Review Article

Role of botulinum toxin injection in treatment of achalasia

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: R Heddle; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Achalasia is an uncommon disorder that can be found in children and adults of any age which typically presents with dysphagia, chest pain, and/or regurgitation of food. With the evolution of treatment options, decisions about optimal treatment have become more complex. This review aims to address the role for botulinum injection in the management of achalasia. After a period of enthusiasm for this treatment in the 1990s, most current guidelines suggest that its role is primarily restricted to adult patients who are unfit for more definitive therapies, such as balloon dilatation, Heller's myotomy with partial fundoplication (usually performed laparoscopically), or peroral endoscopy myotomy (POEM). Idiopathic achalasia occurs due to a loss of the nitric oxide-releasing inhibitory nerves in the lower esophageal sphincter, which creates an imbalance between excitatory input added to intrinsic myotonic tone and inhibitory input. The concept behind botulinum toxin injection for achalasia is that it addresses this imbalance by blocking acetylcholine release from excitatory neurones acting on the lower esophageal sphincter. This results in a decrease in lower esophageal sphincter tone that can allow improved esophageal emptying. This review is based on a Medline search of relevant guidelines and literature, with the aim of identifying when botulinum toxin is an appropriate treatment option for achalasia. We also examine what is known about patient selection, technique, efficacy, duration of efficacy, and best practice in terms of botulinum toxin injection for achalasia.

Keywords: Achalasia; treatment; botulinum toxin

Received: 09 March 2020. Accepted: 29 April 2020; Published: 25 September 2020.

doi: 10.21037/aoe-2019-ach-09

View this article at: http://dx.doi.org/10.21037/aoe-2019-ach-09

Introduction

The incidence of presentation of achalasia in the era of high-resolution manometry appears to be around 2.5/100,000 per year based on incidence studies from South Australia and Central Chicago (1,2). Current guidelines suggest a limited role for botulinum toxin injection into the lower esophageal sphincter, largely confined to older adults where other more definitive therapies are contraindicated because of co-morbidities (3,4).

Achalasia usually presents with symptoms such as dysphagia, chest pain, and regurgitation and, in more advanced cases, with progressive weight loss. The diagnosis is supported by evidence of incomplete esophageal emptying on barium study or endoscopy, absent peristalsis in the lower 2/3 of the esophagus, and a lower esophageal sphincter which fails to fully open. This is in the absence of other structural pathology, such as malignancy or benign mucosal strictures of the distal esophagus or lower esophageal sphincter.

The diagnosis of achalasia is confirmed with high resolution esophageal physiology studies. The manometric features are (I) typically elevated median integrated lower esophageal sphincter relaxation pressure (IRP 4s) values (the actual threshold value depends on the high resolution

catheter used) and (II) absence of normal esophageal peristalsis. Type 1 achalasia meets these criteria and panesophageal pressurizations are weak if present. Type 2 achalasia is characterised by panesophageal pressurizations ≥30 mm mg with ≥20% of swallows, whilst type 3 achalasia is characterised by absent peristalsis but with premature contraction in at least 20% of swallows (5). There is a growing body of evidence that responses to treatment may vary according to achalasia type and patient age, and these factors may influence choice between treatment options. Generally, type 1 and 2 achalasia respond better to disruption or stretching of the lower esophageal sphincter than type 3 (5,6), and in particular botulinum toxin injection appears to have a low success rate with types 1 and 3 achalasia (6).

Although there are 5 botulinum toxin drugs available (7), most studies appear to have used Botox (botulinum toxin type A, Allergan Inc, Irvine, California, USA). This drug is in powder form and is heat sensitive, requiring storage below 8 degrees. It is dissolved in sterile Normal Saline prior to use.

Methods

A Medline search was performed to identify relevant international guidelines, and original publications on the use of botulinum toxin for achalasia. In particular meta-analyses of treatment outcomes for achalasia by subtype were sought, and older studies, which predated current classification of achalasia, were also reviewed looking for data on efficacy, duration of effect, and safety of botulinum toxin injection in treatment of achalasia.

Results

Current guidelines

The 2018 ISDE achalasia guidelines (3), based on a consensus amongst a group of 55 international experts, recommend that botulinum toxin injection for achalasia: (I) has little place in treatment of achalasia in those aged less than 50 years; (II) should mainly be used in those who are unfit for surgery or as a bridge to more definitive therapies such as surgery or balloon dilatation, and (III) repeat injections are safe but less effective than initial treatment.

The American College of Gastroenterology Guideline on Diagnosis and Management of achalasia similarly recommend that botulinum toxin injections be used in those patients who are not good candidates for more definitive therapy (4).

Efficacy of botulinum toxin injection in treatment of achalasia

Andolfi and Fisichella (6) recently reported the results of a meta-analysis of clinical outcome after treatment for achalasia based on manometric subtypes. This study reported outcome data for twenty studies, and showed relatively poor treatment success with botulinum toxin injection for type 1 achalasia (18%), modest success with type 2 achalasia (59%), and again poor success with type 3 achalasia (21%). This study suggests that POEM may be the preferred modality for type 1 and 3 achalasia, and that results with type 2 achalasia are generally good (over 90% success with either laparoscopic Heller's myotomy or POEM) and reasonable results are seen with pneumatic dilatation (84% success).

Three of the larger trials that predate the introduction of high-resolution manometry are also worth noting. Pasricha *et al.* (in 1996) (8) described a group of 31 patients aged 19 to 85 years who underwent injection with 80 units of Botulinum toxin Type A (Allergan Inc., Irvine, California) injected with 4 aliquots of 1 mL (each containing 20 IU of botulinum toxin) in quadrantic fashion into the lower esophageal sphincter as identified at endoscopy. Initial response was seen in 28 of 31 patients (90%). During the first 3 months, 11 of these 28 patients reported worsening symptoms, leading to a total of 14 patients who failed to respond or relapsed quickly. Of these 14 patients, 11 were retreated, and three achieved a sustained remission. By 6 months, 20 of the original 31 were still in remission. Older patients (defined as greater than 50 years of age) were more likely to respond to botulinum toxin.

Annese *et al.* (9) reported a study of 188 achalasia patients who were given varying regimes of intrasphincteric botulinum toxin type A injection, again in quadrantic fashion. Doses included 50 units (group A), 100 units (group B), and 200 units (group C). Patients in group B were given a second dose of 100 units at 30 days after the first. There was 82% initial response rate, and the group that had two injections 30 days apart of 100 IU of botulinum toxin had statistically better outcome with 68% of patients still in remission at 24 months, as compared to approximately 28% in the other two groups.

Dughera *et al.* (10) reported a study on 12 patients aged between 81–94 with a diagnosis of achalasia and significant

Table 1 Role of botulinum (botox) injection in treatment of achalasia

Patient selection: Older individuals with multiple comorbidities, defining them as poor surgical candidates, or with an otherwise limited prognosis; also in patients who need a bridge to definitive therapy
Technique: Botox 25 units [100 units (drawn up in 4 mL normal saline)] injected in each quadrant of the lower esophageal sphincter (LES)
Risks: Adverse events are rare, but can be significant, such as mediastinitis, heart block or transient muscle weakness (few case reports only)
Duration: Duration of effect for achalasia variable, but it appears more prolonged in the elderly
Other considerations: Older patients (>75 years of age) appear to have a better clinical response to botox injection for achalasia, as compared to younger patients; decisions regarding treatment may be better made by a multidisciplinary team meeting
Botox is not part of the routine treatment of achalasia. Botox use in achalasia is reserved for patients with a limited prognosis

co-morbid disease (American Society of Anesthesiologists Class III–IV). They were given two injections of 100 IU of botulinum toxin 30 days apart, and followed serially for 12 months. After 1 year, 70% of the patients were in remission, with an average weight gain of 3 kg.

There are no clear guidelines regarding technique of injection, but generally 4 quadrant injections into the lower esophageal sphincter as identified at endoscopy is the favoured approach. Typically, 25 units of botulinum toxin type A is injected into each quadrant.

Risk of botulinum toxin injection for achalasia

Botulinum toxin was originally discovered as the cause of severe food poisoning caused by Clostridium botulinum bacteria generating this toxin in poorly preserved food. Ingestion of the infected food was often associated with paralysis and sometimes death (11). Given this history, its wide spread use as a therapeutic agent is surprising, and causes one to consider its safety. A retrospective multicentre study by van Hoeij *et al.* (12) addressed this issue and studied the side-effects of botulinum toxin injection, largely for the treatment of diffuse esophageal spasm and achalasia at four tertiary referral hospitals in Europe and North America. Botulinum toxin (type A 100 IU) was injected in 661 patients, and 52 (7.9%) had mild side-effects—usually transient chest pain, heartburn, nausea and vomiting. One patient died after developing acute mediastinitis one week after injection of 100 IU of botulinum toxin into the esophageal body, and died of the resultant sequelae. Overall, however, botulinum toxin would appear to be a relatively safe intervention, and one that can be performed on aged patients and those unsuitable for more invasive measures.

A brief summary of our conclusions is shown in *Table 1*.

Discussion

The literature supports the idea that botulinum toxin should be reserved for patients with achalasia who are not suitable for more definitive procedures such as laparoscopic cardiomyotomy, serial pneumatic dilatation of the lower esophageal sphincter, or peroral endoscopic esophageal myotomy (POEM). Situations where the use of botulinum toxin is likely to be warranted are patients with advanced cardiac or respiratory disease, or a strong indication for use of ongoing anticoagulants or platelet aggregation inhibitors, or with a limited life expectancy due to malignancy, progressive neurological disease or renal insufficiency. It is also likely warranted when a patient presents with marked weight loss from achalasia, and needs nutritional support for a time before definitive therapy.

The advantages of the procedure are that it relatively simple to perform, and has a better safety profile than the more invasive alternatives, often offering quick symptomatic relief. The major disadvantage is that the benefits can be short-lived and are mainly confined to type 2 achalasia.

One problem with some of the older papers is understanding the type of achalasia being studied, such as where achalasia cases are described as either vigorous or classical. The former likely included a mixture of type 2 and perhaps type 3 achalasia and other hypermotile esophageal disorders, and the latter group is likely mainly type 1 achalasia. Any new studies in this area need to document the course of symptoms with a reproducible scoring system over time, and with the achalasia subtype defined according to the Chicago Classification.

The literature has some data suggesting that older age may be associated with a higher sustained response to botulinum toxin injection (8,10). This suggests that there is a need to confirm whether patients aged 75–85 and over

85 years with achalasia do indeed have a better chance of a sustained response to botulinum toxin injection, and whether two doses 30 days apart would optimise this. This would need a multi-centre approach given that this is an uncommon disease. The population over 75 is increasing in much of the world, and achalasia can present into old age at a similar, or possibly increased, rate to that in younger adults (1). Studies are therefore needed to clarify the optimal strategy for managing achalasia in patients over 75 years, in particular, those elderly individuals with other significant medical co-morbidities.

In summary, although laparoscopic cardiomyotomy, balloon dilatation and POEM give more sustained relief of symptoms of achalasia, there is still not cure for this disease, and patients should be made aware of this. Botulinum toxin retains a role in those individuals with poor life expectancy and perhaps those aged over 75 years, especially if they have significant comorbidities. Its advantages are that it is minimally invasive, it has a good safety profile, and it has good rate of initial success, particularly in those with type 2 achalasia.

Finally, we would suggest that multidisciplinary team meetings to discuss interventions for benign esophageal disorders such as achalasia in those with co-morbidities might be of benefit, as therapeutic decisions are becoming more complicated, and these decisions will vary depending on local resources and expertise, achalasia sub-type, co-morbidities and patient preference.

Acknowledgments

We give our thanks to: (I) Mrs Laura Besanko, Medical Scientist, Oesophageal Function Laboratory, Flinders Medical Centre for help with literature search and proof reading; (II) Ms Ros Taylor-Parkins, Library information Officer Southern Adelaide Local Health Service for help with literature search; (III) Ms Chris Re'vell, Secretary Dept of Surgery, FMC, for help with final formatting.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Sarah Thompson) for the series "Achalasia" published in *Annals of Esophagus*. The article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at: http://dx.doi.org/10.21037/aoe-2019-ach-09). The series "Achalasia" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/aoe-2019-ach-09
Cite this article as: Heddle R, Cock C. Role of botulinum toxin injection in treatment of achalasia. Ann Esophagus 2020;3:26.