



## Review Article

## Endoscopic botulinum toxin injection: Benefit and limitation

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## A B S T R A C T

Achalasia is an esophageal motility disorder of unknown cause that manifests as symptoms of difficulty in swallowing, with pooling of food and secretions in the lower esophagus. Endoscopic treatment for achalasia is directed at disrupting or weakening the lower esophageal sphincter (LES). As botulinum toxin (botox) is a potent inhibitor of acetylcholine release from nerve endings, it counteracts the unopposed LES contraction that is mediated by cholinergic nerves, thereby lowering LES pressure. In general, a total dose of 100 IU is endoscopically injected in the LES using a sclerotherapy needle, in four gifts, one in each quadrant. The response rates at 1 month following administration are 78% on average (range, 63–90%). By 6 months, the clinical response rate drops to 58% (range, 25–78%); and by 12 months, this further drops to 49% (range, 15–64%). The predictors of response to botulinum toxin injection (BTI) include age greater than 50 years, and the presence of vigorous achalasia, defined by the finding of esophageal contractile waves, with amplitudes in excess of 40 mmHg. Meanwhile, the duration of illness, baseline radiographic features, initial symptom severity, and sex have not been shown to be predictive of response. Compared to both pneumatic dilation and myotomy, BTI has clearly shown to have been at a disadvantage with respect to therapeutic efficacy. However, BTI has several advantages—such as ease of technique, safety, ease of return to work, and higher success rate in vigorous achalasia—compared with pneumatic dilation and surgical myotomy. Botulinum toxin should be preferentially reserved for patients with significant comorbidity, and is not adequate for conventional treatment with laparoscopic Heller's myotomy or pneumatic dilation, or for patients who are on a waiting list for surgery or who are refusing other forms of treatment.

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## Introduction

Achalasia is an esophageal motility disorder of unknown cause that manifests as symptoms of difficulty in swallowing, with pooling of food and secretions in the lower esophagus. The onset of symptoms is often insidious, and usually occurs between the ages of 25 years and 60 years. An increasing incidence with age has been observed, with an equal male-to-female sex distribution; moreover, symptoms gradually progress over a period of years.<sup>1</sup>

The condition is characterized by degeneration of ganglion cells, predominantly the inhibitory neurons in the myenteric plexus of the lower esophageal sphincter (LES). This leads to a rise in the basal tone of the sphincter, loss of peristalsis in the distal esophagus, and a lack of coordinated LES relaxation, in response to swallowing.

The usual treatment for achalasia—balloon dilation or myotomy of the LES—is aimed at lowering the resting pressure of the sphincter.<sup>2</sup> In the past two decades, intrasphincteric injection of botulinum toxin has emerged as an alternative to pneumatic dilation.<sup>3,4</sup> The hypothesis was based on the concept that the net sphincter tone in the gut results from a balance between excitatory influences (acetylcholine and substance P) and inhibitory influences (vasoactive intestinal peptide and nitric oxide).<sup>5</sup> In

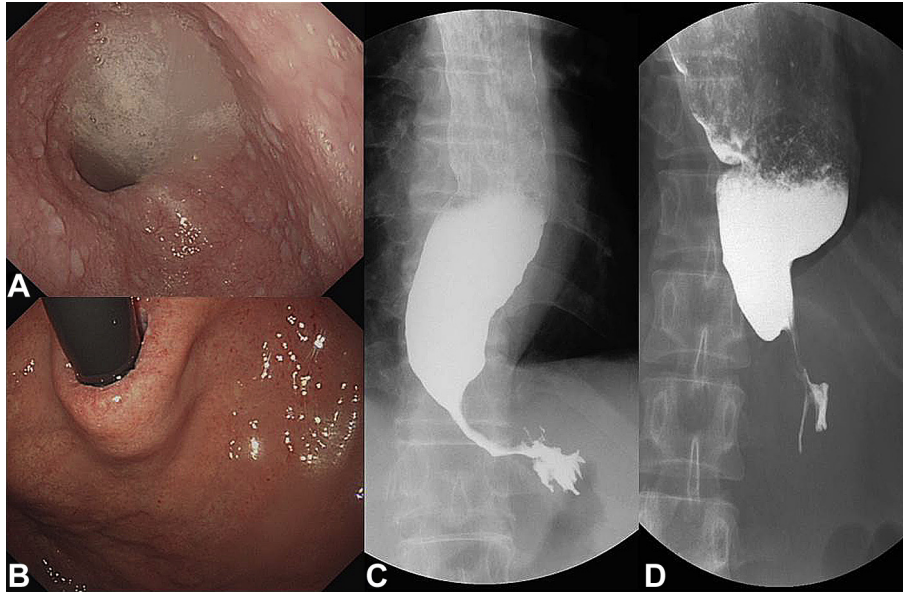
achalasia, this balance may be upset because of the selective loss of the inhibitory nerves,<sup>6–8</sup> resulting in a hypertonic LES that fails to relax. By blocking the release of acetylcholine, locally injected botulinum toxin may restore the LES to a more normal resting tone. It is a safe procedure, being associated with few side effects or complications.<sup>9</sup>

In the early stages of idiopathic achalasia, both barium swallow and endoscopy can be normal. In more advanced cases, endoscopy may show a dilated esophagus with retained food, and some resistance at the gastroesophageal junction (Fig. 1A and B). Barium swallow typically reveals a “bird-beak” image at the junction, with a dilated esophageal body, and an air–fluid level, in the absence of an intragastric air bubble (Fig. 1C and D). Endoscopy is diagnostic in one-third of the patients, whereas barium swallow is diagnostic in two-thirds of the patients. Diagnostic certainty is provided by manometry in 90% of the patients and requires two pathognomonic abnormalities: aperistalsis of the esophageal body and an incomplete relaxation of the LES after deglutition.<sup>10</sup> However, despite the absence of peristalsis, there can still be substantial pressurization within the esophagus. This review discusses the endoscopic botulinum toxin injection (BTI) method, effects of intervention, possible complications, and benefit and limitation.

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**Fig. 1.** Endoscopy showing (A) a dilated esophagus with retained food and (B) tightness, with some resistance at the gastroesophageal junction (GEJ). Barium swallow, showing (C) a “bird-beak” image at the GEJ, with (D) a dilated esophageal body and an air–fluid level.

#### Endoscopic injection technique of botulinum toxin

As botulinum toxin (botox) is a potent inhibitor of acetylcholine release from nerve endings, it counteracts the unopposed LES contraction mediated by cholinergic nerves, thereby lowering LES pressure. In general, a total dose of 100 IU is endoscopically injected in the LES using a sclerotherapy needle, in four injections, one in each quadrant.

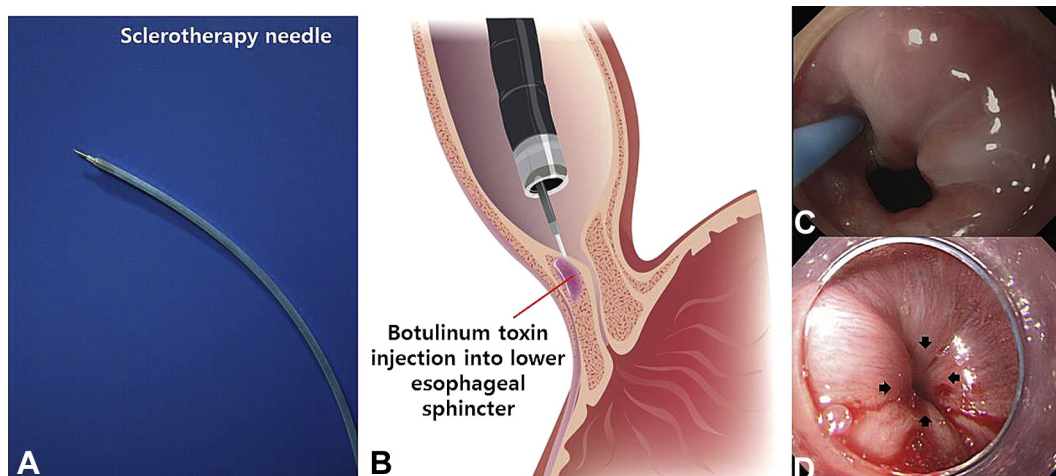
There are only general guidelines concerning the technique of botox injection. An injection needle is used to make the injection at the squamocolumnar junction, of up to 1 cm proximal. An attempt is made to equally space the injections in a circumferential manner, and at the same level (Fig. 2). Attention should be paid to maintaining a perpendicular relationship to the esophageal wall, and avoiding submucosal injection (a visible bleb) or injection outside the esophageal wall. The assistant can usually give feedback regarding the degree of resistance to injection, which should be consistent. Other variations, such as injecting in retroflexion, using endoscopic ultrasound, or using different types of botulinum toxin,

have not gained in popularity.<sup>11</sup> Antibiotics are not usually given, and patients can be discharged immediately, if stable. LES pressure decreases on average by 50% a week after the initial injection, and esophageal emptying improves.<sup>12</sup> Increasing the dose to 200 IU (botox) does not improve the rate of success, whereas repeating a 100-IU injection after 1 month may improve its efficacy.<sup>13</sup>

#### Effects of intervention

BTI was first introduced as a viable treatment for achalasia nearly two decades ago. In their report, Pasricha et al<sup>4</sup> demonstrated symptomatic improvement in 82% of the patients after BTI, compared with 10% of those who received placebo. This trial was followed by a prospective, long-term follow-up study, which showed that two-thirds of patients who received BTI have an improved symptom response, at a mean follow-up of 2.4 years.<sup>14</sup>

In general, a total dose of 100 IU is endoscopically injected in the LES, using a sclerotherapy needle. A large multicenter study



**Fig. 2.** Botox injection method (A) An injection needle is used to make injections at (B, C) the squamocolumnar junction, or up to 1 cm proximally. Then, 100 IU in total is injected in four to five equal volume aliquots, to (D) equally space the injections in a circumferential manner, and at the same level.

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