

## A COMPARISON OF BOTULINUM TOXIN AND SALINE FOR THE TREATMENT OF CHRONIC ANAL FISSURE

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**ABSTRACT**

**Background** Chronic anal fissure is a tear in the lower half of the anal canal that is maintained by contraction of the internal anal sphincter. Sphincterotomy, the most widely used treatment, is a surgical procedure that permanently weakens the internal sphincter and may lead to anal deformity and incontinence.

**Methods** We conducted a double-blind, placebo-controlled study of botulinum toxin for the treatment of chronic anal fissure in 30 consecutive symptomatic adults. All the patients received two injections (total volume, 0.4 ml) into the internal anal sphincter; the treated group (15 patients) received 20 U of botulinum toxin A, and the control group (15 patients) received saline. Success was defined as healing of the fissure (formation of a scar), and symptomatic improvement was defined as the presence of a persistent fissure without symptoms.

**Results** After two months, 11 patients in the treated group and 2 in the control group had healed fissures ( $P=0.003$ ); 13 in the treated group and 4 in the control group had symptomatic relief ( $P=0.003$ ). The maximal voluntary pressures were similar to those at base line in both groups, and the resting anal pressure was reduced by 25 percent in the treated group but not in the control group.

Three patients in the control group later underwent sphincterotomy, and 10 received botulinum-toxin injections (20 U). Of the latter, seven had healed fissures after two months; the other three left the study and underwent surgery. Four patients in the treated group were later re-treated (with 25 U of botulinum toxin); all had healed fissures after two months. One patient in the control group had temporary flatus incontinence after treatment with botulinum toxin. No relapses occurred during an average of 16 months of follow-up.

**Conclusions** Local infiltration of botulinum toxin into the internal anal sphincter is an effective treatment for chronic anal fissure. (N Engl J Med 1998; 338:217-20.)

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**A**NAL fissure, first recognized as a clinical entity in 1934,<sup>1</sup> is a split extending from the anal verge toward the dentate line. Ninety percent of primary fissures are posterior; the pathogenesis is thought to be related to severe constipation or to straining at stool, since the hard fecal bolus may crack the anal canal.<sup>2</sup> A

chronic idiopathic fissure can be clearly recognized as a well-circumscribed ulcer,<sup>3</sup> with symptoms persistently present for more than two months. A characteristic skin tag may develop distally, while proximally a hypertrophy of anal papilla may be observed.<sup>2</sup> The fissure is maintained by contraction of the internal anal sphincter.

Chronic anal fissure is believed to be common and underdiagnosed. An epidemiologic survey conducted in 1994 among proctologic clinics in Italy showed that 10 percent of 15,161 consecutive outpatients were affected by anal fissure.<sup>4</sup> Surgical sphincterotomy is currently performed to provide symptomatic relief and healing. However, the procedure permanently weakens the internal sphincter and may be associated with such permanent complications as anal deformity and incontinence. Two therapeutic approaches — chemical denervation with botulinum toxin and topical application of nitroglycerin ointments — have been proposed as noninvasive alternatives.<sup>5,6</sup> In an open-label study, we observed that chronic anal fissure may be effectively treated with local infiltration of botulinum toxin.<sup>6</sup> Therefore, we conducted a double-blind, placebo-controlled study of botulinum toxin for treatment of chronic anal fissure.

**METHODS****Study Population**

Consecutive symptomatic adults with chronic idiopathic anal fissure were enrolled. Patients with acute fissures, those with anal fissures of various causes (i.e., hemorrhoids, fistula in ano, inflammatory bowel diseases), and those who had previously undergone anal surgical procedures were excluded. The study was approved by the ethics committee of the Catholic University of Rome; all the patients provided written informed consent.

**Study Design**

This was a randomized, double-blind, placebo-controlled study. All the patients underwent a pretreatment evaluation consisting of a clinical assessment, anoscopy, and anorectal manometry. Eligible patients were randomly assigned to one of the two

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study groups according to a computer-generated list. The treating physician did not know the randomization code. In each patient, anal manometry was performed at rest and after maximal voluntary contraction, and the results were compared with the normal range for our laboratory.<sup>7</sup> Each of the 30 participants received 0.4 ml of solution divided into two injections of equal volume. The internal anal sphincter was easily palpated and injected with a 27-gauge needle; the solution was placed close to the fissure on each side. No sedation or local anesthesia was used. Patients in the control group received just saline solution; patients in the treated group received 20 U of botulinum toxin A (Botox, Allergan, Irvine, Calif.; 50 U per milliliter).

#### Follow-up

The patients were advised to eat food with a high fiber content and received a prescription for laxatives. No patient was treated with topical anesthetics before or during the study. All the patients were evaluated by clinical examination, anoscopy, and anal manometry, regardless of their treatment and outcome, one and two months after the injections. If the fissure persisted at the two-month evaluation, the examiner (who remained blinded to the patient's treatment assignment) could decide to re-treat a patient ("rescue" treatment). The re-treated patients always received botulinum toxin; patients in the control group received 20 U, and patients in the treated group received 25 U. Re-treated patients were then evaluated with the same protocol one month and two months after re-treatment. At each visit, the patients could choose to be treated with anal sphincterotomy or to drop out of the study. All the patients were followed clinically until September 1996.

#### Statistical Analysis

The outcome of each group was evaluated clinically (by checking for a healing scar or fissure) and by comparing the strength of the internal and external anal sphincters, as measured by anal manometry. Success was defined as healing of the fissure, and symptomatic improvement was defined as the persistence of an anal fissure without symptoms.

The time course of pressure variations was analyzed with Student's *t*-test. The clinical outcomes of the two groups were compared by means of Fisher's exact test.<sup>8</sup> All *P* values were two-tailed. A *P* value of less than 0.05 was considered to indicate statistical significance.

### RESULTS

From June 1994 to December 1995, 30 consecutive outpatients were enrolled; 15 received botulinum toxin, and 15 received placebo. All the patients reported severe typical pain after defecating, and each had a posterior anal fissure with a large sentinel tag of skin and the exposure of fibers of the internal anal sphincter. The two groups were similar with regard to age, sex, the duration of symptoms, and the resting anal pressure at base line (Table 1). The maximal voluntary pressure at base line was lower in the treated group ( $P < 0.001$ ).

At one month, two patients in the control group and eight in the treated group had healed fissures ( $P = 0.05$ ). Symptomatic relief was reported by 4 patients in the control group and 13 in the treated group ( $P = 0.003$ ).

At two months, 2 patients in the control group and 11 in the treated group had healed fissures ( $P = 0.003$ ), and 4 patients in the control group and 13 in the treated group had symptomatic relief

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE 30 PATIENTS WITH CHRONIC ANAL FISSURE.\***

CHARACTERISTIC	CONTROL GROUP (N=15)	TREATED GROUP (N=15)
Age (yr)†	49±10	38±14
Ratio of men to women	13:2	7:8
Post-defecatory pain (no. of patients)	15	15
Nocturnal pain (no. of patients)	2	2
Duration of symptoms (mo)	17±5	18±8
Resting anal pressure (mm Hg)	102±6	109±8
Maximal voluntary pressure (mm Hg)‡	102±13	71±8

\*Plus-minus values are means ±SD.

† $P = 0.02$  for the comparison between the two groups (by Student's *t*-test).

‡ $P < 0.001$  for the comparison between the two groups (by Student's *t*-test).

( $P = 0.003$ ). During the first two months, three patients in the control group dropped out of the study to undergo sphincterotomy.

#### Control Group

At one month, post-defecatory pain was no longer present in three patients in the control group (including the two with healing scars) and was reduced in one. Nocturnal pain was no longer present in one of the two patients who had previously reported it. As compared with base-line values, the resting anal pressure and the maximal voluntary pressure were unchanged (Table 2).

At two months, an additional patient reported a reduction in post-defecatory pain. Another no longer had nocturnal pain but still had pain after defecation. The resting anal pressure and the maximal voluntary pressure were similar to base-line and one-month values. Of the 13 patients with persistent fissures, 3 refused rescue treatment and underwent sphincterotomy. The remaining 10, all of whom reported having pain after defecation, received 20 U of botulinum toxin each.

At three months (one month after rescue treatment), four patients had healing scars. Two of the six patients with persistent fissures no longer had pain after defecation. The other four had reduced pain; three dropped out of the study and underwent sphincterotomy. The mean maximal voluntary pressures in these 10 patients were similar before and after the rescue treatment. The mean ( $\pm$ SD) resting anal pressure at three months was  $85 \pm 7$  mm Hg, 20.7 percent lower than at two months in these patients.

At four months (two months after the rescue

**TABLE 2.** ANAL PRESSURES IN PATIENTS IN THE CONTROL GROUP.\*

TIME POINT	RESTING PRESSURE	MAXIMAL VOLUNTARY PRESSURE
	mm Hg	
Base line	102±6	102±13
1 mo	98±7	102±12
2 mo	97±7	102±12
3 mo†	85±7‡	92±12
4 mo§	67±7¶	93±23

\*Plus-minus values are means ±SD.

†Values are for 10 patients who received rescue treatment (20 U of botulinum toxin).

‡P=0.05 for the comparison with values at two months (by paired t-test).

§Values are for three patients who received rescue treatment (20 U of botulinum toxin).

¶P=0.03 for the comparison with values at two months (by paired t-test).

treatment), the remaining three patients had healing scars; none had pain after defecation. The mean resting anal pressure in these three patients was 67±7 mm Hg — 37.5 percent lower than their pretreatment values and 43.6 percent lower than their values at two months, but similar to their values at one month. The maximal voluntary pressure was unchanged in these patients.

#### Treated Group

At one month, eight patients in the treated group had healing scars with symptomatic relief. Of the seven patients with persistent fissures, post-defecatory pain was no longer present in one and was reduced in four. Nocturnal pain was no longer present in the two patients who had previously reported it. As compared with base-line values, the resting anal pressure was reduced by 27 percent; the maximal voluntary pressure was not significantly changed (Table 3).

At two months, 11 patients had healing scars. One patient who had had a healing scar at one month now had a fissure. Post-defecatory pain was no longer present in 11 patients and was reduced in 2. Nocturnal pain was not reported by any patient in the treated group. The resting anal pressure was reduced by 25 percent as compared with base-line values and was similar to one-month values. The maximal voluntary pressure was similar to base-line and one-month values.

The four patients who still had fissures were re-treated with 25 U of botulinum toxin. At three months (one month after the second injection), two

**TABLE 3.** ANAL PRESSURES IN PATIENTS IN THE TREATED GROUP.\*

TIME POINT	RESTING PRESSURE	MAXIMAL VOLUNTARY PRESSURE
	mm Hg	
Base line	109±8	71±8
1 mo	79±7†	60±7
2 mo	81±8‡	64±7
3 mo§	83±20	44±9
4 mo¶	75±25	40±10

\*Plus-minus values are means ±SD.

†P=0.01 for the comparison with base-line values.

‡P=0.02 for the comparison with base-line values.

§Values are for four patients who received rescue treatment (25 U of botulinum toxin).

¶Values are for two patients who received rescue treatment (25 U of botulinum toxin).

of these four patients had healing scars and no pain after defecation. The resting anal pressure and the maximal voluntary pressure in the four patients who received the rescue treatment were similar to the values at base line, one month, and two months.

At four months (two months after the rescue treatment), the remaining two patients also had healing scars, and their post-defecatory pain had resolved. The resting anal pressure and the maximal voluntary pressure in the re-treated patients remained similar to the values at base line, one month, and two months.

#### Follow-up

One patient in the control group had flatus incontinence one month after the rescue treatment; this resolved after approximately one week. No other complications or side effects were reported.

Seven patients with healed fissures in the control group who had received rescue treatment were followed for an average of 18±5 months (range, 10 to 24). There were no relapses. All the patients in the treated group were reevaluated periodically for an average of 16±6 months (range, 7 to 26). There were no relapses.

#### DISCUSSION

Anal fissure is currently treated with lateral internal sphincterotomy. This is effective in about 90 percent of cases and must be performed under general or local anesthesia.<sup>9</sup> Despite concern about a higher rate of recurrence, good results are reported for outpatient sphincterotomy performed under local anesthesia.<sup>10</sup>

Surgery for anal fissure is associated with a number of complications, most of which are minimized by the judicious use of surgical techniques.<sup>11</sup> The most common is incontinence, which in 8 to 30 percent of patients is permanent.<sup>12,13</sup> Recently, chronic fissures have been successfully treated with topical nitroglycerin ointment.<sup>5</sup> Two to six weeks of treatment are required to heal 47 to 85 percent of patients.<sup>14,15</sup> A significant reduction of spontaneous and post-defecatory pain was observed five minutes after an application. This treatment is thought to reduce anal pressure and improve local blood flow.<sup>16</sup> The most common side effects are transient headache, occurring in the majority of patients, and anal burning; incontinence has not been reported.<sup>16</sup> Tachyphylaxis after repeated applications has been observed.

Our study demonstrates that botulinum toxin can be used to treat chronic fissures. Fissures healed in all the patients in the treated group after one or two successive injections of botulinum toxin, as compared with 13 percent of the patients who received one injection of saline. The percentage of patients with healing was higher than in our previous open-label study,<sup>6</sup> which showed that 60 percent of patients had healing after a single treatment with 15 U of botulinum toxin. The use of higher doses and the availability of a rescue treatment account for the higher success rate in this study. As in our previous study, manometry confirmed that the injected internal anal sphincter was weakened and that no significant diffusion of botulinum toxin to the external sphincter took place. By contrast, botulinum toxin injected into the external anal sphincter, which is also effective for treating fissures, has been shown to diffuse to the internal sphincter.<sup>17</sup>

The base-line maximal voluntary pressure was higher in the control group than in the treated group. This difference may have reflected differences in the severity of pain and a prevalence of men (men have higher anal pressures)<sup>18</sup> in the control group. This base-line imbalance did not affect the results, since the maximal voluntary pressure remained relatively unchanged in each group. Injections were performed in the internal anal sphincter, which controls the resting anal pressure, not the maximal voluntary pressure.

The injections were easily performed, were painless, and did not cause any local or systemic complications. The muscle weakening produced by botulinum toxin was transient.

Chronic anal fissures may be maintained by local

ischemia.<sup>19</sup> Botulinum toxin may induce healing by simply increasing local blood flow or by more complex mechanisms.<sup>20,21</sup>

In summary, we found local infiltration of botulinum toxin into the internal anal sphincter to be a promising approach to the treatment of anal fissure, particularly if patients are at risk for incontinence. It is less expensive and easier to perform than surgical treatments and does not require anesthesia. A direct comparison of botulinum toxin and topical nitroglycerin ointment should be conducted.

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