Preliminary Experience With Intrasphincteric Botulinum Toxin for Persistent Constipation After Pull-Through for Hirschsprung's Disease

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• Although most children who have Hirschsprung's disease have an excellent result after pull-through surgery, some experience persistent constipation caused by "internal sphincter achalasia." Anal myectomy has been advocated for this problem, but it results in permanent injury to the sphincter and is not universally effective. Botulinum toxin has been safely used to selectively and reversibly weaken a variety of voluntary muscles and sphincters in both adults and children. Injection of botulinum toxin into the internal anal sphincter (IAS) should theoretically produce the same functional result as anal myectomy without permanent sphincter injury. Four children aged 4 to 8 years presented with persistent constipation after a pull-through procedure for Hirschsprung's disease. Two had associated encopresis, both of whom had previous myectomies. The authors performed four-quadrant intrasphincteric botulinum toxin injection (total dose, 15 U). Resting IAS pressure decreased in all children 4 to 8 weeks after injection. Patients have been followed up for 7 to 9 months. One child (with Down's syndrome) remained symptomatically unchanged. The other three families reported significant improvement in bowel function in their children. In two of these, there was a return of symptoms 6 months after injection; one child underwent reinjection with good results. Postinjection incontinence occurred in three children, but resolved after several weeks in the one who did not have encopresis before botulinum toxin injection. These preliminary results suggest that botulinum toxin may represent a less invasive alternative to anal myectomy for children who have severe constipation after surgery for Hirschsprung's disease. If myectomy is contemplated, botulinum toxin may also be useful as a means of predicting which children may benefit.

INDEX WORDS: Hirschsprung's disease, botulinum toxin, anal myectomy, anal sphincterotomy.

MOST CHILDREN who have Hirschsprung's disease have an excellent result after pull-through surgery. However, follow-up studies have documented long-term problems with constipation, encopresis, enterocolitis, and motility disturbances in a minority of patients.[1-3] In some children, obstructive symptoms are felt to be caused by "internal sphincter achalasia" related to abnormal innervation of the sphincter. Many surgeons have advocated internal sphincter myotomy or myectomy for the treatment of this problem.[4-6] Although commonly performed, this operation is not universally effective and requires permanent destruction of the sphincter.

Botulinum toxin injection has been used extensively in skeletal muscle for the treatment of strabismus and spasticity,[7] and in smooth muscle for the treatment of achalasia[8] and anal fissure.[9] It weakens muscle in a focal and transient fashion, and has been safely used in children. This technique could theoretically provide the same effect as internal anal myectomy, but without the potential long-term problems associated with permanent sphincter destruction. We used botulinum toxin injection in four children who had persistent obstructive symptoms after a pull-through procedure, and report our preliminary results.

MATERIALS AND METHODS

This prospective protocol was approved by the Washington University Human Studies Committee. All children were referred because of persistent obstructive symptoms after a pull-through procedure for Hirschsprung's disease. Assessment included history, physical examination, barium enema, and repeat rectal biopsy if not already performed at the referring center. All four children underwent anorectal manometry before and 4 to 6 weeks after botulinum toxin injection. Manometry was performed using a standard water-perfused system, and both resting and squeeze pressures were recorded. At least three measurements of each were made, and the mean value was used. Children were sedated using oral medazolam before manometry.

Botulinum toxin injection was performed in the lithotomy position under general anesthesia. A total of 15 U, in a volume of 0.4 mL, was injected into four quadrants of the internal anal sphincter, at the level of the dentate line (0.1 ml per quadrant). Follow-up information included change in obstructive symptoms, presence of incontinence, presence of complications from the injection, and change in resting sphincter pressure 4 to 6 weeks after injection.

CASE REPORTS

Case 1

This boy presented with neonatal bowel obstruction. A diagnosis of Hirschsprung's disease was confirmed, and a colostomy was performed. A Soave endorectal pull-through was performed at 4 months of age. This was complicated by an anastomotic leak requiring a temporary colostomy, which was subsequently closed. He did well until 18 months of age when persistent obstructive symptoms developed requiring

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frequent enemas and intermittent hospital admissions. There was no fever or toxicity suggestive of enterocolitis. At 4 years of age the child was referred to our center. Repeat rectal biopsy findings showed absence of ganglion cells, and laparoscopic colon biopsy results showed neuronal intestinal dysplasia in the left colon with normal innervation in the right colon. He underwent left hemicolectomy and Duhamel pull-through of the right colon with protecting ileostomy. After ileostomy closure he would not pass stools spontaneously, and a leak developed requiring reformation of the stoma. To prevent a further leak caused by distal obstruction, he underwent anorectal manometry followed by intrasphincteric botulinum injection before closure of the second ileostomy. In the postoperative period he passed stools spontaneously, was discharged home, and did extremely well with no need for enemas or laxatives and no episodes of incontinence. Six months later recurrent obstructive symptoms developed, and a repeat botulinum toxin injection was performed with good results. Three months later he remains free of obstructive symptoms.

Case 2

This girl presented with neonatal bowel obstruction. A diagnosis of Hirschsprung's disease was confirmed, and a colostomy was performed. A Soave endorectal pull-through was performed at 6 months of age. She did well until 2 years of age, when persistent obstructive symptoms developed requiring frequent enemas and laxatives There were no episodes suggestive of enterocolitis. At 4 years of age she was referred to our center. Repeat rectal biopsy findings showed absence of ganglion cells, and laparoscopic colon biopsy results were normal. She underwent Duhamel pull-through of the left colon with protecting proximal colostomy. Because of our recent experience with anastomotic leak after ileostomy closure in case 1, we wished to minimize the possibility of distal obstruction caused by sphincter hypertonicity. She therefore underwent anorectal manometry followed by intrasphincteric botulinum injection before colostomy closure. In the postoperative period she passed stools spontaneously, was discharged home, and continues to do extremely well at 9 months follow-up, with no further need for enemas or laxatives. The parents reported several episodes of incontinence over the first 3 weeks, with none since.

Case 3

This girl with Down's syndrome presented at 9 months of age with constipation. A diagnosis of Hirschsprung's disease was confirmed by rectal biopsy findings, and a primary Soave endorectal pull-through was performed. She did well for 2 months, and then intermittent obstructive symptoms developed requiring enemas and laxatives. Repeat rectal biopsy findings showed normal ganglion cells. A posterior anal myectomy was performed at 3 years of age, with no improvement in symptoms, and development of intermittent incontinence. There was no clinical evidence of enterocolitis. Use of cisapride was ineffective. At 8 years of age she underwent anorectal manometry followed by intrasphincteric botulinum injection. Postinjection she has experienced no significant change in her symptomatology.

Case 4

This boy presented with bowel obstruction at 1 month of age. A diagnosis of Hirschsprung's disease was confirmed, and a colostomy was performed. A Duhamel pull-through was performed at 1 year of age, and the colostomy was closed 4 months later. He did well until 2 years of age, when persistent obstructive symptoms developed requiring frequent enemas. Repeat rectal biopsy findings showed normal innervation. Because of worsening symptoms, he had a diverting ileostomy performed at 3 years of age, a posterior anal myectomy was performed 9 months later, and the ileostomy was closed at age 4. Again periodic obstructive symptoms developed including intermittent incontinence, which were treated with enemas, laxatives, and occasional hospitalization with anal dilatation. Although he did not have fever with these episodes, there was evidence of mild enterocolitis radiologically and endoscopically. He was referred to our center at 4½ years of age, where he underwent anorectal manometry followed by intrasphincteric botulinum injection. After injection he experienced improvement in the severity of his obstructive symptoms, although he continued to require some enemas and laxatives and had no decrease in episodes of incontinence. Six months postinjection worsening abdominal distension and obstructive symptoms developed, and the family is currently wieghing the options for further treatment.

Resting internal sphincter pressures prebotulinum and postbotulinum injection for all four patients appear in Table 1.

DISCUSSION

Botulinum toxin has been shown to be safe in children when used for skeletal muscle problems, and it has been used successfully in the smooth muscle of the lower esophageal and anal sphincters. Our preliminary experience demonstrated that botulinum toxin reproducibly relaxed the internal anal sphincter in children who had Hirschsprung's disease, and appeared to improve obstructive symptoms in three of four patients. The one child who was not improved likely had a significant behavioral component to her symptoms, a problem which is more commonly seen in children who have Down's syndrome.

Incontinence occurred in three of the four patients after injection of botulinum toxin. Two of these patients, both of whom underwent a previous anal myectomy, were already experiencing incontinence before injection, and in the third, the incontinence resolved within several weeks of injection. Incontinence is an underrecognized complication of pull-through surgery for Hirschsprung's disease,[10] and it is not surprising that botulinum toxin may exacerbate this problem. It is also not surprising that postinjection incontinence may be more significant in patients who have already undergone a myectomy.

What is the potential role of botulinum toxin in the management of this problem? Firstly, botulinum toxin could be used as a diagnostic test to determine whether internal sphincter hypertonicity is the cause of the patient's obstructive symptoms, and if successful could be followed by anal myectomy. Secondly, botulinum toxin could be used as a therapeutic modality, and repeated injections could be given when the symptoms reappear. Our patient who has chosen to undergo repeat

Table 1. Internal Anal Sphincter Pressures Preinjection and Postinjection of Botulinum Toxin

Patient No	Preinjection Pressure (mm Hg)	Postinjection Pressure (mm Hg)
1	110	84
2	66	44
3	100	55
4	85	52

injection has had a good second response. Repeated injections of botulinum toxin have been used in patients who have achalasia,[11] as well as in other settings,[7] and appear to be both efficacious and safe. Finally, an argument could be made for the prophylactic use of botulinum toxin injection to prevent postoperative enterocolitis in place of routine rectal irrigations. Further experience with a larger group of patients will be required to determine the appropriate role of this agent for children who have Hirschsprung's disease.

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Discussion

P. Liebert (Eastchester, NY): After having discovered early on doing Soave procedures that they have a variety of problems afterward with both enterocolitis and a gas bloat, I started doing forceful dilatations under anesthesia at the end of the pull-through. I am sure that a number of the sphincter muscles get stretched or ruptured, but since starting to do that I have seen very few of those complications.

My question with this technique is, how do you avoid getting the botox into a venous channel, and what happens if that occurs?

J.C. Langer (response): I don't know what happens if you inject it intravenously. I suspect that the dose we are giving is very tiny and it probably wouldn't have any adverse effect. However, patients with botulism die of what I presume is systemic botox toxicity. The way we avoid that is by withdrawing the plunger before we inject.

J. Lynch (Pittsburgh, PA): Did you dilate them after you injected the botox?

J.C. Langer (response): We haven't been forcibly dilating but you have to put the nasal speculum in as I showed on the slide to be able to see the dentate line. So I suspect there may be some dilatation being done.

A. Coran (Ann Arbor, MI): One of the standard treatments of this problem is to bring them to the operating room under anesthesia and dilate them, and you will get an effect that is very similar, 3 to 6 months of improvement, and then a return of symptoms sometimes. So I wonder whether that is a factor that needs to be controlled a little better to determine whether this is really having a therapeutic effect.

M. Gauderer (Greenville, SC): Can you use this for other sphincters of the GI tract?

J.C. Langer (response): There is significant experience now in adults and children with achalasia. The effect seems to last between 6 months and 1 year, and a lot of gastroenterologists are now using this as the primary mode of therapy.

There is also some experience in the anal sphincter in adults for the treatment of anal fissure, and there is one report of idiopathic constipation in adults injected into the external sphincter. But they had a fairly high incidence of transient incontinence in that series.

As far as I know, nobody has used it in the pylorus.

R. Pearl (Toronto, Ontario): With this wearing off in 6 to 9 months, how would you project this could ever be used permanently either at the GE junction or in the anus for more than just a diagnostic test, which might be a very good use for it?

J.C. Langer (response): I am not prepared to discuss the achalasia experience because I don't have any personal experience with that. But I think most of these children tend to grow out of this problem. This is something that I am not old enough yet to have experienced in a large number of patients of my own, but my more senior colleagues have told me this.

The question is whether you would prefer to do every-6-month injections for a few years or subject a patient to an operation that is going to last forever. Many people have reassured me that a myectomy does not cause incontinence long term, but I have not seen that in the literature, and I remain skeptical about it. I prefer to try and find something that is less invasive.