

Botulinum Toxin in the Treatment of Outlet Obstruction Constipation Caused by Puborectalis Syndrome

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PURPOSE: Puborectalis syndrome has been difficult to treat. We investigated the efficacy of botulinum toxin in treating patients with puborectalis syndrome who had previously failed to respond to electromyographic biofeedback sessions and who refused to use anal dilators. **METHODS:** Of a group of 50 patients with chronic outlet obstruction constipation, four patients with puborectalis syndrome were included in the study. The patients were studied using anorectal manometry, defecography, and electromyography and then treated with 30 units of Type A botulinum toxin, injected into two sites on either side of the puborectalis muscle, under ultrasonographic guidance. **RESULTS:** One patient was lost to follow-up. After treatment in other patients, the frequency of natural bowel movements increased from zero to six per week and laxatives were needed by only one patient. Anorectal manometry demonstrated decreased tone during straining from (mean $\pm$ standard deviation) 96.2 ± 12 mmHg to 42.5 ± 13 mmHg at four weeks ($P = 0.003$) and 63.2 ± 22 mmHg at eight weeks ($P = 0.009$). Defecography performed eight weeks after treatment showed improvement in the anorectal angle, which increased from $94 \pm 11^\circ$ to $114 \pm 13^\circ$ ($P = 0.01$), and evacuation of barium paste. Electromyography demonstrated mild paradoxical contraction. However, 16 weeks after treatment one of these three patients suffered symptomatic recurrence. This patient was re-treated with 50 units of toxin; eight months later he required a further 60 units. Seven months after the last injection he reported normal daily bowel movements without the use of laxatives. **CONCLUSIONS:** Botulinum toxin injection should be considered as a simple therapeutic approach in patients with puborectalis syndrome. The use of higher dosage and a more precise method of toxin injections under transrectal ultrasonography account for the long-term higher success rate. However, because the effects of the toxin wear off within three months of administration, repeated injections could be necessary to maintain the clinical improvement. [Key words: Chronic constipation; Defecation disorders; Outlet obstruction; Puborectalis syndrome; Biofeedback; Botulinum toxin]

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Puborectalis syndrome (PRS) is believed to be a behavioral disorder in which a failure of relaxation or a paradoxical contraction of the puborectalis muscle occurs during attempted evacuation.¹ Although simple to diagnose, PRS has proved to be difficult to treat. The initial phase of management usually involves a high-residue diet to try to elicit rectal voiding. The next step is to use of increasing doses of laxatives and enemas. Neither procedure is effective in solving the problem. A wide variety of surgical and pharmacologic approaches have been proposed, with the aim of eliciting puborectalis muscle relaxation.¹ Several surgical techniques have been described for dividing the puborectalis muscle in patients with constipation who have paradoxical contraction.²⁻⁴ However, surgery produced poor effects and resulted in a high morbidity. Surgical division of the puborectalis muscle has now been abandoned because of the high rate of postoperative incontinence.

An alternative solution is daily, progressive anal dilation, which we have demonstrated to be a simple therapeutic approach in patients with PRS and may also help biofeedback (BF) training.⁵ BF seems to reasonably effective in treating adult patients affected by PRS, with a success rate of between 31 and 89 percent.^{6,7} However, BF is neither universally available nor uniformly successful. A recently described nonsurgical alternative is injection of botulinum toxin Type A (BTX-A) directly into the puborectalis muscle.^{8,9} The aim of this study was to evaluate the efficacy of Type A botulinum toxin in improving the frequency of spontaneous bowel movements in patients who had previously failed to respond to electromyographic biofeedback sessions and who refused to use anal dilators.

PATIENTS AND METHODS

Four patients, who suffered from severe chronic constipation caused by PRS, had previously failed to respond to electromyographic biofeedback sessions,

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and refused to use anal dilators, were enrolled. Diagnosis was made using our protocol for constipation,¹⁰ which includes clinical examination, barium enema, colonoscopy, colonic transit time study, anorectal manometry, defecography, and electromyography (EMG) of the puborectalis muscle.

The inclusion criteria for treatment with Type A botulinum toxin were the following: 1) incomplete, prolonged, and difficult evacuation with constant use of enemas, laxatives, and digital defecation; 2) number of evacuations less than three per week; 3) normal colonic transit time study; 4) failure to relax perineal floor during straining at physical examination; 5) inability to achieve evacuation of barium paste during defecography, with lack of a measurable increase in the anorectal angle between rest and attempted evacuation; 6) increased activity of the puborectalis muscle at electromyography performed with needle electrode; and 7) high pressure levels during straining at anorectal manometry.

The study protocol was reviewed and approved by the Institutional Committee of the Catholic University of Rome. Each patient provided written informed consent for the study.

Thirty units of BTX-A (Botox®, Allergan, Irvine, CA), diluted in saline to 50 U/ml, were injected into two sites on either side of the paradoxically contracting puborectalis muscle under electromyographic guidance. The sites of injection were visualized by means of transrectal ultrasonography (Fig. 1). The toxin was injected with the patient in the left lateral position; sedation was not required.

Anal resting pressure, maximal voluntary contraction (*i.e.*, the maximal voluntary increase above the resting tone), and pressure on straining were evaluated four and eight weeks after the treatment. At the same times the degree of paradoxical contraction was also evaluated, using EMG. Changes in anorectal angle during straining were measured by defecography eight weeks after botulinum toxin injection.

RESULTS

From January to June 1996, of a group of 50 patients with chronic outlet obstruction constipation, 4 patients (3 males), with an age range of 38 to 70 years, were included in the study. All of the patients reported a history, ranging from 5 to 20 years, of incomplete, prolonged and difficult evacuation requiring the continual use of enemas, laxatives, and digital defecation (Table 1). The patients failed to respond to electromyographic biofeedback sessions and refused to use anal dilators. All biofeedback sessions were performed with an intra-anal EMG sensor. Each patient received one hour-long biofeedback session every week for three months.

Physical examination during straining showed a failure to relax the perineal floor in all of the patients. In all cases defecography showed failure to expel rectal contents during defecation and EMG documented an increased activity of the puborectalis muscle. All of the patients underwent anorectal manometry, which revealed high pressure levels during straining.

Only three patients attended follow-up evaluations.

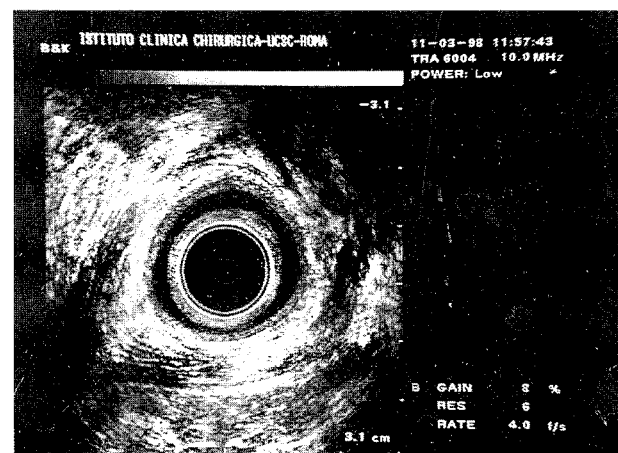


Figure 1. Identification by transrectal ultrasonography of the site of injection into the puborectalis muscle.

Table 1.
Clinical Characteristics and Parameters of Bowel Habits Before Botulinum Toxin Treatment

Patients	1	2	3	4
Age (yr)	70	66	48	38
Gender	M	M	M	F
Bowel habits				
Duration of constipation (yr)	8	20	12	5
Spontaneous bowel movement	No	No	No	No
Evacuation effort	Always	Always	Always	Usually
Incomplete evacuation	Always	Usually	Usually	Always

The fourth patient was lost to follow-up. The immediate clinical results (within 8 weeks of the BTX-A injection) were good in these three patients. All of them were satisfied with the therapy and none of them complained of incontinence. No systemic or local complications related to the treatment were observed. Natural bowel movements (*i.e.*, without the use of laxatives, bowel stimulants, or suppositories) increased from zero to six per week. The frequency of laxative use before treatment was reported by the patients as being a mean of 6.5 times per week; after BTX-A, laxatives were needed by only one patient and only once per week. Similarly, before treatment the patients required enemas a mean of 4.6 times per week, whereas after BTX-A an enema was not required by any patient.

Anorectal manometry demonstrated a decrease in tone during straining at four and eight weeks when compared with baseline value (Fig. 2), whereas, at the same times anal resting pressure and maximal voluntary contraction were unchanged (Table 2). Paradoxical contraction patterns at EMG were decreased in all the patients, and the anorectal angle measured during straining increased from (mean $\pm$ standard deviation) $94 \pm 11^\circ$ before treatment to $114 \pm 13^\circ$ at eight weeks ($P = 0.01$).

The patients were followed up for an average of 24 (range, 16–28) months; in two of the patients no relapse occurred during this period. However, the third patient suffered symptomatic recurrence 16 weeks after treatment. He was re-treated with 50 units of botulinum

toxin, and the clinical symptoms improved. Eight months after the second BTX-A treatment, the patient complained of a further relapse. He reported worsening defecation starting approximately eight weeks after the second treatment. However, the defecatory difficulties were not as severe as before treatment. The patient was treated with 60 units of BTX-A; seven months after this injection he reported normal daily bowel movements without any laxative use.

DISCUSSION

Botulinum toxin is one of the most lethal of biologic toxins. Paralysis occurs within a few hours. Bot-

Table 2.
Resting Anal Tone and Maximal Voluntary Contraction Before and After Botulinum Toxin Injections

	Before Treatment	Four Weeks After Treatment	Eight Weeks After Treatment
Resting anal tone	70 ± 10	$70 \pm 5^*$	$76 \pm 12^\dagger$
Maximal voluntary contraction	106 ± 21	$103 \pm 15^\ddagger$	$110 \pm 10^\S$

Figures are mean $\pm$ standard deviation in mmHg.

* $P = 1.0$ vs. baseline value.

$^\dagger P = 0.3$ vs. baseline value.

$^\ddagger P = 0.4$ vs. baseline value.

$^\S P = 0.6$ vs. baseline value.

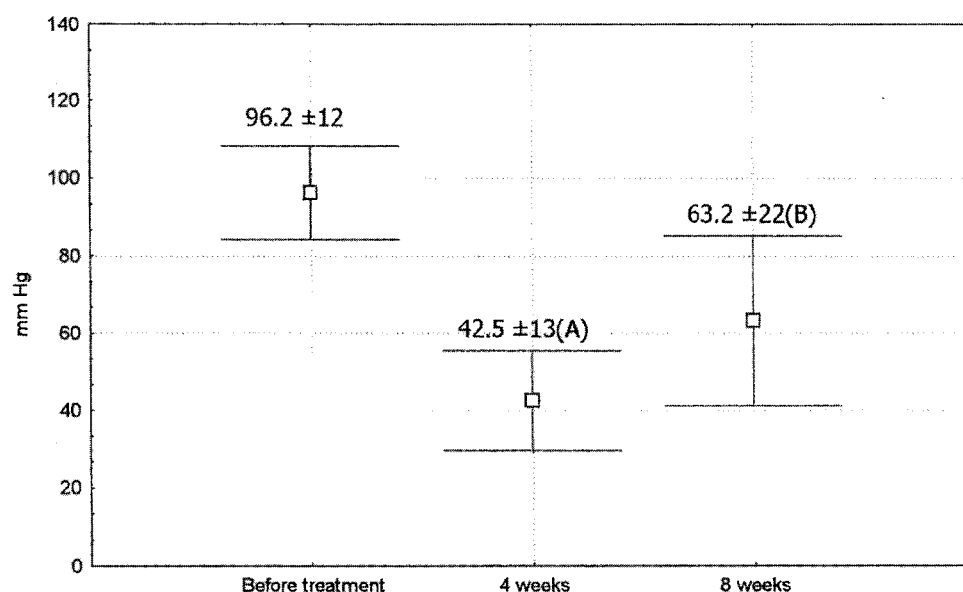


Figure 2. Pressure during straining before and after botulinum toxin injections. The data are expressed as means $\pm$ standard deviation. (A): $P = 0.003$ vs. baseline value; (B): $P = 0.009$ vs. baseline value.

ulium toxin exerts its effects on the peripheral nerve terminal at the neuromuscular junction, resulting in a flaccid paralysis.^{11, 12} The extreme potency in causing the neuromuscular paralytic condition is because of irreversible and selective multiphasic blockade of acetylcholine release from peripheral nerve endings.¹¹ Transmission of neuromuscular impulses resumes after the growth of new axon terminals, and clinical weakening of muscles is seen for three to four months.¹¹ The toxin has been used to weaken striated muscle in the treatment of disorders such as blepharospasm and spasmodic torticollis.

However, in addition to its potent skeletal neuromuscular blockade, botulinum toxin is also capable, within the autonomic nervous system, of blocking ganglionic nerve endings, postganglionic parasympathetic nerve endings, and those parasympathetic nerve endings at which acetylcholine is the transmitter.^{11, 12} This inhibition, first suggested *in vitro*, was later demonstrated *in vivo*, in which botulinum toxin could inhibit contraction of gastrointestinal smooth muscle.¹²⁻¹⁵

Botulinum toxin has also been used to weaken the external anal sphincter⁸ and puborectalis muscle selectively in patients with constipation affected by Parkinson's disease¹⁶ or in subjects with severe constipation caused by anismus.⁹ Hallan and coworkers⁸ demonstrated that the toxin relaxes the puborectalis muscle; as a consequence, the anorectal angle increases during straining, and evacuation is possible. However, despite good results, the effect of botulinum toxin injections is fairly short term.⁸ Joo and coworkers⁹ used 6 to 15 units of Type A botulinum toxin, injected under EMG guidance into the external anal sphincter or the puborectalis muscle. Of four patients, who had failed to respond to conventional BF, all improved with this treatment. However, the authors note that long-term results are only 50 percent successful.⁹

The present study provides further evidence of the usefulness of BTX-A in the management of alimentary tract dysfunction. Botulinum toxin seems to be a promising treatment in patients with PRS. It is less expensive and easier to perform than biofeedback training and does not depend on the patient's willingness to complete treatment. In our experience there were no observable side effects or complications, and symptomatic improvement was achieved in three patients. Anorectal manometry showed that pressure values declined after treatment; as expected, pressure during straining was lower than the pretreatment value in all patients. De-

fecography showed improvement in the anorectal angle during straining and in evacuation of barium paste. In the current study all of the patients had decreased contraction patterns at EMG, thus verifying that the BTX-A successfully weakened the inappropriately contracted muscle. In each case subjective reports were in accordance with the objective manometric, defecographic, and EMG findings. In the absence of any other treatment, these results could be attributed only to the effect of botulinum toxin.

In an effort to maximize the amount of botulinum toxin delivered to the puborectalis muscle, we used transrectal ultrasonography to guide injections. Because the EMG-guided method of injecting botulinum toxin into the puborectalis muscle is a "blind" technique, it is possible that in patients who did not respond to or relapsed early after a response the needle was not inserted into the puborectalis muscle or was only partially inserted into it, respectively. This also may be the reason why it is necessary to reinject some patients with the toxin for a second or third time before a satisfactory response can be achieved. Despite a more precise method of botulinum toxin injection under ultrasonographic guidance, repeated injections were needed in one of our patients to maintain clinical improvement. Nevertheless, when using botulinum toxin for the first time at fixed doses, variable clinical responses can be observed. This phenomenon may be caused by several factors, including the dilution volume used, a single or multiple strategy for injection, the presence or absence of specific antibodies, and variability in the amount of active drug present in a single vial;¹¹ the muscle activity may also play an important role.¹⁷

In summary, botulinum toxin seems to be a promising approach for the treatment of defecatory dysfunction caused by PRS. No adverse systemic effects or permanent sphincteric damage resulted from the injections of the toxin, which relieved the contraction of the puborectalis muscle, allowing resumption of normal rectal voiding. The use of higher dosage and the availability of a more precise method of toxin injections by means of transrectal ultrasonography account for the higher long-term success rate. In any case, further investigation of the efficacy and safety of BTX-A treatment are indicated before its general use can be advocated.

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