

## INTRASPINCTERIC BOTULINUM TOXIN FOR THE TREATMENT OF ACHALASIA

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**Abstract Background.** Achalasia is a disorder of swallowing in which the lower esophageal sphincter fails to relax. We report the use of botulinum toxin, a paralytic agent, for the treatment of this condition.

**Methods.** In a double-blind trial, 21 patients with achalasia received either 80 units of botulinum toxin or placebo, injected endoscopically into the lower esophageal sphincter. One week later, the response to treatment was assessed on the basis of changes in the symptom scores (measured on a scale from 0 to 9), pharyngo-esophagograms, and results of esophageal manometric and scintigraphic studies. Patients who received placebo initially were subsequently treated with botulinum toxin. After six months, esophageal scintigraphy was repeated.

**Results.** One week after treatment, the mean decrease in the symptom score was 5.4 points for the patients treated with botulinum toxin and 0.5 point for the placebo group ( $P=0.001$ ). The mean decrease in the

pressure of the lower esophageal sphincter was 33 percent in the treatment group, as compared with a mean increase of 12 percent in the placebo group ( $P=0.02$ ), and the mean increase in the width of the opening of the lower esophageal sphincter was 204 percent in the treatment group, as compared with a mean decrease of 14 percent in the placebo group ( $P=0.02$ ). Nineteen of the 21 patients treated with botulinum toxin had symptomatic improvement initially; after six months 14 patients were still in remission. This improvement was accompanied by a decrease in esophageal retention that was sustained at six months (46 percent, as compared with a pretreatment value of 77 percent;  $P=0.04$ ). There were no serious adverse effects.

**Conclusions.** Injection of botulinum toxin into the lower esophageal sphincter is an effective, safe, and simple method of treatment for achalasia, with results that are sustained for several months. (N Engl J Med 1995;332:774-8.)

**A**CHALASIA is a disorder of esophageal motility characterized by the absence of peristalsis, an elevated pressure of the lower esophageal sphincter, and the failure of the lower esophageal sphincter to relax during swallowing. The usual treatment for achalasia — balloon dilation or myotomy of the lower esophageal sphincter — is aimed at lowering the resting pressure of the sphincter.<sup>1</sup>

We hypothesized that locally injected botulinum toxin, a potent inhibitor of the release of acetylcholine from nerve endings, could be effective in the treatment of achalasia. This hypothesis was based on the concept that the net sphincter tone in the gut results from a balance between excitatory influences (acetylcholine and substance P) and inhibitory influences (vasoactive intestinal peptide and nitric oxide).<sup>2</sup> In achalasia, this balance may be upset because of the selective loss of the inhibitory nerves,<sup>3-5</sup> resulting in a hypertonic lower esophageal sphincter that fails to relax. By blocking the release of acetylcholine, locally injected botulinum toxin may restore the lower esophageal sphincter to a more normal resting tone.

In a pilot trial, we found that intraspincteric injection of botulinum toxin had the potential to be useful in the treatment of achalasia.<sup>6</sup> Here we present the results of a placebo-controlled trial of this agent in patients with achalasia.

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## METHODS

### Patients

Symptomatic adults with clinical, radiographic, and manometric features of achalasia were considered for enrollment in the trial. We excluded patients younger than 18 years of age, pregnant women, patients with a history of esophageal myotomy or perforation, and those with a coexisting condition found on initial upper gastrointestinal endoscopy (esophageal ulcers, Barrett's esophagus, esophageal varices, or carcinoma of the esophagus or stomach). The study was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins Hospital. Informed consent was obtained from all patients.

### Study Design

The study was designed as a randomized, double-blind, placebo-controlled trial. All patients underwent a pretreatment evaluation consisting of a clinical assessment, esophageal manometry, pharyngo-esophagography, and radionuclide studies of esophageal retention. After the diagnosis of achalasia had been established by upper gastrointestinal endoscopy, the patients were randomly assigned to receive an injection of either 80 units of botulinum toxin or a similar volume of normal saline, as described below. Both the patients and the endoscopists were unaware of the treatment assignments.

One week after the initial injection, all patients were reevaluated clinically as well as by esophageal manometry, pharyngo-esophagography, and radionuclide studies, after which the assignment code for each patient was broken. The patients who did not have a clinical remission (as defined below) after the administration of normal saline were treated at this time with an intraspincteric injection of botulinum toxin. The patients who did not have a remission after the initial injection of botulinum toxin were given a second injection of the same dose of toxin (within six weeks after the code had been broken in most cases).

### Clinical Assessment

During the week after the initial injection, the patients were interviewed each day by a physician who was unaware of the treatment assignments. The symptomatic response was evaluated on the basis of a modified symptom score,<sup>7</sup> which was the sum of the individual scores for three symptoms of achalasia: dysphagia, regurgitation, and chest pain. The frequency of each of these symptoms was graded

**Table 1. Base-Line Characteristics of 21 Patients with Achalasia Treated with Botulinum Toxin or Placebo.**

CHARACTERISTIC	BOTULINUM TOXIN (N = 11)	PLACEBO (N = 10)	P VALUE
	<i>mean (range)</i>		
Age (yr)	47 (19–72)	54 (22–74)	0.48
Ratio of men to women	6:5	4:6	1.01
Symptoms			
Score	7.1 (5–9)	5.9 (4–9)	0.07
Duration (yr)	3 (0.25–9)	3.9 (0.5–10)	0.44
No. of esophageal dilations	0.7 (0–2)	0.6 (0–2)	0.62
Esophageal function			
Pressure (mm Hg)	47 (18–67)	47 (16–81)	0.44
Retention at 5 min (%)	81 (44–97)	80 (50–94)	0.50
Diameter (cm)	5 (2.5–7)	5 (2–8)	0.65

on a scale of 0 to 3 (0, none; 1, occasional; 2, daily; 3, with each meal). Thus, the maximal total score was 9 points. Clinical remission was defined as a score of 3 or less during follow-up, and failure of treatment (or relapse) as a score of 4 or more. Patients were also questioned about the occurrence of potential complications of the injections, such as fever, chest pain, systemic weakness, influenza-like illness, and reflux. This protocol was repeated during the first week after the injection of botulinum toxin in the patients who had initially received placebo.

#### Follow-up Studies

The patients were contacted by telephone about every four weeks to assess the clinical response to the injection. They were asked to return for a follow-up study of esophageal retention after six months.

#### Esophageal Manometry

Esophageal manometry was performed by a slow-station pull-through method with the use of a solid-state motility catheter (Series P33, Konigsberg Instruments, Pasadena, Calif.) and with two circumferential sensors (outer diameter, 5.2 mm; length, 3.1 mm) and two directional sensors connected to a computerized manometric recording system. The pressure of the lower esophageal sphincter was analyzed by a physician who was unaware of the name of the patient and the treatment assignment. The physician recorded the end-expiratory value in the area of the segment with the highest pressure, avoiding swallowing-related changes in pressure. The values obtained from the two circumferential sensors were averaged.

#### Esophageal-Retention Studies

After an overnight fast, the patients ate a semisolid meal (19 g of cornflakes, 120 ml of milk, and 1 g of sugar) radiolabeled with 0.5 mCi (18.5 MBq) of <sup>99m</sup>Tc-diethylenetriaminepentaacetic acid. Serial images of the chest were obtained in the posterior projection with the patient sitting erect in front of a gamma camera connected to a computer. Esophageal retention was expressed as the percentage of radioactivity in the esophagus 2, 5, 10, and 20 minutes after ingestion of the food.

#### Videofluorography and Pharyngoesophagography

Patients were asked to swallow 10-ml volumes of a thin barium sulfate suspension (Barospense, 70 percent weight per volume; Lafayette Pharmaceuticals, Lafayette, Ind.). After six swallows, the height of the barium-fluid level above the lower esophageal sphincter and the maximal width of the esophagus were measured. The luminal size of the open lower esophageal sphincter was noted. Diaphragmatic movement was observed under fluoroscopy. A video recording was made of each swallow.

#### Endoscopy and Intrasphincteric Injection

Flexible upper gastrointestinal endoscopy was performed while the patients were under conscious sedation with a combination of intra-

venous fentanyl and midazolam. The lower esophageal sphincter was visualized endoscopically by identification of the sphincteric rosette, typically seen at the squamocolumnar junction. Botulinum toxin (Oculinum, Allergan, Irvine, Calif.) was injected through a 5-mm sclerotherapy needle into the region of the lower esophageal sphincter. Aliquots of 1 ml each (20 units of botulinum toxin per milliliter of saline) were injected into quadrants, for a total of 80 units. In the placebo group, equal volumes of saline were injected. The procedure was performed on an outpatient basis in most cases, and the patients were allowed to eat later the same day.

#### Statistical Analysis

Unless otherwise specified, the results were analyzed with the Wilcoxon signed-rank test for paired nonparametric data and the Mann-Whitney two-sample test for unpaired nonparametric data. Data are expressed as means  $\pm$ SD, and all P values are two-tailed.

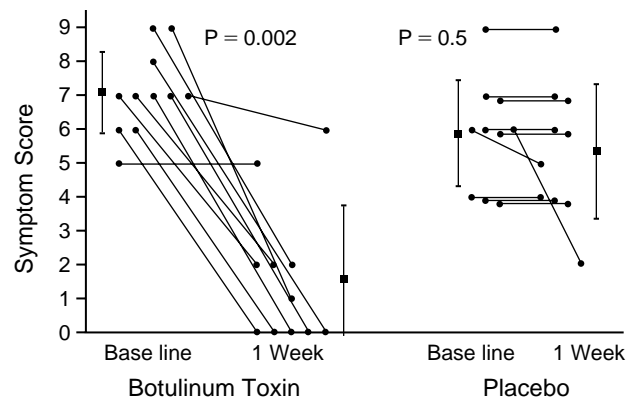
## RESULTS

A total of 21 patients were enrolled in the trial, of whom 11 initially received botulinum toxin and 10 received placebo. The two groups were similar in terms of age, sex ratio, the duration and severity of illness, and the number of previous esophageal dilations (Table 1).

#### Clinical Response to Initial Injection

One week after the initial injection, the mean symptom score in the treatment group had decreased from  $7.1 \pm 1.2$  to  $1.6 \pm 2.2$  ( $P = 0.002$ ), whereas the mean symptom score in the placebo group had decreased from  $5.9 \pm 1.6$  to  $5.4 \pm 2.0$  ( $P = 0.50$ ) (Fig. 1). The injection of botulinum toxin resulted in clinical improvement in 9 of the 11 patients; 5 patients became completely asymptomatic, but 2 did not have any improvement. One patient in the placebo group had an initial clinical response that lasted less than 10 days, after which the symptoms returned.

In the treatment group, all three components of the symptom score — dysphagia, regurgitation, and chest pain — improved. All the patients had maximally



**Figure 1. Changes in Symptom Scores One Week after Treatment with Botulinum Toxin or Placebo in Patients with Achalasia.** The mean ( $\pm$ SD) scores for each group are represented by the squares and vertical bars. A score of 3 or less indicates clinical remission.

severe dysphagia before treatment, with a mean dysphagia score of 3. One week after treatment, the score was 0.8 ( $P < 0.001$ ). Similarly, the mean regurgitation score decreased from 2.6 before treatment to 0.3 one week after treatment ( $P < 0.001$ ). Although not all patients had chest pain or discomfort initially, among those who did the mean score decreased from a pretreatment value of 1.4 to a post-treatment value of 0.4 ( $P = 0.06$ ).

#### Changes in Objective Measurements of Esophageal Function

One week after the injection, the mean decrease in the pressure of the lower esophageal sphincter was 33 percent in the treatment group, as compared with a mean increase of 12 percent in the placebo group ( $P = 0.02$ ) (Table 2). Among the nine patients who had such measurements before and one week after treatment, the mean pressure decreased from  $45 \pm 17$  to  $27 \pm 12$  mm Hg ( $P = 0.008$ ). The pressure of the lower esophageal sphincter did not change significantly in the placebo group (Fig. 2).

One week after the injection, the mean decrease in esophageal retention five minutes after the ingestion of food was 35 percent in the patients treated with botulinum toxin, as compared with a mean increase of 3 percent in the placebo group ( $P = 0.11$ ). The mean five-minute retention decreased from  $81 \pm 18$  to  $54 \pm 36$  percent ( $P = 0.02$ ) in the treatment group but did not change appreciably in the placebo group (Fig. 2).

The injection of botulinum toxin also resulted in improvement in several measurements recorded during pharyngoesophagography one week after treatment (Table 2). The mean increase in the width of the opening of the lower esophageal sphincter was 204 percent in the treatment group, as compared with a mean de-

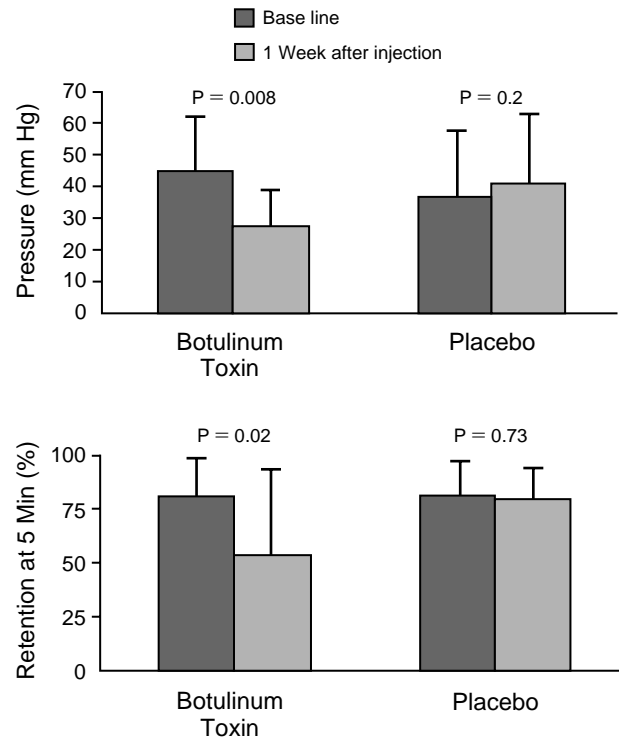


Figure 2. Mean ( $\pm$ SD) Pressure of the Lower Esophageal Sphincter (Upper Panel) and Five-Minute Esophageal Retention (Lower Panel) One Week after the Injection of Botulinum Toxin or Placebo.

crease of 14 percent in the placebo group ( $P = 0.02$ ). The mean decrease in the height of the barium column was 21 percent in the treatment group, as compared with a mean increase of 22 percent in the placebo group ( $P = 0.006$ ). The injection of botulinum toxin resulted in significant improvement in the above indexes

as compared with the pretreatment values (Table 2). In the placebo group, there were no significant differences between base-line and postinjection values.

#### Response to Botulinum Toxin in Patients Initially Receiving Placebo

All patients in the placebo group later received botulinum toxin. Their mean symptom scores decreased from  $5.9 \pm 1.6$  before treatment to  $0.7 \pm 0.8$  one week after the administration of botulinum toxin ( $P < 0.001$ ). This decrease was accompanied by significant improvement in esophageal retention, with the five-minute retention decreasing from 79 to 63 percent ( $P = 0.01$ ).

#### Subsequent Clinical Course

As mentioned above, 19 of the 21 patients had improvement during

Table 2. Esophageal Function at Base Line and One Week after Treatment with Botulinum Toxin or Placebo.

MEASURE OF ESOPHAGEAL FUNCTION	NO. OF PATIENTS*	AT	AFTER	P VALUE†	% CHANGE‡	P VALUE§
		BASE LINE	INJECTION			
<i>mean (<math>\pm</math>SD)</i>						
<b>Pressure (mm Hg)</b>						
Placebo	7	37 ± 19	41 ± 22	0.2	+12	0.2
Botulinum toxin	9	45 ± 17	27 ± 12	0.008	-33	
<b>Opening width (mm)</b>						
Placebo	10	4.4 ± 2.4	3.2 ± 2.1	0.13	-14	0.02
Botulinum toxin	9	3.2 ± 1.0	7.7 ± 5.8	0.05	+204	
<b>Diameter (cm)</b>						
Placebo	10	5.0 ± 1.9	4.9 ± 1.9	0.31	-4	0.34
Botulinum toxin	10	4.7 ± 1.4	3.9 ± 1.5	0.01	-12	
<b>Barium height (cm)</b>						
Placebo	10	16 ± 7	19 ± 5	0.15	+22	0.006
Botulinum toxin	10	15 ± 5	11 ± 5	0.03	-21	
<b>Retention at 5 min (%)</b>						
Placebo	9	82 ± 15	80 ± 11	0.73	+3	0.11
Botulinum toxin	10	81 ± 18	54 ± 36	0.02	-35	

\*The number of patients for whom paired comparisons were available.

†P values are for the comparison with the corresponding base-line values.

‡The mean change from the base-line value to the postinjection value in each patient (i.e., not derived from the base-line and postinjection results shown).

§P values are for the comparison between groups.

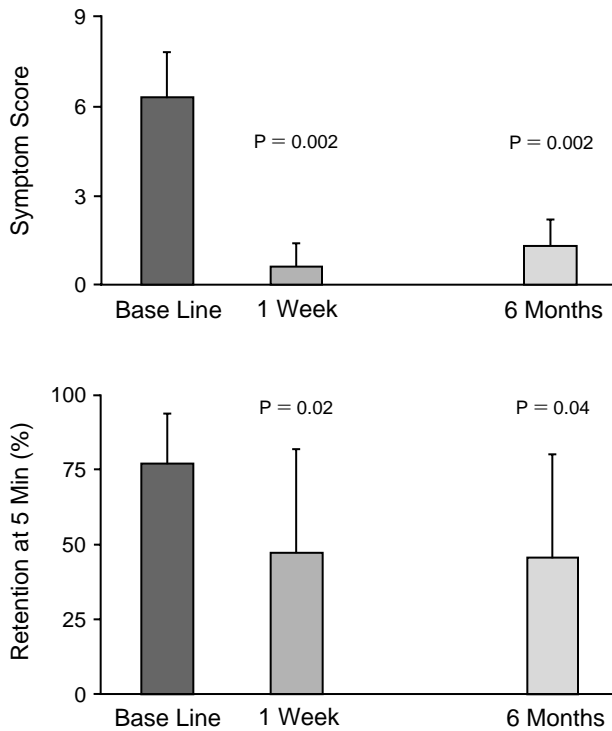


Figure 3. Long-Term Results in 10 Patients Treated with Botulinum Toxin.

The upper panel shows the mean ( $\pm$ SD) symptom scores at base line, one week after the injection of botulinum toxin, and six months after the injection. A score of 3 or less indicates clinical remission. The bottom panel shows the mean values for esophageal retention. The P values are for the comparisons with base-line values.

the first week after the injection of botulinum toxin. During the first two months after the injection, 8 of these 19 patients reported worsening of their symptoms, bringing to 10 the total number of patients who had no response or a relapse soon after treatment. Nine of these 10 patients received a second injection of botulinum toxin, and 3 of the 9 had symptomatic remissions. By six months, 14 patients were still in remission, 11 after receiving a single injection.

#### Long-Term Follow-up

The patients were followed for a median of 9 months (range, 7 to 16), and follow-up data at 6 months were available for 10 of the 14 patients in remission. (The other four patients, though still in remission, had not yet returned for follow-up studies as of this writing.)

The mean symptom score at six months among these 10 patients was 1.3 (Fig. 3), which is markedly lower than their base-line score of 6.3 ( $P < 0.001$ ). The improvement in esophageal retention was sustained during this period. The mean value for five-minute retention was 77 percent at base line, 47 percent one week after the administration of botulinum toxin ( $P = 0.02$ ), and 46 percent after an average of six months ( $P = 0.04$ ) (Fig. 3). Clinical improvement was

accompanied by an average weight gain of 5.5 kg among the patients who had reported a weight loss before treatment.

Of the seven patients who had no response or a relapse soon after treatment with botulinum toxin, three underwent pneumatic dilation, with satisfactory clinical improvement. Three patients decided against further treatment, and one patient was lost to follow-up.

#### Complications

There were no serious adverse effects of any of the injections. Five patients in the treatment group and three in the placebo group had transient mild chest pain after the injection. One patient in the treatment group had mild heartburn that was easily controlled by antacid therapy. Another patient reported a transient facial rash that lasted less than 24 hours. No impairment of diaphragmatic movement was seen on fluoroscopy after the injection.

#### DISCUSSION

Local injection of botulinum toxin is currently being used in the treatment of several disorders characterized by skeletal-muscle spasm (such as strabismus and a variety of dystonias), with good results and few adverse effects.<sup>8</sup> We previously demonstrated that botulinum toxin significantly reduces the resting tone of the lower esophageal sphincter in piglets.<sup>9</sup> In this study we found that local injection of botulinum toxin is effective in patients with achalasia, a disorder in which the lower esophageal sphincter fails to relax. Ninety percent of the patients had improvement initially, and two thirds continued to be in remission six months after treatment. These results compare favorably with the approximately 65 to 90 percent rate of improvement after one or more sessions of pneumatic dilation,<sup>7,10-12</sup> as well as with the 64 to 95 percent rate of improvement after myotomy.<sup>10,11</sup> It should be noted, however, that the duration of follow-up in our study was not sufficient for us to draw any conclusion about the long-term benefit of botulinum toxin in patients with achalasia.

The symptomatic improvement in our patients was accompanied by significant improvement in all objective tests of esophageal function. The pressure of the lower esophageal sphincter fell by about 40 percent, the esophageal diameter decreased by 17 percent, and five-minute esophageal retention on scintigraphy improved by 33 percent. These changes are similar to those usually reported after pneumatic dilation.<sup>7,13-18</sup> The discrepancy between clinical and objective measures of improvement in some of our patients is also similar to that noted in patients treated with pneumatic dilation.<sup>7,15,16</sup> Our results therefore support the previously held notion that a return to normal esophageal emptying is not necessary for successful treatment of symptoms of achalasia.<sup>12,16</sup>

The clinical response to botulinum toxin in our patients is expected to wane with time, as it does in patients with skeletal-muscle disorders.<sup>8</sup> Symptoms seem

to recur about a year after the initial injection. Preliminary data suggest that at least some patients in whom symptoms recur have equally good responses to the initial and to a repeated injection.

Pneumatic dilation is currently considered the treatment of choice for achalasia. However, it causes esophageal perforation in 1 to 13 percent of patients.<sup>19</sup> An important advantage of therapy with botulinum toxin is its relative simplicity and safety. Unlike pneumatic dilation, this approach contributes little or no additional risk to that associated with upper gastrointestinal endoscopy.

Botulinum toxin has been used in thousands of patients with skeletal-muscle conditions, with few side effects.<sup>8</sup> Although long-term data on its use in patients with smooth-muscle disorders are lacking, our findings support the notion that treatment is relatively safe. The role of intrasphincteric botulinum toxin in the treatment of achalasia requires further definition, but our results suggest that it will prove to be an effective mode of therapy for patients with this disorder.

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**CORRECTION**

**Intrasphincteric Botulinum Toxin for the Treatment of Achalasia**

Intrasphincteric Botulinum Toxin for the Treatment of Achalasia . On page 776, in Table 2, the first P value in the last column should have been 0.02, not 0.2, as printed.