The Role of Botulinum Toxin in the Gastrointestinal Tract

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Introduction

Botulinum toxin, produced by Clostridium botulinum, is a potent toxin that inhibits the release of acetylcholine from nerve terminals and causes paralysis of skeletal muscle. Although it has eight major serotypes, only two types (A and B) have long-lasting period of action and are used in clinical practice. Botulinum toxin (Botox) injections have been utilized in a multitude of clinical indications, including strabismus, hemifacial spasm, and cervical dystonia [1–3].

In 1993, it was hypothesized that onabotulinumtoxinA (Botox) may have a similar effect on gastrointestinal smooth muscle. This was tested by injecting Botox into the lower esophageal sphincter of five piglets and comparing the effect with the injection of normal saline [4]. A tone reduction of about 60% was observed without evidence of toxicity [4]. In the same year, Botox was injected for the first time in a therapy-resistant achalasia patient, and eventually 2 years later. In 1995, it was demonstrated that intrasphincteric injection of botulinum toxin in humans had the potential to be useful in the treatment of achalasia [5, 6]. Since then, Botox has been used increasingly in the GI tract in various applications described in this review.

Upper Esophageal Sphincter Dysfunction

Botox has been in use in the field of otorhinolaryngology and Neurology, as a relatively safe and efficacious treatment of facial nerve disorders such as hemifacial-spasm, laryngealdystonia, oromandibular dystonia, and spasmodic torticollis [7, 8].

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Dysphagia and deglutition problems combined with aspiration are caused by spasticity, hypertonus, or delayed relaxation of the upper esophageal sphincter (UES). UES dysfunction during swallowing has been reported in numerous acute and progressive neurological conditions including, but not limited to, brainstem stroke, motor neuron disease, Parkinson's disease, myasthenia gravis, and inclusion body myositis [9–13].

Management of impaired UES relaxation varies across individuals and intervention can be pharmacological, compensatory, rehabilitative, or surgical in nature [14]. Compensation includes the use of postural strategies and voluntary maneuvers. Rehabilitation programs are designed to target impaired UES and include jaw exercises, the Shaker exercises, and the Mendelsohn maneuver [14]. In cases where patients have demonstrated minimal benefit from a trial of compensatory therapy and rehabilitation, they may be considered for surgical or pharmacological interventions. Surgical intervention includes cricopharyngral myotomy and upper esophageal dilatation. The pharmacological intervention consists of injection of Botox into the cricopharyngeus.

The first use of Botox in this setting was described in 1994 in a series of seven patients. Conventional therapy (i.e., lateral cricopharyngotomy and laser dissection of the UES) was replaced by Botox injection with complete resolution of symptoms in five of seven patients [15]. Since this initial 1994 study, cricopharyngeal Botox injection has been reported in over 200 patients with dysphagia of varying etiologies with success rates ranging between 43% and 100%. However, a Cochrane database Systemic review published in 2014 concluded that no randomized controlled studies are available and there is insufficient evidence to recommend its use in clinical practice, hence, it was not possible to reach a conclusion on the efficacy and safety of botulinum toxin as an intervention for people with UES dysfunction [14].

Achalasia

Achalasia is a disorder characterized by a failure of the lower esophageal sphincter to relax with swallowing and by a lack of esophageal peristalsis. The etiology, for the most part, is unknown. It is characterized manometrically by insufficient relaxation of the lower esophageal sphincter (LES) and loss of esophageal peristalsis; radiographically by aperistalsis, esophageal dilation, with minimal LES opening, "bird-beak" appearance and poor emptying of barium; and endoscopically, by dilated esophagus with retained saliva, liquid, and undigested food particles in the absence of mucosal stricturing or tumor [16].

Achalasia was first described and termed by Sir Thomas Willis in 1672, when he suggested that the disease is due to the loss of normal inhibition in the distal esophagus [17].

Since then, new ideas on the etiology and pathophysiology of the disease have been promoted leading to various theories in identifying the nature of motor disturbances in esophageal regions. This includes cardiospasm, esophageal muscle

failure, and physical obstruction [18]. Subsequently, a body of evidence has emerged showing that idiopathic achalasia is indeed caused primarily by the loss of the inhibitory innervation of the esophageal myenteric plexus. However, the initiating cause remains elusive [16].

These abnormalities stem from impairment of the inhibitory innervation to the esophageal smooth muscle and the lower esophageal sphincter [19]. The smooth muscle of the distal esophagus is innervated by the preganglionic vagus nerve fibers with cell bodies located in the dorsal motor nucleus [20]. The postganglionic excitatory neurons release acetylcholine while the inhibitory neurons release nitric oxide and vasoactive intestinal polypeptide resulting in esophageal and LES contractions and relaxations, respectively [21, 22]. The inhibitory neurons also play a role in normal peristalsis. At baseline, the esophageal muscle is in a contractile state. With swallowing, the inhibitory neurons are excited, which results in esophageal relaxation. A coordinated series of relaxation followed by contraction in a cephalic-caudal direction results in peristalsis [23]. In patients with achalasia, there is loss of the inhibitory neurons, resulting in failure of LES relaxation and loss of esophageal peristalsis [24].

Idiopathic achalasia is rare, has an insidious onset, and disease progression is gradual. Patients typically experience symptoms for years prior to seeking medical attention. A recent population-based study reported mean incidences of 0.3–1.63 per 100,000 people per year in adults [25, 26]. The mean duration of symptoms was 4–6 years prior to diagnosis [27]. Most frequent symptoms are dysphagia toward solids (91%) and liquids (85%), regurgitation (76%), heartburn (52%), chest pain (41%), and weight loss (35%) [28]. In the early stages of the disease, dysphagia may be very subtle and can be misinterpreted as dyspepsia, poor gastric emptying, or stress. The presence of heartburn due to food stasis can add to this confusion. As the disease progresses, difficulty swallowing characteristically occurs with both solid foods and liquids. The dysphagia is more to solids than liquids.

When achalasia is suspected, a primary barium esophagogram with fluoroscopy is a useful diagnostic test (Fig. 1) [29].

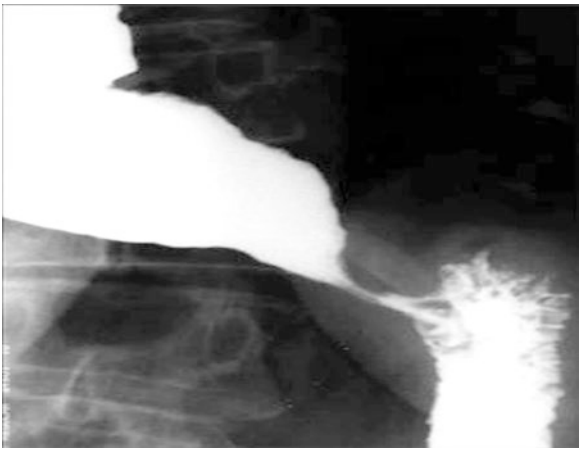

Fig. 1 Barium esophagogram showing "bird-beak" appearance of achalasia

Esophagogram findings include dilation of the esophagus, a narrow esophagogastric junction with "bird beak" appearance, aperistalsis, and poor emptying of barium. A variation of barium swallow, named "timed barium swallow," which includes measuring of a barium column height 1 and 5 min after upright ingestion of a large barium bolus, has been used to assess esophageal emptying after therapy [30]. The primary role of esophagogastroduodenoscopy (EGD) in the workup of achalasia is focused on ruling out a mechanical obstruction or pseudoachalasia as they can mimic achalasia. Endoscopic evaluation in these patients often demonstrates a dilated esophagus with retained food or saliva and a puckered gastroesophageal junction [16].

By definition, an assessment of esophageal motor function is essential for the diagnosis of achalasia. Achalasia is diagnosed on high-resolution manometry by an elevated median integrated relaxation pressure (IRP), which indicates impaired EGJ relaxation, and absence of normal peristalsis. According to the Chicago Classification (CC, version 3.0 [CC-3]) of patterns of esophageal pressurization on high-resolution manometry, achalasia is subtyped into Type I (classic achalasia), Type II, and Type III (spastic achalasia). These subtypes have important implications for management [31].

Achalasia is a chronic condition and current treatment options in achalasia are aimed at reducing the hypertonicity of the LES by pharmacologic, endoscopic, or surgical means.

For patients who are at low surgical risk, pneumatic dilation or surgical myotomy should be performed to treat achalasia. Per-oral endoscopic myotomy (POEM) is a promising new endoscopic technique for performing myotomy. The aim of all endoscopic and surgical treatments are to weaken the LES by cutting its circular muscle fibers [32]. Initial success rates are high with either modality (85% for pneumatic dilation and 90% for surgical myotomy); however, about one-third of patients have recurrence of symptoms within 4–6 years [33].

The two most frequently used pharmacological drugs are nitrates and calcium-channel blockers. Medical therapy is the least effective treatment option in patients with achalasia, and should be considered in patients who are unwilling or unable to tolerate invasive therapy and for patients who have failed Botox injections [34].

Botox therapy is strongly considered in patients who are not good candidates for more definitive therapy with pneumatic dilation or surgical myotomy. Botulinum toxin A, which blocks the release of acetylcholine from the nerve terminals, is directly injected into the LES. EGD for the injection of Botox is often performed under conscious sedation using a combination of intravenous fentanyl and versed or under monitored anesthesia care using predominantly propofol. The lower esophageal sphincter will be visualized endoscopically by identification of the sphincteric rosette, seen at the squamocolumnar junction. Botox is injected using a 5-mm or 7-mm sclerotherapy needle (other injection needles have been used based on the center) into the region of the lower esophageal sphincter. Aliquots of 1 ml each (20–25 units of botulinum toxin per milliliter of saline) are injected into quadrants, for a total of 80–100 units [35].

Table 1 Randomized trails comparing Botox injection to Balloon dilation and myotomy for treatment of achalasia

Author	Compared to	*N*	Response rate (30 day) Botox group vs. non-Botox group	Recurrence rate (12–24 month) Botox group vs. non-Botox group
Zaninotto et al. [42]	Surgical myotomy	80	66% vs. 82% ($p < 0.05$)	87.5% vs. 34% ($p < 0.05$)
Zhu et al. [41]	Balloon dilation and balloon dilation + Botox	90	75% vs. 85% vs. 93%	84% vs. 64% vs. 43%
Mikaeli et al. [40]	Balloon dilation	40	Not available	85% vs. 47% ($p < 0.05$)
Ghoshal et al. [39]	Balloon dilation	17	86% vs. 80% (p = NS)	71% vs. 25% ($p = 0.027$)
Vaezi et al. [38]	Balloon dilation	42	Not available	68% vs. 30% ($p < 0.01$)
Muehldorfer et al. [37]	Balloon dilation	24	75% vs. 83% (p = NS)	100% vs. 40% ($p < 0.05$)

More than 80% of cases have a clinical response by 1 month, but response fades rapidly, with less than 60% of patients in remission at 1 year [36]. Findings from six randomized trials comparing Botox with pneumatic dilatation and laparoscopic myotomy are shown in Table 1. These studies demonstrated comparable relief from dysphagia, but a rapid deterioration in patients treated with Botox after 6–12 months compared to the two other modalities [37–42].

The most common complications of esophageal Botox injections are mild and related to the injection procedure or the decreased LES pressure. The occurrence of transitory chest pain and gastroesophageal reflux has been reported after 0–30% of procedures. Thus far, no serious adverse events have been reported in secondary or pre-appraised publications. However, a number of case reports have been published on severe complications after esophageal Botox injections including one death due to pneumothorax [43].

Botox injection is less invasive compared with surgery and can be easily performed with endoscopy. As seen in Table 1, initial success rates with Botox are comparable to pneumatic dilation and surgical myotomy [44]. However, patients treated with Botox have more frequent relapses and a shorter time to relapse. Greater than 50% of patients with achalasia treated with Botox require retreatment within 6–12 months. Repeated Botox injections can negatively impact the outcome of subsequent myotomy [45].

Hypertensive Esophageal Disorders

This group of esophageal motility disorders is a somewhat rare but troublesome group of disorders that can lead to severe symptoms including nausea, regurgitation, dysphagia, and chest pain [46]. Using esophageal manometry, esophageal motility abnormalities are classified as achalasia (discussed previously) and other abnormal motility patterns, which are in turn subclassified into

hypercontracting, hypocontracting, or discoordinated motility disorders. Since the introduction of Botox for the treatment of achalasia in 1995, its utility has been expanded to a spectrum of esophageal motility diseases, most importantly diffuse esophageal spasm (DES), nutcracker esophagus, and hypertensive lower esophageal sphincter. These conditions are also collectively called hypercontractile esophageal disorders.

There are limited data on the prevalence of hypercontractile esophageal disorders. The prevalence of these conditions among individuals with atypical chest pain appears to be between 4% and 13% [47]. The underlying pathophysiology for these conditions is relatively unknown. DES has been associated with an impairment of inhibitory innervation and malfunction in endogenous nitric oxide synthesis [48]. Nutcracker esophagus and hypertensive LES are due to overactivity of excitatory innervation or asynchrony of the smooth muscle response due to hypercholinergic state [49].

The typical symptoms of patients with DES are dysphagia associated with retrosternal chest pain. Many of the patients with nutcracker esophagus or hypertensive LES have no symptoms. The diagnosis of these patients is often made through esophageal manometry after a normal endoscopic examination. Each of these conditions has distinct manometric findings, and diagnosis is often made once manometric criteria are met.

Multiple therapies have been used to treat diffuse DES, nutcracker esophagus, and hypertensive LES, the most effective treatment has not been established yet. Calcium channel blockers and tricyclic antidepressants have been shown to be effective in the treatment of dysphagia and chest pain, respectively, and they have been considered as the first-line treatment for these conditions [50–52].

For patients who do not respond to the first-line treatment, injection of Botox or oral nitrates (isosorbide 10 mg or sildenafil 50 mg on an as-needed basis for pain) is considered as the next treatment option [53, 54].

Typically, 100 units of Botox is diluted in 4 ml saline. During the EGD, aliquots of 0.5 ml Botox are injected in the four quadrants at 2 cm above the gastroesophageal junction, and 5 cm more proximally using a standard sclerotherapy needle. In spastic esophageal motor disorders, Botox is injected at several levels close to the lower esophageal sphincter and in the distal esophageal body. It is important to avoid submucosal injection or injection outside the esophageal wall. Symptom relief occurs in 70–90% of patients within 30 days after the procedure. However, >50% of patients require repeat treatment within 6–24 months. The procedure is performed on a day-case basis and patients are allowed to eat as tolerated.

Botox injection in these patients has been shown to improve the symptoms of dysphagia significantly, but has no or minimal effect on chest pain, regurgitation, or heartburn [55]. Interestingly, injections into the esophageal body, application of more injection sites per procedure, history of previous injections, and increasing the dose did not increase the risk of complications [43].

Gastroparesis

Normal gastric motility results from a complex series of events that requires coordination of the sympathetic and parasympathetic nervous systems, neurons, and pacemaker cells of Cajal within the stomach and the smooth muscle cells. Abnormalities of this process can lead to a delay in gastric emptying [56]. Gastroparesis is defined by delayed gastric emptying in the absence of a mechanical obstruction [57]. The age-adjusted prevalence of gastroparesis is 9.6 per 100,000 persons for men and 38 per 100,000 persons for women [58].

The etiology for over half of the patients with gastroparesis in unknown and, therefore, these are classified as idiopathic gastroparesis. Both long-standing diabetes mellitus and hyperglycemia are associated with delayed gastric emptying. In the former, this occurs through diabetic neuropathy. Neuropathy causes abnormal postprandial proximal gastric accommodation and difficulties with antral motor function [59, 60]. Medications (including narcotics and dopamine agonists) have shown to delay gastric emptying [61]. Previous gastric and thoracic surgery can result in gastroparesis due to intentional or accidental injury to the vagus nerves [62]. Several common neurologic disorders are associated with gastroparesis, which include multiple sclerosis and Parkinson's disease [63].

Patients with gastroparesis can present with nausea, vomiting, abdominal pain, early satiety, postprandial fullness, bloating, and weight loss. The vomitus may contain food ingested several hours previously [57].

Initial evaluation of patients with gastroparesis includes endoscopy and cross-sectional imaging to exclude mechanical obstruction. The most commonly used and cost-effective modality to diagnose gastroparesis is a 4 h scintigraphic gastric emptying scan [64, 65].

Treatment options for gastroparesis include dietary changes, prokinetic drugs, antiemetics, correction of malnutrition and electrolyte disturbances, jejunal feeding, parenteral nutrition, gastric neurostimulation therapy, and surgery.

The first step in management is dietary counseling and nutritional support. For severe cases, enteral nutrition should be established, before consideration of medical, endoscopic, or surgical therapy [66, 67].

Dopamine type 2(D2) receptor antagonists have been the most studied and utilized family of medications for the treatment of gastroparesis. Notable in this family of drugs are metoclopramide and domperidone, of which, the former has been in use for close to 40 years [68–70]. Macrolides (erythromycin), 5-HT4 receptor agonists, ghrelin agonists, 5-HT3 receptor antagonists, and cannabinoid-1 agonists have been used as well with variable degrees of response in gastroparesis [66].

Invasive interventions include intra-pyloric botulinum toxin injection, venting gastrostomies, gastric electric stimulators, and pyloromyotomy (surgical or endoscopic). Since the late 1990s, there has been conflicting evidence regarding the efficacy of intra-pyloric botulinum toxin in the management of gastroparesis. The first data on the intrapyloric application of Botox in patients with gastroparesis was published in 2002 [71]. Injection of 100 units of Botox into the pylorus in patients with diabetic gastroparesis showed 50% improvement in their symptoms and gastric

emptying tests. Further, open-labeled trials showed promising evidence of improvement in gastric emptying tests, symptoms, and SF-36 scores with an intra-pyloric injection of 200 units Botox [72, 73]. Miller et al. demonstrated the effectiveness of repeat injections but at the same time raised a question regarding long-term outcomes of the procedure [73]. Two additional randomized trials reported improvement on gastric emptying tests without significant symptomatic improvement [74, 75]. A small retrospective analysis of 21 patients with a mean follow-up of 2 years demonstrated a 62% response to treatment compared to 19% non-responders. The mean response duration was 4.2 months. Weight gain and increased insulin requirement were observed in the diabetic group with greater effectiveness in the diabetic population compared to idiopathic gastroparesis [76]. Thus far, one of the largest studies published was a retrospective trial of 179 patients including 81 with diabetic gastroparesis and 76 idiopathic gastroparesis cases, and suggested a better response in women, younger patients (<50 years old) and those with idiopathic gastroparesis [77]. Ukleja et al. concluded in a review article that it is important to emphasize that improvement in gastric emptying has not been shown to correlate with symptom improvement in this patient population. Hence, assessing response to Botox treatment based on gastric emptying studies has its own limitations [78]. Thus, despite the fact that it is currently not recommended, due to limited availability of medical treatment options, physicians should consider Botox as a trial therapy before directing patient with refractory gastroparesis for more aggressive treatment such as surgical interventions including placement of jejunostomy tube or gastric electrical stimulator and gastrectomy.

Sphincter of Oddi Dysfunction

Sphincter of Oddi dysfunction (SOD) refers to a clinical syndrome that occurs because of the abnormal sphincter of Oddi (SO) contractility. It has been defined by an excessively high baseline sphincter pressure of ≥40 mmHg [79]. Elevated pressure in the sphincter can lead to pancreatitis, chronic right upper quadrant pain, and elevated liver function tests. A subgroup of these patients has only elevated pressure above 40 mmHg with pain and is designated "sphincter of Oddi dysfunction type III." Controversy exists concerning the best management of this subgroup. Performing sphincterotomy during endoscopic retrograde cholangiopancreatography (ERCP) is considered one of the treatment options. The risks associated with sphincterotomy include bleeding perforation and pancreatitis, and the results following endoscopic sphincterotomy are often disappointing [80]. Therefore, the concept of trial of Botox prior to sphincterotomy has been entertained. Pilot studies have shown a substantial decrease in the SO pressure with the use of Botox injection [81], but there are no placebo-controlled studies available formally evaluating the effect of Botox injection on SOD type III. One study has shown that 50% of patients receiving Botox for SOD (type III) had some improvement of their pain. It has also served as a predictor to determine who may respond to endoscopic sphincterotomy [82].

However, long-term follow-up of patients with SOD type III has shown no benefit from ERCP and sphincterotomy to the extent that it has been recently proposed to discard the concept of SOD type III from GI functional gastrointestinal disorders (i.e., Rome IV criteria) [83]. This undermines the usefulness of any intervention of the SO (sphincterotomy or Botox) in patients with type III SOD.

New and novel indications for Botox injection in SO have been proposed. Recently, Botox has been successfully used to temporarily reduce the SO pressure after distal pancreatectomy to prevent pancreatic fistula formation. Injecting Botox pre-operatively has reduced the incidence of fistula formation significantly without any major or minor side effects [84].

Anal Fissure

An anal fissure is a common benign anorectal condition that may result from high anal pressure. Fissure is a tear in the anoderm distal to the dentate line. Anal fissures may be acute or chronic. Acute fissures may result from local trauma or may be secondary to an underlying medical/surgical condition. Chronic anal fissure fails conservative management and requires a more aggressive approach [85].

Fissure is the result of the stretching of the anal mucosa beyond its normal capacity. Once the tear occurs, it begins a cycle leading to repeated injury. The exposed internal sphincter muscle beneath the tear goes into spasm. This results in severe pain, pulling apart the edges of the fissure and subsequent impair healing of the wound. Repeated trauma results in a chronic anal fissure in 50% of patients [86].

Anal fissures most often affect infants and middle-age individuals, and the most common causes are the passage of hard stool, prolonged diarrhea, vaginal delivery, or anal sex [87].

Patients with an acute anal fissure present with sharp pain associated with the passage of bowel movements. Some describe a small amount of bright red blood on the stool or the toilet paper. Other less frequent complaints include perianal pruritus and/or skin irritation. Patients with a chronic fissure typically have less intense pain. The most common location of a fissure is posterior midline. Deep fissures can extend to the external anal sphincter. Chronic fissures are often characterized by sentinel pile and hypertrophic anal papillae resulting from chronic inflammation [88].

This first line of treatment for anal fissure is a combination of supportive measures and a topical vasodilator. Conservative measures include increase dietary fiber (or fiber supplements) and water intake to soften and bulk the stool, Sitz baths a few times a day, and topical analgesics such as 2% lidocaine jelly [89–91]. Commonly used topical vasodilators include nifedipine (0.2% or 0.3%) and nitroglycerin (0.2% or 0.4%) ointments. These therapies have a response rate ranging from 60% to 90%, and a recurrence rate of 30–40% [92, 93]. For patients who fail medical treatment, the next step is either Botox injection or a lateral sphincterotomy. One of the main concerns with surgical option for the management of anal fissures is incontinence. In patients with high risk of incontinence such as multiparous women and elderly, Botox injection is considered as the first line of treatment option for refractory fissures.

The first use of Botox in anal fissure was reported in 1993 when the first case was treated using 2.5 units of Botox injected into the external anal sphincter [94]. Injection of Botox into the anal sphincter can help relax the hypertonic anal sphincter muscle and, in turn, improve healing of anal fissures. Botox is typically injected into the internal anal sphincter on either side of the fissure using a 27-gauge needle [95]. The most common dose for injection is 10–20 units of Botox. A recent meta-analysis showed a range of 5–150 units of Botox being used in various settings [96]. The same study did not show any dose-dependent efficiency or complication rate.

Botox injection has been shown to be superior to topical vasodilators in the treatment of chronic anal fissure; however, in long-term follow-up may not differ significantly from vasodilators [97, 98]. Thus, botulinum toxin has proven to be a valid option in patients with chronic anal fissures who desire a non-surgical intervention or those with certain grades of incontinence.

Randomized trials have compared the efficacy and side-effect profile of Botox injection with lateral sphincterotomy. Sphincterotomy has a higher healing rate and a lower recurrence rate than the intra-sphincteric injection of Botox. Botox injection has a reported recurrence of up to 40–50% [99]. The risk of incontinence in Botox injection, however, is less than lateral sphincterotomy (7% vs. 35%) [100]; therefore, Botox injection appears to be a simple noninvasive technique that avoids the greater risk of incontinence and it could be used as the first therapeutic approach in patients without clinical risk factors of recurrence [101, 102].

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