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Endoscopic injection therapy for achalasia and other esophageal motility disorders

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ABSTRACT

Botulinum toxin (BT) injections have been proposed to treat achalasia and hypertensive esophageal motility disorders. They affect lower esophageal sphincter (LES) and esophageal muscle function by inhibiting acetylcholine release and thus preventing neuromuscular conduction. BT injection in the LES is effective to treat achalasia but the improvement is limited to few months. As a consequence, recent guidelines recommend BT in achalasia patients who are not good candidates for more definitive therapy with pneumatic dilation or myotomy. BT might be a good option for patients with esophago-gastric junction obstruction without a firm diagnosis of achalasia. However, response to BT injection is not predictive of response to a more invasive therapy. BT injection in both the LES and the esophageal body might have a short-term efficacy to relieve dysphagia in patients with diffuse esophageal spasm or nutcracker esophagus. Usually BT is administrated as 1 cc aliquots with 20 units of toxin per milliliter into the LES and/or the esophageal body for a total dose of 100 unit international. BT injections are usually safe. Moderate chest pain might be reported following the injection. Three cases of death were reported due to acute mediastinitis and pseudoaneurysm. Finally, there is a theoretical risk of increased difficulty to perform esophageal myotomy in patients who previously received BT therapy due to the potential risk of fibrosis.

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1. Introduction

Achalasia and other esophageal motor disorders have been confounded by the need to use a mechanical therapeutic approach to a disorder of abnormal motility. To a large degree, this paradox has continued as a result of our ineffectual attempts to pharmacologically repair the complex perturbations in neurotransmitter function and their consequent effects on bolus transit in esophageal motility disorders. Progress has been made, however, with the application of botulinum toxin (BT) injections to the lower esophageal sphincter (LES) and, perhaps, esophageal body to these disorders. BT affects esophageal LES function by inhibiting acetylcholine release from cholinergic neurons, preventing neuromuscular conduction. With attenuation of this stimulatory effect on esophageal smooth muscle, the toxin helps to restore the balance of excitatory and inhibitory neural inputs, which is lost with inflammatory denervation and decreases in inhibitory neurotransmitters nitric oxide and vasoactive intestinal polypeptide (Figure 1). As a result, intrasphincteric and perhaps esophageal body injections of BT have become potential therapeutic options in treating esophageal motility disorders (Table 1) (Figure 2).

Although this therapy has been implemented in clinical practice for almost two decades its precise role and method of injection in patients with esophageal motor disorders is uncertain. In part, these questions result from balancing the effective but short-term effectiveness of BT injection with the favorable long-term results of pneumatic dilation (PD) and myotomy, the limited data in use for treatment of motor disorders distinct from achalasia and the concerns over the effect on future therapies. In this chapter, we will review the indications and techniques of BT administration for esophageal motility disorders.

Abbreviations: ACG, American College of Gastroenterology; BT, botulinum toxin; DCI, distal contractile integral; EGJ, esophago-gastric junction; EGJOO, esophago-gastric junction outflow obstruction; EUS, endoscopic ultrasonography; HRM, high resolution manometry; IRP, integrative relaxation pressure; LES, lower esophageal sphincter; PD pneumatic dilation; SNARE, soluble N-ethylmaleimide-sensitive fusion attachment protein receptor; VAMP, vesicle-associated membrane protein; VIP, vasoactive intestinal polypeptide; UI, unit international

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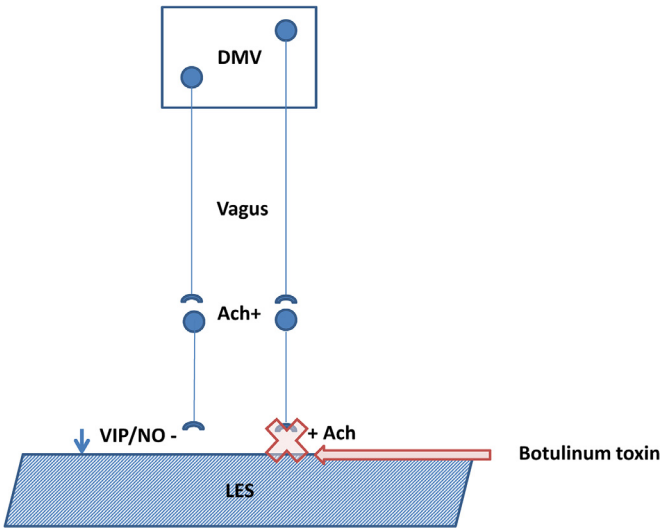

Fig. 1. Illustration of esophageal physiology with excitatory/ inhibitory pathway. NO—nitric oxide, VIP—vasoactive intestinal polypeptide, Ach—acetylcholine, DMV—dorsal motor nucleus of the vagus, LES—lower esophageal sphincter.

2. The indications of BT are summrized in Table 1

2.1. Achalasia

2.1.1. Primary

In 1995, Dr. Pasricha and colleagues published their seminal study on the use of BT in primary esophageal achalasia. Since this time, over 300 articles have been published discussing the role of BT treatment in achalasia. A Cochrane Meta-Analysis examining seven studies comparing BT injection to PD demonstrated similar effects on lower LES pressure and remission at four weeks. PD, however, was significantly more durable than BT at 6 and 12 months, underscoring the theme of previous studies that injection therapy is relatively short lived when compared to other achalasia therapies intended to last years if not a lifetime. As a result, the American College of Gastroenterology Guidelines on Achalasia recommend that "BT therapy is recommended in patients who are not good candidates for more definitive therapy with PD or surgical myotomy (strong recommendation, and moderate quality evidence)" [1]. More specifically, one can expect an average duration of symptom improvement for nine months though the range is variable and improving with patient age and type I-II (but not end stage achalasia). Thus, BT might be a reasonable option in very old patients or in patients with severe comorbidities who are at high risk for PD or myotomy. The presence of varices might be an indication for BT injection [2,3].

Other indications that might be considered is in patients where the diagnosis of achalasia is not firm due to incomplete criteria, achalasia may be due to opioid use, or it is not clear if recurrent symptoms after dilation or myotomy are due to incomplete myotomy. In these cases, a trial of a less invasive therapy can be used first. Unfortunately, there are no clear data predicting the response to subsequent and more definitive achalasia therapy based on the initial response to BT.

2.1.2. Antibody mediated secondary achalasia

Achalasia may occur secondary to tumor synthesized paraneoplastic antibodies, such as Type 1 antineuronal nuclear antibody (ANNA-1 or anti−Hu), type 1 Purkinje cell cytoplasmic antibody (PCA-1 or anti−Yo), and N-type calcium channel antibodies that replicate a physiology similar to primary achalasia. In these patients, often with a poor prognosis due to the type of tumor (commonly small cell lung) or advanced stage, an effective and safe treatment is required without the necessity for years of effectiveness. Case reports and personal experience suggests that BT can be effective in treating achalasia in these patients.

2.2. Esophagogastric junction outflow obstruction

The manometric pattern of esophago-gastric junction outflow obstruction (EGJOO) is defined in the Chicago Classification as elevated median integrative relaxation pressure (>15 mmHg with the Sierra vintage device), sufficient evidence of peristalsis such that criteria for types I-III achalasia are not met [4]. Although originally felt to be a consistent cause of dysphagia, more recent studies have cast doubt on the clinical relevance of this finding. For example, studies have demonstrated on long term follow up that 40%-70% of patients will have spontaneous resolution of the symptoms leading to performance of the index manometry [5,6]. As a result, investigators have sought further indicators that might correlate this pattern with dysphagia such as using an integrative relaxation pressure of 20 mm Hg [7], increased distal contractile integral or hypercontractile esophagus [6] or abnormal bolus transit on impedance measurement [8]. Others intuitively use delayed esophageal emptying on esophagography. Recent data suggested that the occurrence of pan-esophageal pressurization and/or esophageal shortening during rapid drink challenge test (200 ml free drinking as fast as possible) performed during esophageal high-resolution manometry (HRM) might be predictive of dysphagia severity in patients with EGJOO [9,10]. It remains to be determined if this test might help to select good candidates for treatment.

Nevertheless, it is not surprising that the treatment response to interventions such as myotomy or dilation is variable [11]. BT has been used in some of the patients with favorable response. For example, in one series of 36 patients with incomplete LES relaxation, 58 and 55% of patients had >6 and 12 months relief of symptoms, respectively, with a single injection trial [12]. As a result, BT injection in patients with EGJOO becomes not only a safe therapeutic option but to some degree a potential screening test for more durable therapy upon recurrence of symptoms.

2.3. Hypertensive esophageal motility disorders

The effectiveness of BT in treating hypertensive esophageal motility disorders is not well defined. This is as a result of the few studies performed all of lacked control groups. There is also variability in the location of BT injection. Finally, different types of hypertensive motility disorders were included in the series. Thus, diffuse esophageal spasm (DES), jackhammer, and nutcracker esophagus that are grouped under the term of esophageal hypercontractility might have different pathophysiology and/or natural history leading to various responses to BT injection.

Table 1
Botulinum use in esophageal motility disorders.

Indication	Dose (per injection)	Injection site	Response
Achalasia	20 units	4 quadrants of LES	+++
Diffuse esophageal spasm	12.5 units	8 injections 2 and 7 cm above the esophagogastric junction	+?*
EGJOO	20 units	4 quadrants of LES	++?

* Better for dysphagia than chest pain

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