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EDITORIAL

Use of *Clostridium botulinum* toxin in gastrointestinal motility disorders in children

Ricardo A Arbizu, Leonel Rodriguez

Ricardo A Arbizu, Leonel Rodriguez, Center for Motility and Functional Gastrointestinal Disorders, Division of Gastroenterology, Department of Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, United States

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Correspondence to: Leonel Rodriguez, MD, MS, Center for Motility and Functional Gastrointestinal Disorders, Division of Gastroenterology, Department of Medicine, Boston Children's Hospital, Harvard Medical School, 300 Longwood Avenue, Boston, MA 02115,
United States. leonel.rodriguez@childrens.harvard.edu
Telephone: +1-617-3556055
Fax: +1-617-7300043

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Abstract

More than a century has elapsed since the identification of *Clostridia* neurotoxins as the cause of paralytic diseases. *Clostridium botulinum* is a heterogeneous group of Gram-positive, rod-shaped, spore-forming, obligate anaerobic bacteria that produce a potent neurotoxin. Eight different *Clostridium botulinum* neurotoxins have been described (A-H) and 5 of those cause disease in humans. These toxins cause paralysis by blocking the presynaptic release of acetylcholine at the neuromuscular junction. Advantage can be taken of this blockade to alleviate muscle spams due to excessive neural activity of central origin or to weaken a muscle for treatment purposes. In therapeutic applications, minute quantities of botulinum neurotoxin type A are injected directly into selected muscles. The Food and Drug Administration first approved botulinum toxin (BT) type A in 1989 for the treatment of strabismus and blepharospasm associated with dystonia in patients 12 years of age or older. Ever since, therapeutic applications of BT have expanded to other systems, including the gastrointestinal tract. Although only a single fatality has been reported to our knowledge with use of BT for gastroenterological conditions, there are significant complications ranging from minor pain, rash and allergic reactions to pneumothorax, bowel perforation and significant paralysis of tissues surrounding the injection (including vocal cord paralysis and dysphagia). This editorial describes the clinical experience and evidence for the use BT in gastrointestinal motility disorders in children.

Key words: Botulinum toxin; Gastrointestinal motility disorders; Children; Swallowing disorders; Gastroparesis; Defecation disorders

Core tip: *Clostridium botulinum* toxin has been used to alleviate symptoms associated to muscle spams due to excessive neural activity of central origin or to weaken a muscle for treatment purposes. In therapeutic applications, minute quantities of botulinum neurotoxin type A are injected directly into selected muscles. Ever since, therapeutic applications of botulinum toxin have expanded to other systems, including the gastrointestinal tract. This editorial presents the current evidence and evaluates the clinical experience for the use of botulinum

toxin in gastrointestinal motility disorders in children.

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SWALLOWING DISORDERS

Cricopharyngeal achalasia

Cricopharyngeal achalasia is characterized by abnormal relaxation of the upper esophageal sphincter associated to abnormal coordination with pharyngeal contraction resulting in oropharyngeal dysphagia and at times resulting in aspiration. The disorder has been treated with medications, dilatations, botulinum toxin (BT) and myectomy. BT has been reported as safe and effective in patients with cricopharyngeal achalasia[1-3], particularly in those who failed medical therapy and are poor surgical candidates, as a diagnostic tool in complex cases[3], to alleviate symptoms until surgery can be safely performed[4] and to provide relief for residual symptoms after myotomy[5] with minimal side effects reported. In our experience the potential complications with the use of BT in cricopharyngeal achalasia can be important so we recommend its use for experienced hands, particularly ENT surgeons.

Esophageal achalasia

Esophageal achalasia is a disease of unknown etiology characterized by loss of esophageal peristalsis and failure of the lower esophageal sphincter (LES) to relax with swallowing. Decrease in nitric oxide synthase containing nerve fibers and interstitial cells of Cajal in the distal esophagus have been proposed as potential causes[6]. It is an uncommon condition in pediatrics and has an estimated incidence that ranges from 0.11-0.18/100000 children per year[7,8]. Symptoms vary with age of presentation. Progressive dysphagia, vomiting and regurgitation are common complaints in older children[9]. Initial diagnostic studies include barium swallow and upper endoscopy, but esophageal manometry is considered to the gold standard test for diagnosis and will provide diagnostic certainty in approximately 90% of the cases[10,11]. The goal of treatment in children with achalasia is to improve bolus transport across the LES by reducing the pressure at that level. Current treatment options include pharmacotherapy, pneumatic dilation, surgery or injection of BT and recently the Peroral Endoscopic Myotomy[12]. BT is endoscopically injected at the LES with a sclerotherapy needle in 4 different quadrants. The short-term efficacy of BT in treating esophageal achalasia has been well established in adults. Multiple double blind placebo controlled studies have revealed BT to be safe and effective in reducing symptoms and improving esophageal clearance in adults with esophageal achalasia[13]. It has been described to be as effective as pneumatic dilation[14-17] and comparable to surgical myotomy[18] in the short term (< 6 mo). It has been reported to improve residual symptoms after myotomy and pneumatic dilations[19]. It has been recommended primarily in those who are poor surgical candidates resulting in important symptomatic response[20]. BT has also been used as a diagnostic tool in cases where diagnosis of achalasia is not clear and to indicate definitive therapy[21]. Most of the information of BT use in children is found as case reports and case series. Most authors reported a short-lived (2-6 mo) improvement on symptoms[9,22-24]. Walton *et al*[22] reported a single case with sustained clinical improvement of 8 mo after a single BT injection. Khoshoo *et al*[25] reported BT as a safe and less invasive alternative for symptomatic relief of symptoms in 3 children with achalasia. They also observed weight gain prior to surgery and noted that it could also be a choice in patients with incomplete response following balloon dilatation or myotomy[25]. Hurwitz *et al*[24] found that among children receiving BT as initial treatment for achalasia, 83% responded to therapy with a mean duration of effect of 4.2 mo and more than half of responders required additional procedure 7 mo after receiving BT. Another study demonstrated an inverse relationship between pre-BT LES resting pressure and duration of response[23]. All authors agree that BT should be reserved for children with achalasia who cannot undergo pneumatic dilatation or surgery or to alleviate residual symptoms after these interventions.

BT has been also reported as useful in the management of esophageal spastic disorders in adults[26], to our knowledge no reports are available for this indication in children. The only fatality related to the use of botulinum toxin for gastrointestinal motility disorders has been reported in an adult patient with esophageal spasms who developed a fatal mediastinitis[27].

GASTRIC DISORDERS

Gastroparesis

Gastroparesis is defined as the presence of upper gastrointestinal symptoms with evidence of delayed gastric emptying by a standardized gastric transit study in the absence of mechanical obstruction. Symptoms classically include nausea, vomiting, early satiety, bloating, postprandial fullness, abdominal pain, and weight loss. The etiology of gastroparesis in the pediatric population is limited to a few studies. An observational descriptive analysis of a large pediatric population with gastroparesis reported that approximately 70% of the cases were idiopathic[28]. Another series found gastroparesis to be associated with post-viral gastroenteritis (18%), medications (18%), post-surgical (12.5%), mitochondrial disease (8%) and diabetes mellitus (2%-4%)[29]. Gastroparesis has been treated with medications and in some cases

with surgical interventions aiming to facilitate the transfer of bolus from stomach to small bowel. The endoscopic application of BT injections in gastroparesis has been well studied in adult patients. Multiple large uncontrolled studies have demonstrated symptom improvement with the use of BT[30-32]. However, two small randomized control studies showed no significant difference between BT and placebo on symptomatic as well as gastric emptying improvement[33,34], but some concerns have been raised about the power of such studies. In pediatrics, Rodriguez *et al*[35] assessed the long-term clinical outcomes after intra-pyloric BT injection in children with gastroparesis. After the first injection, 33% of patients reported no response and 67% described improvement in their symptoms. The mean duration of improvement was 3 mo and no significant side effects were reported[35]. From their analysis they also described that older age and vomiting were predictive of response to the initial injection, and male sex predicted response to repeated injections. There are currently no guidelines that indicate the timing of BT injections in pediatric patients with gastroparesis, but the consensus is that its use should be limited to patients that fail medical therapy with prokinetics and before more invasive interventions are considered (gastrojejunostomy, gastric electric stimulator). Although have not observed complications with its use in gastroparesis we have noticed short-lived vomiting in some patients followed by complete resolution of symptoms.

DEFECATION DISORDERS

Chronic constipation is one of the most common complaints at the pediatric offices. Although constipation may have several etiologies, in most children no underlying etiology can be found. Symptoms refractory to aggressive therapy with stool softeners and laxatives should prompt further work up to rule out etiologies like Hirschsprung's disease and internal anal sphincter (IAS) achalasia.

Hirschsprung's disease

Hirschsprung's disease (HD) is characterized by obstructive defecation due to distal colonic aganglionosis caused by a defect in cranio-caudal migration of neuroblasts leading to lack of relaxation resulting in functional obstruction. The diagnosis is confirmed by rectal biopsy demonstrating absence of ganglion cells in the submucosa and myenteric plexus. The treatment of HD consists in surgical removal of the aganglionic segment. Despite many improvements in diagnostic and surgical techniques, many patients continue to exhibit symptoms after surgical correction. The treatment of obstructive defecation initially consists of rectal dilatations to avoid stricturing of the surgical anastomosis. Some advocate performing a myectomy for those who fail medical therapy and dilatations, but results are variable with some reporting good outcomes[36] and others reporting only a moderate success[37] with complications like fecal incontinence. Due to the inconsistent efficacy and concerns of permanent incontinence, other non-invasive and self-limited alternatives have been contemplated, including use of topical nitric oxide[38] and BT. Langer *et al*[39] reported significant clinical improvement in 3/4 children as well as reduction of IAS resting pressure at 4-8 wk post-BT. Minkes *et al*[40] also reported clinical improvement in 14/18 children and described an association between clinical improvement and a post-BT decrease in IAS resting pressure. Another study showed an improvement in short and long-term obstructive symptoms, frequency of enterocolitis episodes and short-term decrease in hospitalization rates in 30 children with HD and prolonged use of BT[41]; 7 patients developed transient fecal incontinence; and, 1 patient reported anal pain after the BT injection. Elevated IAS resting pressure was associated with higher clinical success. A recent report by Han-Geurts *et al*[42] reported similar findings, with clinical improvement in 25/33 (76%) and decrease in hospitalizations due to enterocolitis. Importantly, they reported 2 children developing transient pelvic muscle paresis with walking impairment. General consensus is to use BT for those patients with obstructive defecation and elevated anal canal resting pressure. In our experience BT is more effective when IAS resting pressure is over 50 mmHg.

IAS achalasia

The hallmark of IAS achalasia is absent IAS relaxation with balloon rectal distention in the presence of ganglion cells on rectal biopsy. Some have called it ultra-short segment Hirschsprung's disease. The treatment of IAS achalasia has been aimed at relieving obstructive defecation with dilations or myectomy. IAS myectomy has been reported to be effective in relieving obstructive symptoms and helping achieve normal bowel control in children with IAS achalasia[43,44]. However, it is associated to fecal incontinence. BT has shown excellent results in relieving functional obstructive symptoms and has become the treatment of choice for IAS achalasia[41,45-47]. In several studies, transient fecal incontinence was the most common minor complication reported that resolved within 4 wk after BT injection[41,45,46]. Foroutan *et al*[48] demonstrated that BT has similar efficacy and less complications when compared to myectomy. Nevertheless, a recent meta-analysis found that regular bowel movements and short and long-term improvements were more frequent after surgery with no difference in the continued use of laxatives or rectal enemas, episodes of constipation and soiling and, overall complication rates between the two procedures[49]. BT should be considered the first option of treatment for IAS achalasia.

Chronic anal fissure

Chronic anal fissure is a common and benign anorectal condition associated to elevated anal canal

resting pressures, although other factors might also play a role. The classic symptom is pain on or after defecation that is often severe and may last from minutes to several hours. Most fissures occur in the posterior midline of the anal canal[50]. By definition, an acute anal fissure typically heals within 6 wk with conservative local management, while a chronic anal fissure fails medical management at times requiring more aggressive interventions[51]. Lateral internal sphincterotomy is a surgical technique commonly used to treat chronic anal fissure. It has been favored by most surgeons because it offers long-lasting relief in sphincter spasm by permanently weakening the IAS. However, it may lead to anal deformity and incontinence in 8%-30% of patients that can be permanent in a subset of patients[50]. BT injection to the IAS has been demonstrated to improve healing in chronic anal fissure in adult studies. In a randomized placebo controlled study BT demonstrated to be superior to placebo in healing of chronic anal fissure at two month follow up (73% *vs* 13%), only a small number of patients required a second injection and no relapses were reported after a 16-mo follow up[52]. Its use has also been shown to be effective when used in combination with topical nitroglycerin[53]. Pediatric studies have shown that BT injection to the external anal sphincter is an effective therapy in children with chronic anal fissures[54,55]. Nonetheless, there is discrepancy in the injection site when compared to adult studies. Prospective and long-term studies are needed to evaluate BT therapy in children with chronic anal fissures.

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