Parkinsonism and Related Disorders xxx (2017) 1–5

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Pilot cohort study of endoscopic botulinum neurotoxin injection in Parkinson's disease

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ARTICLE INFO

Article history:
Received 1 July 2017
Received in revised form
12 August 2017
Accepted 20 August 2017

Keywords:
Parkinson's disease
Botulinum neurotoxin (BoNT) injection
Gastrointestinal dysfunction
Dysphagia
Gastroparesis
Constipation

ABSTRACT

Background: Gastrointestinal symptoms, such as dysphagia, postprandial bloating, and defecatory straining are common in Parkinson's Disease (PD) and they impact quality of life. Endoscopic botulinum neurotoxin (BoNT) injection has been used in the treatment of dysphagia, gastroparesis and chronic anismus.

Aims: To examine the feasibility, safety and efficacy of endoscopically delivered BoNT injection to distal esophagus, pylorus or anal canal aiming at relieving regional gastrointestinal symptoms in patients with PD.

Methods: This is a retrospective open cohort pilot study to assess the clinical response to endoscopic BoNT injection on selected PD patients with symptoms and identifiable abnormalities on high-resolution manometry and wireless motility capsule, to generate early uncontrolled data on feasibility, tolerability, safety and efficacy. Baseline symptoms and response to therapy were assessed by questionnaires.

Results: Fourteen PD patients (10 M:4 F), mean age 73 (range: 62-93) were treated. Three patients had esophageal Botox for ineffective esophageal motility (IEM) (n = 1), esophago-gastric junction outlet obstruction (EGJOO) & IEM (n = 1), and diffuse esophageal spasm (DES) (n = 1). Nine patients were treated with pyloric BoNT injection for gastroparesis with mean gastric transit time of 21.2 h; range 5.2 −44.2 h. Two patients received anal Botox for defecatory dyssynergia ((Type I) (n = 1) and overlap (slow-transit and dyssynergic) constipation (n = 1). Endoscopic BoNT injection (100-200 units) was well tolerated and there were no significant adverse events.

Conclusions: Endoscopic BoNT injection to esophagus, pylorus or anal canal is safe, well-tolerated and leads to symptomatic improvement that lasts up to several months. The procedure can be repeated as needed and combined with other therapies.

1. Introduction

Over the past decade, there has been increasing awareness and interest in the gastrointestinal (GI) neuromuscular dysfunction of PD, since it may impact quality of life, increase health care costs, and lead to emergency room visits and hospitalizations [1-4]. The etiology of such dysfunction is multifactorial, resulting from alterations of both intrinsic and extrinsic gut innervation. Alpha-synuclein deposition has been found throughout the enteric nervous system, often described in a retro-caudal gradient, with a higher burden in the upper gut [5]. The extrinsic nervous system is also involved, with a high level of Lewy bodies found in the dorsal motor nucleus of the vagus that influences gastrointestinal motility [6]. The enteric nervous system continues to be a promising prospect as a peripheral marker of PD [7].

Clinically, most of the GI dysfunction in PD is subacute or chronic. Dysphagia is common in patients with advanced PD and is associated with a high prevalence of underlying motility disturbances on high resolution manometry (HRM) but of unclear clinical significance [8]. Other symptoms, such as nausea or early satiety, may reflect underlying gastroparesis, small bowel transit delay, or both, and may be associated with small bowel bacterial overgrowth. In a recent study utilizing wireless motility capsule (WMC) testing, 35% of PD patients with functional GI symptoms exhibited

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http://dx.doi.org/10.1016/j.parkreldis.2017.08.020
1353-8020/

gastroparesis, 20% small bowel transit delay, while 8% had combined transit abnormalities [9]. In another study of PD patients with constipation, 89% had abnormal high resolution anorectal manometry (HRAM), exhibiting variable degrees of defecatory dyssynergia (DD) with abnormal balloon expulsion, diminished rectal sensation or absent recto-anal inhibitory reflex. Further, 62% of patients exhibited colonic transit delay by WMC study, while 57% had combined HRAM and transit abnormalities, suggesting of overlap constipation [10].

One potential interventional approach to treat symptoms, such as dysphagia, postprandial fullness, or constipation in patients with PD could be the use of botulinum neurotoxin (BoNT) injections. First used in the treatment of dysphagia in esophageal achalasia [11], BoNT has been applied in many other settings (such as gastroparesis and chronic anal fissures with anismus) with variable clinical impact [12]. BoNT produced by *Clostridium botulinum* exerts its dose- and volume-dependent paralytic effect by inhibiting acetylcholine release at the neuromuscular junction; the duration of paralysis is dependent on the eventual restoration of neuromuscular function that follows axon terminal sprouting [13].

In this pilot cohort series, we report the feasibility, safety and efficacy of endoscopically delivered BoNT injection to several GI sites aiming at relieving symptoms in patients with PD. Specifically, we examined if injection of the esophago-gastric junction (EGJ) and distal esophagus might improve dysphagia, pyloric BoNT injection could improve gastroparesis symptoms and PD drug pharmacodynamics, and if anal sphincter injection might improve defecatory difficulties and constipation. Our promising preliminary experience calls for the need of further studies, particularly randomized control trials against sham treatments. If further validated and its long-term merits established, BoNT injection therapy may play a very useful role in improving the quality of life of many PD patients.

2. Patients and methods

Design: This was a retrospective, open, cohort pilot study to assess the clinical response to BoNT injection on highly selected patients with advanced PD, disturbing and resistant symptoms and identifiable abnormalities on HRM, HRAM and WMC to generate preliminary, uncontrolled data on feasibility, tolerability, safety and efficacy. The study was approved by the Institutional Research Board of Stanford University, was conducted at the Neurogastroenterology and Motility Center of Silicon Valley Gastroenterology, in Mountain View, CA, and was considered exempt from the need for individual informed consent from participating patients.

Patients: All patients had abdominal complaints that were recorded upon questioning and formal questionnaire-based assessment. To meet entry criteria, all patients had to have symptoms of at least a 2-months' duration and no structural abnormality to explain them. Patients with PD and GI symptoms were first fully assessed by several tools, such as HRM, WMC and HRAM. A detailed initial history and physical examination were conducted to exclude any other plausible explanation for the patients' symptoms and additional tests were ordered as indicated for diagnosis. ***Inclusion criteria***: We included patients with [1] esophageal dysphagia and underlying HRM abnormalities [2]; bloating, postprandial fullness, belching nausea and weight loss and underlying gastroparesis by WMC; and [3] constipation and defecatory dyssynergia by HRAM. A detailed review of patient's medical, endoscopic, manometric, and WMC records was then performed to ensure proper inclusion in the study. ***Exclusion criteria***: Patients <18 years old and those with obstructive esophageal, gastric or colonic disease by endoscopic studies. Of note, the study, albeit community-based, was on a referral population to a GI motility unit.

Questionnaires: To qualify for inclusion into the study, patients had to be symptomatic on a simple and previously validated general GI questionnaire. In this questionnaire, the symptoms were graded with scores for dysphagia, regurgitation, postprandial coughing and aspiration, chest fullness, early satiety, bloating, belching, abdominal pain, nausea, weight loss, defecatory straining, incomplete evacuation, and constipation (0 = no symptom, 1 = mild symptom, 2 = moderate symptom, and 3 = severe symptom, occurring at various frequencies [once a week = 0, 2 to 6 times a week = 1, 7 to 15 times a week = 2, and more than 15 times a week = 3] [8-10]. Neurological assessment of the patients was made using the previously validated modified Hoehn and Yahr scale (score 0-5) [14]. The duration of PD was recorded in years since the time of diagnosis. Variable regimens of PD therapies were used and not discontinued for the performance of the BoNT injection or thereafter. Such therapies included carbidopa-levodopa, pramipexole, ropinirole, rotigotine, rasagiline, rivastigmine, and amantadine in various doses and schedules. Upon follow up, one month after injection, patients were asked if they felt that the treatment was effective and they were scored as: 0, no response to the treatment, would not repeat; 1, treatment helpful but uncertain about a repeat procedure; and, 2, treatment helpful and worth repeating as needed.

Endoscopic BoTox injection: For the injection of BoNT to the esophagus and pylorus, a flexible endoscopy was performed under conscious sedation or propofol anesthesia. Utilizing the sclerotherapy needle, 100-200 units of BoNT were then administered in 4 quadrants of the EGJ, lower esophagus and pylorus respectively, as needed [12]. For the anal canal, a flexible endoscope and sclerotherapy needle were used to inject the sphincter in 4 quadrants with 100 units (Fig. 1).

Data analysis: Clinical information, including age, gender, and gastrointestinal symptoms, was collected in all patients. Gastric emptying time (GET) longer than 5 h was diagnostic of gastroparesis; colonic transit time (CTT) longer than 59 h defined colonic transit delay. Statistical analysis was performed using Minitab Express software. Data are presented as box plots.

3. Results

Table 1 depicts the demographics of our patient population and highlights the therapeutic objectives sought. The reasons for intervention to the esophagus and/or EGJ were dysphagia, regurgitation, chest fullness, odynophagia, throat clearing, or postprandial cough and aspiration. The reasons for pyloric injection were early satiety, bloating, epigastric pain, nausea, weight loss, and/or impaired levodopa pharmacodynamics. Finally, the reasons for anal injection therapy were defecatory straining, incomplete evacuation, and constipation. The frequency and severity of key symptoms at baseline was quantified by questionnaires and is shown in Fig. 2 and most patients had symptoms from several regional GI domains. Constipation and defecatory straining were the predominant symptoms, followed by dysphagia, weight loss, postprandial bloating, abdominal pain, nausea/vomiting and coughing/aspiration. The decision to proceed with injection therapy was based on both clinical indications (i.e. symptom severity), as well as objective evidence of regional dysfunction by HRM, WMC and HRAM as highlighted in Table 2. All endoscopic procedures were performed using propofol anesthesia and they were well tolerated except for one case of pyloric BoNT injection that was associated with self-limited, mild to moderate epigastric pain, not requiring narcotics or other interventions. The cumulative response scores for the 3 groups are shown in Fig. 3 (left). Only 1/14 patients had no response whatsoever (score 0). The median duration of the BoNT effect was 8.3 months (range 1–23 months; 95% median CI 2–13.6) (Fig. 3, right). Three of the patients had repeat procedures

Please cite this article in press as: G. Triadafilopoulos, et al., Pilot cohort study of endoscopic botulinum neurotoxin injection in Parkinson's disease, Parkinsonism and Related Disorders (2017), http://dx.doi.org/10.1016/j.parkreldis.2017.08.020