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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.