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Botulinum toxin injection for childhood constipation is safe and can be effective regardless of anal sphincter dynamics☆,☆☆,★

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ABSTRACT

Background: Childhood constipation is common. Previously, internal anal sphincterotomy has been used for hypertensive/non-relaxing sphincters; however, recent benefit has been shown with Botulinum Toxin (BT) injections. The aim is to investigate BT, including response duration, symptom association and effectiveness in relation to sphincter dynamics.
Methods: Retrospective study of 164 children receiving sphincter BT for severe constipation unresponsive to medication management. Charts reviewed for symptoms, anorectal manometry (ARM) findings and response defined by decreased pain or increased defecation. Patients were grouped: normal sphincter pressure (≤50 mmHg), elevated (>50 mmHg), normal and abnormal rectoanal inhibitory reflex (RAIR).
Results: There were 142 analyzed and 124 completed ARMs; 98 (70%) had positive response with 57% lasting greater than 6 months. 36 had normal sphincter pressure with 24 (69%) responding. 88 had elevated pressure with 60 (68%) responding ($p = 0.87$). 90 normal RAIRs with 64 (71%) responding. 34 abnormal RAIRs with 22 (64%) responding ($p = 0.41$). With logistic regression, fecal incontinence prior to BT was a predictor of poor response ($p = 0.02$). The most common side effect was fecal incontinence typically resolving within week with equal frequency regardless of sphincter dynamics.
Conclusions: BT is effective for children with chronic constipation. Patients with fecal incontinence are less likely to respond. More than half had prolonged beneficial response. Those with normal and abnormal sphincter dynamics had similar responses and without differences in side effects. Therefore, injection may be considered in patients with intractable constipation unresponsive to medication, regardless of anal sphincter dynamics.
Level of Evidence: Level III (Treatment Study: Retrospective comparative study).

Chronic constipation is common in childhood, accounting for 5% of pediatrician visits, and up to 25% of gastroenterology visits [1]. Although constipation has been studied extensively, much remains unknown about the underlying pathophysiology of presentation with various hypothesized etiologies differing based on age and symptoms [2]. Pelvic outlet dysfunction, in which stool transits the colon normally but is difficult to excrete, leading to stool retention and eventual colonic dilation, is believed to be an important cause of constipation [3,4].

A large percentage of children with outlet dysfunction in functional constipation are thought to be due to voluntary withholding behavior [5]. A common hypothesis on its pathophysiology is that a child has episodes of hard stool associated with pain leading to fear and anxiety related to defecation, thus resulting in withholding behavior, increased stool retention and the development of a cycle that is difficult to break [6]. The current management for withholding activities involves a combination of medication, dietary interventions and behavioral modifications [5] to induce increased frequency of soft bowel movements, and reinforcement of non-painful stool passage.

It is not known if long-term withholding and other causes of outlet obstruction change anal sphincter pressures and dynamics, however some patients with chronic constipation have been found to have abnormal anal sphincter dynamics on anorectal manometry. These abnormalities could be a condition present from birth or acquired, and include internal anal sphincter achalasia (IASA) defined by an incomplete rectoanal inhibitory reflex (RAIR) upon rectal distention with normal suction rectal biopsies [7]. This entity has been previously implicated

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in outlet obstruction chronic constipation in selected patients. Traditionally, an internal sphincterotomy was done for patients with abnormal sphincter dynamics [8] including IASA, sphincter hypertonicity, neuronal dysplasia and Hirschsprung disease [9,10]. Sphincter myotomy often resulted in improvement of symptoms, however concern remains about performing a surgical procedure on the anal sphincter that can lead to permanent long-term side effects such as irreversible incontinence [11].

Recent studies have shown that the use of Botulinum toxin A injection into the internal anal sphincter, can lead to improved defecation patterns in constipated patients with outlet dysfunction [12–14]. Botulinum toxin A is a neurotoxic protein that acts as a muscle relaxant of the anal sphincter by its binding of nerve terminals [15,16]. This may lead to easier and more frequent passage of stool with less pain, particularly in patients with high resting pressure or lack of normal sphincter relaxation during defecation [12,13]. The intervention may be more acceptable to parents than a myotomy as it is non-surgical, with transitory effects that decrease over time and can be performed in the outpatient setting.

Chemical denervation of the anal sphincter with Botulinum toxin injections is considered a promising intervention and small studies have reported a positive response [12,17] in patients with outlet-type constipation. However much remains unknown regarding efficacy, safety and appropriate patient population for this form of treatment. The aim of this study is to investigate the effect of Botox, including response duration, symptom association, side-effects and effectiveness in relation to anal sphincter dynamics in children with outlet obstruction chronic constipation.

1. Methods

1.1. Study population

We completed a retrospective chart review over 7 years (2006 - 2013) of patients with chronic constipation based on the ROME III criteria [18,19] who had presented to a tertiary center at Massachusetts General Hospital for Children pediatric gastroenterology clinic, referred mostly by their primary gastroenterologist due to treatment failure. Specifically, we focused on those who were medication dependent or unresponsive to medical treatment with persistence of symptoms of constipation for at least 3 months prior to injection, and had completed a clinically indicated anorectal manometry to assess sphincter function. Only those patients that had received Botulinum toxin injections were included in the study. We received approval from the institutional review board prior to data collection.

1.2. Anorectal manometry

Water perfusion anorectal manometry (ARM) was completed approximately 4 hours after the patient received a glycerin suppository or enema. Patients were given a very brief and light inhaled anesthesia, sevoflurane, prior to the ARM. Patients were studied in the left lateral decubitus position with hips and knees bent to 90 degrees. A water perfused 4-channel anorectal motility catheter (4.5mm outer diameter) with openings spaced circumferentially 1 cm apart and a balloon of 300ml maximum capacity at the distal end was inserted into the anal canal. All side holes were perfused with normal saline at a rate of 0.5 ml/min. Pressures were measured by pressure transducers in each perfusion line and connected to a PC through a PolyGram interface (Medtronic, Ireland). Before each study, calibration of the PolyGram equipment was performed.

1.2.1. Resting pressure

The probe measured the sphincter pressure as it was retracted stepwise, at an interval of 0.5 cm using the stationary pull-through method. The pressure was recorded after 15 seconds of stable sphincter readings.

1.2.2. RAIR

The catheter was positioned in such a manner that the balloon was in the rectum and at least 2 channels were in the high-pressure zone (sphincters) recording the baseline pressure. The rectoanal inhibitory reflex was assessed by progressively inflating the rectal balloon using the catheter with balloon starting at 10 ml followed by 20 ml, 40 ml and 60 ml. If there was no response to 60ml, the balloon size was increased to 120 ml. A normal reflex was characterized by an anal sphincter pressure drop of at least 25% from baseline [20].

Patients were divided into separate groups based on the anorectal manometry results: normal sphincter pressure (<=50mmHg) or elevated pressure (>50mmHg). The normal resting pressure cutoff was based on prior studies of healthy children where the normal anal sphincter pressure was found to be 43 +/− 8 mmHg [21]. Patients were also separated into two groups based on RAIR results: Those with normal or abnormal RAIR response (classified as less than 25% relaxation including those with no relaxation).

1.3. Botulinum toxin injection

All patients with a high resting pressure received Botulinum toxin A injections. Additionally, some patients with normal pressure, but with a long history of symptoms of chronic constipation and unresponsiveness to treatment also received injections due to intractability of their disease. Following anorectal manometry testing, with the patient in the left lateral position and while the patient was under general anesthesia, preparation of perineal area was done with Betadine. 100U of Botulinum toxin A (Botox, Allergan, Ireland) powder was diluted in 5ml normal saline to a concentration of 100U/5 ml. The injection dose was based on weight (6U/kg) with a maximum of 100U, divided equally into four quadrants of the internal anal sphincter (two anterior lateral injections followed by two posterior lateral injections) injected intramuscularly via the anal canal.

A gastroenterologist followed the patients after the Botulinum toxin injection to assess symptom improvement including increased frequency, decreased pain and medications as well as possible complications. Botulinum toxin is thought to lose potency after three to six months [22]. Therefore, if there was a recurrence of symptoms that had initially improved with injections, families were given the option to proceed with repeat injections.

1.4. Data collection

The charts were reviewed for comorbidities, medications and ARM results (baseline resting sphincter pressure and RAIR). Additionally, presenting symptoms including pain, fecal incontinence and stool infrequency defined as bowel movements less than every third day, were obtained. The primary outcome assessed was response defined by a decreased pain with defecation or increase frequency of defecation at least 2 weeks after injection. At that visit the patient was on the same bowel regimen as prior to injection, however it may have been altered at subsequent visits. The response information was based on parental description on a severity scale and/or frequency scale as noted in the physician note. Follow up time was determined based on symptoms at the last appointment at which the patient was seen by a gastroenterologist. Side effects were assessed at the visits after injection.

1.5. Statistical analysis

Chi-square and t-test analysis were completed via the Stata program (Texas, USA). Logistic regression was completed for multivariable analysis. A significance level of $p<0.05$ was used for all statistical analysis.

2. Results

2.1. Demographics

164 patients met the criteria for the study; however 23 were excluded due to lack of follow up after injection. Therefore, 141 patients were analyzed and 124 of these patients also completed anorectal manometry prior to injection.

The baseline characteristics of the patients are included in Table 1. The patients presented with various symptoms typical of constipation and a protracted treatment history. There was no statistical difference between the two pressure groups in demographics including age and sex or in presenting symptoms of fecal incontinence, infrequency or pain between groups. There were statistically more patients in the normal RAIR group who had pain with defecation as compared to the abnormal RAIR group; however, the percent with fecal incontinence and infrequency were similar. It is also important to note that patients with normal RAIR did have a significantly higher sphincter pressure (66 mmHg) than those with abnormal RAIRs (56 mmHg) ($p<0.01$), although both groups mean pressure was considered high. There were similar amounts of stimulants, laxative and rectal medication used in all the groups.

2.2. Response

Response was defined as a decrease in defecatory pain or an increase in frequency of stool passage. Of the 141 patients receiving Botulinum toxin injections, 98 (70%) had a positive response. Seventy children (60%) had increased stooling frequency and 62 (44%) had decreased pain with defecation. Thirty-four (24%) were able to wean down or off of their laxatives after treatment.

Patients were evaluated for symptoms at each follow up visit. Twenty-seven patients (20%) had initial improvement lasting at least 2 week followed by a clinical course suggesting that the Botulinum toxin effect had lost efficacy prior to 6 months. Among the other patients who had a beneficial response, 47 (33%) of the patients had a response lasting between 6 and 12 months, and 24 (17%) who had a response that lasted longer than one year.

2.3. Anal sphincter dynamics

Based on the above definitions of elevated and normal sphincter pressures, of those who underwent anorectal manometry with Botulinum toxin injection: 36 (29%) patients had normal sphincter pressure, while 88 (71%) had elevated pressures prior to receiving an injection. Of those with normal pressure, 24 (69%) had a significant positive response and of those with elevated pressure, 60 (68%) had a significant positive response. There was no statistical difference in response between the high pressure and normal pressure groups ($p=0.87$). No difference was found in the type of improvement or in the persistence of symptoms between the groups (Table 2).

Examining the sphincter relaxation, 90 (73%) had a normal RAIR. 65% of those with abnormal RAIR responded to treatment, whereas 71% of those with normal RAIR had a response. The difference was not statistically different ($p=0.41$).

Seventeen patients (14%) had both abnormal RAIRs and high resting pressure. These patients had similar response rates (71%) as the other groups. Finally, there were 9 patients with Hirschsprung disease who had completed surgery and 6 of these patients (67%) responded to the Botulinum toxin injection.

2.4. Symptoms

With logistic regression controlling for symptoms, fecal incontinence prior to Botulinum toxin injection, was found to be a predictor of poor response ($p= 0.02$), while symptoms of infrequency and pain had no significant correlation to response. Additionally, the regression analysis revealed that age, gender, sphincter pressure or RAIR response were not significant predictors of response.

2.5. Side effects

Out of the 141 patients who received the injections, 99 received Botox only once. Forty-two patients received additional doses of Botox after the initial injection due to loss of efficacy, with twenty-five receiving one additional dose and 17 patients received 3 or more doses (Range 3-7 doses). The doses were given between 3 months and 3 years after the initial injection. The decision to repeat an injection was made by both the parent and physician in a patient who had had an initial positive response to Botox but lost efficacy of response over time and thus had recurrence of constipation symptoms. The ARM results and demographics of this group of patients with repeated injections were not statistically different than those that only received one injection. The outcome of the repeat injections was not included in the efficacy analysis as the study was assessing response to initial injection only. Thus, only safety data was obtained from these repeated injections. Overall, the patients received a total of 203 separate Botulinum toxin injections, all of which were analyzed for safety.

Out of the 203 separate Botox injections given, twenty-eight (16%) patients reported a side-effect to an injection. Twenty-one (10%) of the total injections led to persistent or increased stool leakage, which was expected due to decrease anal sphincter tone after injection. Of the 21 with fecal soiling following the procedure, 7 had fecal incontinence prior to treatment. In these, it was not possible to determine if Botox was responsible for worsening fecal incontinence. Other less frequent side effects post-injections were increased stool urgency in 3 (2%) and urinary incontinence in 2 cases (1%). Rare side effects included pruritis ani and rectal prolapse, each encountered in one patient.

Table 1
Demographics.

	Overall	High pressure	Normal pressure	p Value	Normal RAIR	abnormal RAIR	p Value
N	141	88	36		90	34	
Male	85 (61%)	57 (65%)	19 (56%)	0.33	53 (59%)	23 (67%)	0.37
Age (# years)	1-18 (7.3)	2-16 (7.4)	1-18 (6.7)	0.16	1-16 (7.1)	1-18 (7.9)	0.86
Pressure (mmHg)	30-130	72.5	40.6	<0.01	66.3	56.6	0.03
Symptoms							
Fecal Incontinence	51 (36%)	32 (36%)	15 (43%)	0.54	34 (38%)	12 (35%)	0.76
Painful	98 (69%)	64 (73%)	24 (68%)	0.52	69 (77%)	19 (56%)	0.02
Infrequent	66 (47%)	41 (46%)	18 (51%)	0.78	43 (48%)	16 (47%)	0.90
Medications							
Laxatives	117 (83%)	77 (88%)	31 (89%)	0.94	79 (88%)	28 (82%)	0.72
Osmotics	45 (32%)	29 (33%)	12 (34%)	0.31	32 (36%)	9 (27%)	0.34
Rectal	15 (11%)	7 (8%)	5 (14%)	0.30	9 (10%)	3 (9%)	0.84

For continuous variables, median is presented. For dichotomous variables, percent is presented.

Table 2
Response to Botulinum toxin injection based on baseline sphincter pressure and RAIR.

	Overall	High pressure	Normal pressure	P value	Normal RAIR	Abnormal RAIR	p Value
N	141	88 (71%)	36 (29%)		90 (73%)	34 (27%)	
Response	90 (70%)	60 (68%)	24 (69%)	0.17	64 (71%)	22 (65%)	0.41
Increase frequency	70 (50%)	46 (52%)	18 (51%)	0.41	47 (52%)	10 (30%)	0.01
Less Pain	62 (44%)	41 (47%)	14 (40%)	0.85	40 (44%)	19 (56%)	0.07
Med Wean	34 (24%)	25 (28%)	5 (14%)	0.23	15 (16%)	4 (12%)	0.59

The majority of the side effects resolved within one week of the injection, with many of the fecal incontinence symptoms resolving within 1 to 2 days. Three patients had increased fecal incontinence for 2 weeks, while an additional 2 patients had fecal incontinence that lasted a month. There were 2 patients with fecal soiling lasting greater than 1 month however it was unclear if this was worsened due to Botulinum toxin injection as they had fecal incontinence prior to injection. Additionally, the patient with pruritis ani post injection lasted greater than 1 month when the patient was lost to follow up. The stool urgency after injection resolved within 1 week as did the rectal prolapse. One patient with urinary incontinence had resolution of symptoms within 1 week; however, one patient had persistent intermittent enuresis lasting greater than one month. The patient's physician noted on the chart that it was likely related to behavioral comorbidities (Fig. 1).

Patients with normal pressure had the same frequency of side effects, predominantly transitory fecal incontinence, as did the high-pressure group. Similar findings were seen in the RAIR groups. Patients with side effects lasting greater than one week were from both the normal and high sphincter pressure groups with a similar prevalence.

3. Discussion

In this study, Botulinum toxin injections appear to be an effective treatment for pediatric patients with chronic constipation. To our knowledge this is the largest published cohort of patients who received Botulinum toxin for constipation and additionally, the only one to correlate anal sphincter dynamics to outcome. Presumably by relaxing and decreasing the anal sphincter tone, our study found that Botulinum toxin injections resulted in increased frequency of bowel movements and decreased pain with defecation in patients with diverse anal sphincter dynamics. Therefore, we believe, it may be beneficial to pediatric patients with persistent symptoms of chronic constipation unresponsive to medication interventions.

Previous studies have demonstrated a response in children to Botulinum toxin injection into the anal sphincter with IASA with a non-relaxing sphincter, or with an elevated sphincter pressure [12]. Keshtgar et al completed a randomized controlled trial comparing the use of Botulinum toxin injection to myotomy in 42 patients with a hypertonic and non-relaxing internal anal sphincter and found comparable results in each group, therefore supporting the use of Botox rather than proceeding with a surgical procedure [23]. Chumpitazi et al studied 73 patients retrospectively with a non-relaxing internal anal sphincter and chronic constipation, and found 89% had symptom improvement based on a scale assessing symptom characterization and laxative use [13].

Although the majority of studies using Botulinum toxin injections have focused on the use in patients with Hirschsprung disease or IASA, recently more emphasis has been placed on using Botulinum toxin injections on all patients with chronic constipation, regardless of the sphincter dynamics [24]. Keshtgar et al treated a small group of 31 patients with constipation, and found a significant improvement in symptom score [24], while Ahmadi et al completed a randomized controlled trial on 88 patients with chronic constipation without evaluating anal sphincter dynamics and found a large decrease in symptoms in response to Botulinum toxin injections as compared to controls treated conventionally [25].

Our retrospective review demonstrates that patients with normal sphincter dynamics had a similar response to the Botulinum toxin injection as those with abnormal sphincters supporting the use of the intervention for patients with chronic constipation and not limited to those with atypical sphincter function. This suggests that the injection may not only act on sphincter dynamics, but may also prevent other causes of constipation such as withholding behavior related to pain. Therefore, it is possible that Botulinum toxin A may have a role in a more general chronic constipation population.

As the exact mechanism of outlet obstruction constipation is unclear, there may be some patients who have greater benefit depending on the etiology of the symptoms. Based on our multivariate regression analysis, patients with fecal incontinence at presentation are less likely to respond. Fecal incontinence may be an indicator of more severe or further progression of disease (for example due to presence of megarectum), as compared to those with only pain or decreased frequency who may have milder or earlier disease. This suggests that there may be a role for Botulinum toxin treatment in patients unresponsive to conventional medication management with earlier signs of constipation and prior to the development of fecal incontinence. Evidence has shown that earlier treatment of constipation may lead to more favorable outcomes [5].

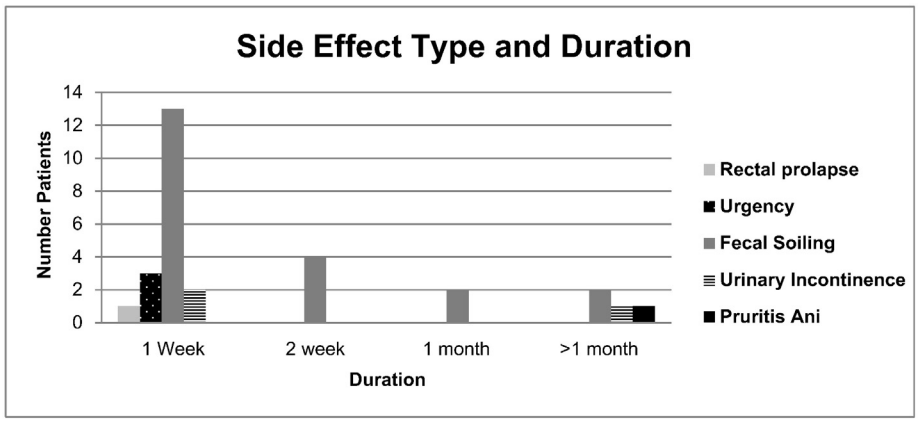

Fig. 1. Type of symptoms and duration of symptoms until resolution vs. number of patients with side effect.

Botulinum toxin injections are predicted to maintain efficacy for 3 to 6 months after treatment [22]. However, approximately half of the cases treated with an initial dose of Botox had a beneficial response lasting greater than six months with seventeen percent noting a response greater than one year. Therefore, suggesting that Botulinum toxin injections may serve as a bridge intervention as children's symptoms can often improve with time and patient maturity.

As shown, Botox injections can lead to decreased pain with defecation, therefore reducing anxiety associated with bowel movements and thus decreasing withholding behavior, a frequent etiology of constipation [26,27]. There may be a specific role for Botox injection in patients, particularly around toilet training age when there is an increased fear of having a bowel movement, in order to interrupt the cycle of stool withholding and encourage normal stooling patterns. The treatment may help alleviate the symptoms while the patient matures so that when the Botulinum toxin efficacy wanes, the patient may have become comfortable with toilet use and has stopped the tendency to withhold.

As many parents are concerned about long-term treatment and daily medication use in young patients, including osmotic and laxatives, Botulinum toxin injections could possibly serve as an alternative. Twenty two percent of our patients were able to wean down or off their medical bowel regimen after the initial injection. Laxative use may decrease by the use of a one-time injection, thus providing alternative options to already frustrated parents.

Our study shows that the side effects from the injection are mild and mostly self-resolved. Many of the patients were followed for greater than a year and some had multiple injections, with no indication of significant adverse effects. The most common effect, which was expected due to a relaxed internal sphincter, was stool leakage. However, many of the patients had resolution of this within a day or two, and almost all had resolution within a week. The most concerning noted effect was urinary incontinence, which resolved within the week for one patient and was likely behavioral in the other. This would support the avoidance of injecting into the anterior quadrant to prevent the unlikely possibility of a urethral injury.

Botox appears to be a safe intervention with the biggest risk being associated with the anesthesia necessary for injection. Additionally, it is interesting to note that although there was a relaxation of sphincter tone in those with normal pressure, there was not an increase incidence of stool leakage as compared to those with starting high pressure internal sphincter. Therefore, this study suggests that injection may be considered in all patients with outlet obstruction, regardless of anal canal baseline pressure and before or instead of anal sphincterotomy. Recently transcutaneous needle-free injections have been used for anal fissures and constipation. This could reduce the risk of using a needle injection including intravascular injection or needle stick injury [24].

There are several limitations to this study. First, it is a retrospective, chart review and therefore all the information is based on what is recorded by the physician in the patient's chart, which may not be an accurate reflection of response. There is also no placebo group and therefore lacks in a control group for comparison. As only a subset of the patients with normal sphincter pressure received the injection, this may be a self-selected group with other factors that led to a response. Additionally, the sphincter pressure was measured under light anesthesia with sevoflurane which may lead to lower values. However, it should be noted, that all the patients underwent the same procedure and anesthesia intervention, thus the effects of anesthesia should be consistent throughout all patients.

4. Conclusion

Overall, the results of this large retrospective study are promising and encourage the consideration of Botulinum toxin injections for persistent chronic constipation, particularly early in the disease process. Abnormal anal sphincter dynamics do not predict response to Botulinum toxin injection and therefore injection may be considered in all patients with outlet obstruction, regardless of anal sphincter baseline pressure. A prospective, randomized placebo-controlled trial comparing Botulinum toxin injections with continued conservative therapy is needed, in addition to examination of populations that may have improved response such as the toilet training age.

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