralfate Levomopromazine Domperidone Gaviscon Metoclopramide		Domperidone Omeprazole	Metoclopramide Lansoprazole
Dose Botox injected (IU)	200/150/200	150	200
Pre-Botox symptom score			
Nausea	10	10	6
Bloating	6	4	6
Early satiety	7	4	6
Abdominal distension	6	4	6
Vomiting	10	10	5
Total subjective score	33	22	29
Post-Botox symptoms			
Nausea	0	2	2
Bloating	2	0	3
Early satiety	2	0	3
Abdominal distension	2	0	3
Vomiting	0	0	2
Total subjective score	6	2	13
Relative improvement in total score	81%	91%	55%

Patient 2

A 48-year-old man who had previously undergone an SPK, received 150 IU of botulinum toxin. He has had a long-lasting response and remains almost symptom-free 8 months after injection.

Patient 3

A 55-year-old man who had a previous total pancreatectomy for chronic alcoholic pancreatitis and is currently on the waiting list for a pancreatic islet-cell allograft received a total of 200 IU of botulinum toxin. This produced an improvement in symptom severity lasting between 6 to 8 weeks. He has also been referred for consideration of an implantable gastric stimulator.

Discussion

Botulinum toxin is a neurotoxin with a mechanism of action via the irreversible inhibition of acetylcholine release from nerve fibers, leading to muscle paralysis. Although irreversible, muscle function can return 2 to 6 months later via the generation of new axonal sprouting.¹² Endoscopic botulinum injection has been used to treat

gastrointestinal smooth-muscle disorders such as esophageal achalasia¹³ and sphincter of Oddi dysfunction.¹⁴ Several studies have been reported evaluating the use of botulinum toxin to treat diabetic-related gastroparesis.

Ezzadine and associates¹⁵ found a 55% improvement in patients' subjective symptom scores at 2 weeks and 6 weeks after botulinum injection, and a 52% improvement in gastric emptying as measured by scintigraphy techniques at 48 hours and 6 weeks after injection. In a case study involving a single patient with type 1 diabetes, Gupta and associates¹⁶ demonstrated a return of normally coordinated peristaltic activity in the antroduodenal region after botulinum injection, with an improvement in the patient's level of nausea and vomiting. Lacy and associates¹⁷ have shown a substantial decrease in symptom scoring in 8 type 1 diabetic patients after a botulinum injection. However, of 2 randomized controlled trials performed to date, neither found a significant difference in either symptom scoring ($P = \text{NS}$; $P = .42$) or solid or liquid gastric emptying ($P = \text{NS}$) between botulinum toxin and placebo.^{18, 19} Despite this lack of superiority of botulinum over placebo, our results are supported by those of Ben-Youssef and associates,¹¹ who have also used botulinum toxin to treat diabetic gastroparesis after pancreas transplantation in 3 patients. They reported an improvement in subjective symptom scoring from 67% to 87% after botulinum toxin injection.

The case series presented here is small, and although the symptom severity score has been used in previous work,¹¹ it is a subjective scale and has not been validated. The long-term effects of the use of botulinum toxin in diabetic gastroparesis are unknown, and further work is warranted to evaluate the benefits of repeated injections over time.

In our experience, however, endoscopic injection of botulinum toxin has given some symptom relief in the short term, with 1 patient experiencing a sustained response. Botulinum therapy may be particularly useful in transplant patients while the patient is being stabilized on immunosuppressant therapy and as an alternative to prokinetics and their associated problems with immunosuppression toxicity. This is particularly important for pancreas transplant patients who require enteric drainage, as this may further delay absorption of immunosuppressants and increase the risk of acute rejection in the early postoperative period.²⁰

Diabetic gastroparesis has been shown to improve after SPK. In 8 diabetic patients, Gaber and associates reported a substantial improvement in gastrointestinal symptoms, the rate of gastric emptying and gastric electrical activity following SPK.²¹ A significant improvement in electro-gastrography ($P \leq .0159$) and total gastrointestinal symptom score ($P = .0001$), along with an improvement in other markers of autonomic function, such as the postural adjustment ratio ($P \leq .0085$) and the Valsalva ratio ($P \leq .0348$), also have been shown after SPK.²² An improvement in autonomic function is thought to occur because of long-term normoglycaemia that pancreas transplantation can achieve.²³ Botulinum therapy may be a useful treatment option while patients with diabetic gastroparesis wait for a pancreas transplant or islet-cell allograft, or as a short-term treatment in the early postoperative period while awaiting the return of normoglycemia.

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