



## High Dose Botox Injection for Patients with Internal Anal Sphincter Achalasia Persistent to Posterior Internal Anal Sphincter Myectomy

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### Abstract

**Introduction:** one of the most common reported chief complaints in visits to pediatricians is constipation. Although in a majority of cases with no anatomical defect, dietary manipulation, stool softeners, and oral laxatives are successful, some patients fail to respond.

Internal Anal Sphincter (IAS) Achalasia is one of the causes of constipation. It results in failure of IAS relaxation and has similar clinical presentation to Hirschsprung's disease with absence of rectosphincteric inhibitory reflex on anorectal manometry (ARM) and presence of ganglion cells on rectal biopsy.

Although posterior internal anal sphincter myectomy (ISM) is considered the standard treatment for IASA, some cases fail to respond and present with intractable constipation which may be associated with soiling.

This research aims to assess the role of botox injection for treatment of patients who presented with intractable constipation and have already been treated by posterior IAS myectomy.

**Materials and Methods:** Internal anal sphincter Botox injection was performed (with a dose of 20 U/Kg) in 14 patients with internal anal sphincter achalasia (IASA); who had presented with intractable constipation after being treated by posterior internal anal sphincter

myectomy. Patients were followed for 2 years after injection.

**Result:** of all 14 patients with persistent constipation (resistant to oral laxatives), 12 patients (85.7%) had regular bowel function for more than 6 months after botox injection therapy ( $P < 0.05$ ).

Of all 14 patients that had needed rectal enema for defecation, no patient needed rectal enema after botox injection therapy ( $P < 0.05$ ). Of 5 patients with fecal soiling before botox injection therapy (4 had occasional soiling, and 1 had soiling every day without social problems) only a single patient experienced transient fecal soiling for 2 weeks after botox injection therapy ( $P < 0.05$ ).

No patient needed another botox injection in 2 years of follow up.

**Conclusion:** IAS Botox injection therapy (BIT) was successfully used to manage IASA patients who had presented with intractable constipation after posterior myectomy. This method significantly reduces the need for laxatives and rectal enema; and improves constipation, fecal soiling and bowel movements at the same time.

## Keywords

- Internal Anal Sphincter
- Achalasia
- Constipation
- Myectomy
- Botulinum Toxin
- Hirschsprung's Disease

## Introduction

One of the most common reported childhood chief complaints is constipation, comprising up to 1 in 5 of pediatric gastroenterological complaints and 3% of all visits to pediatricians.<sup>1-4</sup>

Although in the majority of cases with no anatomical defect, dietary manipulation, stool softeners, and oral laxatives are successful, some patients fail to respond to conventional treatment.<sup>5</sup>

For the first time, Hurst in 1934 proposed that one of the possible pathogenetic mechanisms of these types of idiopathic constipation might be internal anal sphincter (IAS) relaxation failure rather than a spasm.<sup>6</sup>

Internal Anal Sphincter (IAS) Achalasia, is identified in up to 4.5% of childhood chronic constipations; with similar clinical presentation to Hirschsprung's disease and is diagnosed by the absence of rectoanal inhibitory reflex (RAIR) in anorectal manometry (ARM), the presence of ganglion cells and normal Ach Eactivity on rectal suction biopsy and no transitional region on barium enema.<sup>7-10</sup>

Although posterior myectomy with all its reported complications has been considered as the treatment of choice for IASA for over 50 years; since 1997, after Langer and Birnbaum's preliminary experience with intrasphincteric botulinum toxin injection in Hirschsprung's disease patients with

persistent constipation after pull-through surgery, satisfying short-term results have been reported following this less invasive procedure.<sup>9, 11-13</sup>

However, some IAS Achalasia patients failed to respond even to posterior myectomy and presented with intractable constipation.

In this study, we evaluate botox injection treatment (BIT) in IAS achalasia patients presented with intractable constipation after posterior myectomy.

### Materials and Methods

The records of 35 patients suffering from internal anal sphincter achalasia (IASA) whom had been treated by posterior internal anal sphincter myectomy during 2011-2015 were reviewed.

Posterior myectomy was carried out at the dentate line toward the proximal and samples were taken. All of our cases suffered from intractable constipation along with soiling or not. Before undergoing surgery, all patients had a barium enema and anorectal manometry. All patients had an absence of rectoanal inhibitory reflex (RAIR) on anorectal manometry (ARM), normal rectal biopsy and no transitional region on barium enema.

In all there were 14 patients (8 boys and 6 girls) with a Mean age of 95 months. Their symptoms persisted and they all had Constipation Grade 3, Resistant to laxatives and diets and 5 had fecal soiling.

Botox was mixed with 5ml of non-preserved sterile saline and 20U/kg was injected by a 27-gauge needle under general anesthesia, in the lithotomy position, at the level of dentate line, in

four quadrants into the intersphincteric groove. Laxatives were continued after injection in all cases.

All patients were clinically followed up for up to 2 years, symptoms, defecation's pattern and stool diameter were evaluated.

Improved defecation pattern for more than 4 weeks was considered successful.

All collected data were statistically analyzed by SPSS application.

A P-value of less than 0.05 was considered significant.

### Results

Of all 14 patients with persistent constipation (resistant to oral laxatives and oral softeners), 12 patients (85.7%) had regular bowel function for more than 6 months after botox injection therapy ( $P < 0.05$ ).

Of all 14 patients that had needed rectal enema for defecation, no patient needed rectal enema after botox injection therapy ( $P < 0.05$ ).

Of 5 patients who had fecal soiling before botox injection therapy (4 had occasional soiling and 1 experienced soiling every day), only a single patient experienced transient fecal soiling for 2 weeks after botox injection therapy ( $P < 0.05$ ).

Although all 14 patients were resistant to oral laxatives, no patient reported any defecation problem with laxatives after botox injection therapy. ( $P < 0.05$ )

No patient needed another botox injection in 2 years of follow up.

## Discussion

The internal anal sphincter(IAS) is constructed by a special smooth muscle ring that has a major role in maintaining the anorectal continence and resting pressure. Any physical or functional IAS disorder, (IAS resting pressure or incomplete RAIR) results in passive incontinence or constipation and subsequent obstructive symptoms, due to failure of IAS relaxation.<sup>11, 14</sup>

Although the specific pathogenesis and pathophysiology of IAS Achalasia is yet to be known, but altered intramuscular innervations, nitrergic nerve depletion, cholinergic hyperplasia and abnormal peptidergic innervation are suggested to be responsible.<sup>15-17</sup>

In a study by Puri and Oueit was shown that in IASA PGP 9.5-immunoreactive and synapsin I-positive nerve fibers is reduced or absent.<sup>17</sup>

Achalasia is one of the uncommon causes of childhood constipation due to the IAS relaxation failure. Rectoanal inhibitory reflex(RAIR) is the relaxation of IAS due to distention of the rectum and any abnormality regarding this reflex or orhypertonicity of IAS can result in constipation.<sup>13</sup>

A theory was suggested by Hurst in 1934 proposing that IAS relaxation failure as one of the possible pathogenic mechanisms of idiopathic constipation and not its spasm.<sup>6</sup>

IAS achalasia clinically presents similar to Hirschsprung's disease, having symptoms

and signs such as delayed meconium passage, abdominal distention, vomiting and constipation with or without soiling. These presentations were formerly attributed to Hirschsprung's disease and the disease was sometimes classified as ultra-short segment type of Hirschsprung.<sup>6, 16</sup>

Doodnah and Puri published diagnostic criteria for IASA:

An ARM which shows absence of rectosphincteric reflex and presence of marked rhythmic activity of IAS muscle on rectal balloon inflation, presence of ganglion cells with normal AchE activity in rectal suction biopsy and the absence of transitional region on enema.<sup>10, 14</sup>

Also Hirakawa et al. reported diagnostic histochemical criteria for IAS achalasia: increased AchE-positive nerves and absence of NADPH-diaphorase activity in the IAS biopsy.<sup>19</sup>

But patients with IAS Achalasia may have some medical presentations that differentiate them from the control patients:

They have less fecal soiling, less withholding behavior and earlier onset of symptoms starting at birth in 40% of cases.

In IAS achalasia, the Basal range of internal anal sphincteric resting pressure is about 45-150 mmHg, while the normal range is 33-100 mmHg.

A pressure of 40 to 300 ml (mean  $146 \pm 82$  ml, normal value  $< 20$  ml) is the threshold for rectal sensation.<sup>16</sup>

Posterior IAS myectomy with all its reported

complications has been considered as the treatment of choice for IASA for over 50 years, yet, since 1997, after Langer and Birnbaum 's preliminary experience with intrasphincteric botulinum toxin injection in HD patients with persistent constipation after pull-through surgery, satisfying short-term results have been reported following this less invasive procedure<sup>9, 11-13</sup>

Botulinum toxin is a powerful neurotoxin that blocks acetylcholine release at neuromuscular junctions.<sup>5, 20</sup>

This toxin has been successfully used to treat hypertonicity of both striated and smooth muscles for therapeutic and aesthetic purposes.

Nowadays (over a century and a half since German physician John Muller came up with the term "botulism" in 1869, and almost 4 decades since the ophthalmologist Alan B. Scot used botulinum neurotoxin-A (BoNT-A) to treat strabismus in humans in 1979), botulinum toxin (botox) has been increasingly used for aesthetic purposes (wrinkle treatment for glabellar and perioral lines) and also therapeutic purposes (treatment for strabismus, esophageal achalasia, chronic constipation, chronic anal fissure, torticollis, blepharospasm, biliary dyskinesia and etc).<sup>21</sup>

Botulinum toxin acts on the neuromuscular junction by interfering with acetylcholine release from presynaptic cholinergic neurons; so BIT theoretically could have similar effects to posterior myectomy, without the potential long-term complications resulting from with permanent damage to the sphincter.<sup>16, 20</sup>

Nevertheless, BIT failure was reported in some patients, but it's not clear whether it was a failure of treatment itself or was the result of other problems such as insufficient dose, injecting outside of internal anal sphincter or misdiagnosis.

In a similar study by Ciamarra P. et al on 20 patients, eight patients experienced bowel movement within 2 days and 18 cases within 3 days of the BIT. Two cases remained constipated for more than 3 days and were considered treatment failures. Although in some of these failure cases repeating the treatment were helpful; thus repeating the treatment should be carried out before considering a child a treatment failure. Sixty percent of parents rated the treatment excellent; it was considered excellent in 35% of physician.<sup>16</sup>

But according to our study, none of the patients needed a repeat of IAS injection.

In the study by Irani K. Rodriguez L., 24 patients with constipation who had an elevated IAS resting pressure underwent botox injection in the IAS and were followed for 6 months. In 22 of the 24 patients constipation improved, with the duration of treatment efficacy varying from 1 week to 1 year. In 12 patients lasting at least 6 months.<sup>13</sup>

In a study by Foroutan. H. et al in 2008, 28 patients with IAS were treated in two groups with either posterior internal anal sphincter myectomy or intrasphincteric botox injection to compare their efficacy for the treatment of internal anal sphincter achalasia (IASA). In either groups, the same efficacy was reported, also intrasphincteric botox injection was recommended as a less invasive treatment which should be considered as first line

therapy in IASA; not only because of its similar local effect as posterior internal anal sphincteric myectomy, but also its ability to improve visceral dysautonomia and bowel motility at the same time.<sup>7</sup>

In another study by Almoutaz A. Eltayeb et al on the role of botulinum toxin in the management of chronic constipation in 20 patients, 6 cases had an excellent response, 12 cases experienced a good response but in 2 cases the response was poor and thus needed another injection. The duration of response was 3 to 6 months.<sup>5</sup>

The study of Dan Carter and Ram Dickman in 2018 showed that BTX-A treatment is effective for the treatment of obstructive symptoms after pull-through surgery for Hirschprung Disease as well as for the treatment of IAS Achalasia.<sup>22</sup>

In a study by Jin-Yang Liu, a 16-year-old patient with congenital megacolon and difficulty of bowel movement for more than 10 years, was successfully treated with Botox injection.<sup>23</sup>

In a meta-analysis by Friedmacher and Purion the efficacy of posterior IAS myectomy versus intrasphincteric Botox injection in IAS achalasia, in the botox group, rate of non-response and need for subsequent surgery and also transient fecal incontinence was significantly higher (  $P=.04$ ,  $P<0.0001$  respectively).

Also, a good response to treatment demonstrated by regular bowel movements were considerably more in the posterior IAS myectomy group ( $P=0.04$ ).<sup>11</sup>

As mentioned before, posterior IAS myectomy has been the treatment of choice for IAS achalasia

for over half of a century and appears to be more effective, but IAS botox injection is also a less invasive alternative treatment and due to its transient effect, all complications are assumed to be temporary.

In our study, IAS achalasia patients who had been managed with posterior myectomy and presented with intractable constipation were successfully treated with IAS botox injection, as it significantly reduced the need for laxatives and rectal enema, improved constipation, fecal soiling and bowel movements with a significant P-value of 0.05.

## Conclusion

In conclusion, IAS Botox injection therapy (BIT), is a less invasive and symptom-relieving treatment to manage IASA patients presented with hyper-spasticity-induced intractable constipation after posterior myectomy, But it needs more long-term follow-up.

## Ethical Consideration

This study was approved by Organizational Committee of Ethics in Biomedical Research of Shahid Beheshti University of Medical Sciences with code number IR.SBMU.RICH.REC.1399.020.

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## Conflict of interests

There is no conflict of interests

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