

Effectiveness of higher doses of botulinum toxin to induce healing in patients with chronic anal fissures

Giuseppe Brisinda, MD, Giorgio Maria, MD, Gabriele Sganga, MD, Anna Rita Bentivoglio, MD, PhD, Alberto Albanese, MD, and Marco Castagneto, MD, FACS, Rome, Italy

Background. Botulinum toxin induces healing in patients with idiopathic anal fissures.

Methods. One hundred-fifty patients with posterior anal fissures were treated with botulinum toxin injected in the internal anal sphincter on each side of the anterior midline. Subjects were randomized into 2 treatment groups based on the number of units of botulinum toxin injected. Patients in group I were treated with 20 units of botulinum toxin and, if the fissure persisted, were retreated with 30 units. Patients in group II were treated with 30 units and retreated with 50 units, if the fissure persisted.

Results. The 2 groups were comparable in age, gender distribution, duration of symptoms, resting pressure, and maximum voluntary pressure at anorectal manometry. One month after the injection, examinations revealed complete healing in 55 patients (73%) from group I and 65 patients (87%) from group II ($P = .04$). Five patients from group II reported a mild incontinence of flatus that lasted 2 weeks after the treatment and disappeared spontaneously. The values of the resting anal pressure ($P = .3$) and the maximum voluntary pressure ($P = .2$) did not differ between the 2 groups. At 2 months' evaluation, a healing scar was found in 67 patients (89%) from group I and 72 patients (96%) from group II. A relapse of the fissure was observed in 6 patients (8%) from group I who had a healing scar at 1 month, and 2 other patients never healed. A persistent fissure was present in 3 patients from group II who had no other symptoms.

Conclusions. Botulinum toxin injected into the internal anal sphincter is effective in managing anal fissures and avoiding permanent complications. All patients were treated with the active drug and healed after 1 or 2 successive treatments. The results also confirm that higher doses account for a higher success rate, with little increase in complications or side effects, which is probably related to the diffusion of the toxin to the external sphincter. (*Surgery* 2002;131:179-84.)

From the Departments of Surgery and Neurology, Catholic University Hospital Agostino Gemelli, Rome, Italy

ANAL FISSURE is a distressing condition. Surgical sphincterotomy, which is performed widely to provide symptomatic relief and healing, is highly effective despite complications.¹⁻⁵ Most episodes of incontinence are minor, but in a small subgroup of patients, incontinence seems to be permanent,¹ and it is directly related to the length of the sphincterotomy.²

Alternative approaches, without any risk of permanent internal anal sphincter injury, have been proposed to treat this condition.⁶⁻¹³ Chemical denervation with botulinum toxin is a versatile tool for targeting the weakening of smooth muscle in the

gastrointestinal tract. The advantage of injections of botulinum toxin into the internal anal sphincter in patients who have chronic fissures is that the ensuing reduction in resting tone for 4 or more months should allow the fissures to heal; this avoids the need for operations.

Previous studies have shown a healing rate ranging from 60% to 76% after a single infiltration of 15 or 20 units, respectively, of botulinum toxin in the internal anal sphincter.^{9,13} Furthermore, 20 units of dosage is more effective in producing long-term healing without increasing complications.¹⁰ However, in all these studies, botulinum toxin was injected close to the fissure in the posterior aspect of the internal anal sphincter. At a dose of 20 units, choosing a different injection site improves the clinical outcome and induces a greater decrease in resting anal pressure. Recent work showed that in patients with a posterior chronic anal fissure, injection on either site of the anterior portion of the internal sphincter was

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Reprint requests: Dr Giorgio Maria, Istituto di Clinica Chirurgica, Policlinico Universitario Agostino Gemelli, Largo Agostino Gemelli, 8, I-00168 Roma, Italy.

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more effective in inducing healing than injection in the posterior site.¹² Resting anal pressure was significantly lowered compared with pretreatment values in both groups of patients, but the pressures were significantly lower in patients who received injections in the anterior site when compared with those who received posterior injections. Moreover, there was a healing rate of 96% in 25 patients treated with 20 units of botulinum toxin injected in the anterior site of the internal anal sphincter.¹¹

Despite the reported success of botulinum toxin, its use has not been widely adopted, possibly because the optimal dose and method of administration require validation. In view of these findings, a prospective, randomized study of patients with chronic anal fissures was initiated to provide more evidence regarding the choice of dosage regimens of botulinum toxin (20 or 30 units) injected in the anterior site of the internal anal sphincter to induce healing in patients with idiopathic posterior chronic fissures. The complications and the long-term results in both groups of patients were also evaluated.

PATIENTS AND METHODS

From January to June 1998, patients with consecutive symptoms, who were affected by chronic anal fissures, were scheduled for treatment at the Department of Surgery of the Hospital Agostino Gemelli; all were eligible for the inclusion in the study. The diagnosis of a chronic anal fissure was based on the following clinical criteria: (1) evidence of a posterior circumscribed ulcer with a large sentinel tag of skin, (2) induration at the edges and exposure of the horizontal fibers of the internal anal sphincter, and (3) symptoms (post-defecatory, as well as nocturnal pain and bleeding, or both) persistently present for over 2 months. Exclusion criteria were an acute anal fissure associated with defined pathologies (eg, inflammatory bowel diseases, human immunodeficiency virus infections, hemorrhoids, fistulas-in-ano, anal abscesses, and anal or perianal cancer) and previous surgical procedures on the anal canal. The study protocol was reviewed and approved by the Institutional Committee of the Catholic University of Rome. Each patient provided a written informed consent to the study.

Study design. This was a randomized, double-blind study. Eligible patients affected by posterior anal fissures were randomly assigned to 1 of the 2 treatment groups according to a computer-generated list; both received an injection in the internal anal sphincter on each side of the anterior midline. One hundred-fifty patients with anal fissures were

enrolled. All patients reported severe pain, typical after defecating, and each had a posterior anal fissure with a large sentinel tag of skin and exposure of fibers of the internal anal sphincter. Subjects were randomized into 2 treatment groups based on the number of botulinum toxin units injected. Patients in group I were treated with 20 units (0.4 mL) of botulinum toxin and, if the fissure persisted, were retreated with 30 units (0.6 mL). Patients in group II were treated with 30 units (0.6 mL) and retreated with 50 units (1 mL) if necessary.

All patients underwent a pretreatment evaluation, including a clinical examination and an anorectal manometry. Anorectal manometry was performed at rest and after maximum voluntary contraction and was compared with the normal range from similar reports.⁹⁻¹¹ The resting anal tone and maximal squeeze pressure (eg, the maximal voluntary increase above resting tone) were measured according to a stationary pull-through technique.¹⁴ After a baseline evaluation, active toxin was administered to all patients. One and 2 months after the treatment, patients underwent the same evaluation as performed at baseline. At 2 months' follow-up, 1 examiner, blinded on the injected dosage regimens, evaluated the outcome. The outcome of each group was evaluated clinically and by comparing the strength of the internal and external anal sphincters as measured by anorectal manometry. The study end point was the evaluation of complete healing after botulinum toxin injections. Healing of the fissure was considered a success, whereas persistence of the anal fissure was considered a failure even with a symptomatic improvement.

Operative technique. Vials containing 100 units of lyophilized botulinum toxin A (Botox) were stored at a temperature of -20°C and diluted in saline solution to 50 U/mL before the injections. The lower rounded edge of the internal anal sphincter, about 1 to 1.5 cm distal to the dentate line, was felt on physical examination. The groove between it and the external sphincter, the so-called intersphincteric groove, was easily palpated in all patients, and the internal anal sphincter was injected with a 27-G needle, with the patient lying on his or her left side. The injection volume was 0.4 mL in patients from group I and 0.6 mL in patients from group II. Each patient received 2 injections. In group 1, each patient received 0.2 mL of solution containing 10 units of botulinum toxin, which made a total of 20 units. In group 2, each patient received 0.3 mL of solution containing 15 units of botulinum toxin, which made a total of 30 units. The same procedure was used in cases of retreat-

ment. Neither sedation nor local anesthesia were used during the procedure.

Clinical care, follow-up, and outcome measures. No patient was treated with topical anesthetic agents or laxative therapy before or during the study. At each check-up, the patients were asked whether, despite any local pain, they wanted to stay in the study. If not, they were offered lateral internal sphincterotomy. If the fissure persisted at 2 months' evaluation, the examiner could decide to retreat the patient. The patients from group I who were retreated received 30 units of botulinum toxin in the same site as the first injection. The patients from group II who were retreated received 50 units of botulinum toxin. Patients who were retreated were then evaluated with the same protocol 1 month and 2 months after the retreatment. The patients were followed up clinically until June 2000.

Statistical analysis. All statistical elaborations were obtained with Statistica for Windows version 4.5 (Statsoft, Tulsa, Okla). The results were expressed as mean \pm SD; differences between manometric data were compared by the Student *t* test for paired samples, whereas differences between percentages were analyzed by the chi-square test.¹⁵ Probability values of less than .05 were considered significant.

RESULTS

The 2 groups were comparable in terms of age, gender distribution, duration of symptoms, resting pressure, and maximum voluntary pressure at anorectal manometry. The baseline characteristics are reported in Table I. The internal anal sphincter was easily palpated in all patients. No complications during the procedure were observed in any patient.

One-month evaluation. One month after the injection, examination revealed a healing scar in 55 patients (73%) from group I. Compared with pretreatment records, a symptomatic improvement was noted in another 15 patients (20%). The other 5 patients (7%) had persistent fissures. Nocturnal pain disappeared in all patients who had previously reported it. Post-defecatory bleeding disappeared in 12 patients. At the same time, in patients from group I, the mean resting pressure (Table II) was 31% lower than the baseline value ($P < .001$); the maximum voluntary squeeze pressure did not change ($P = .6$). Examinations 1 month after the injection revealed a healing scar in 65 patients (87%) from group II. Symptomatic improvement was noted in 10 patients (13%). Post-defecatory and nocturnal pain disappeared in all the patients who had previously reported it. Post-defecatory

bleeding disappeared in 20 patients. Five patients had mild incontinence of flatus ($P = .02$ vs group I) that lasted 2 weeks after treatment but disappeared spontaneously. Mean resting pressure (Table II) was 32% lower than the baseline ($P < .001$), and the maximum voluntary squeeze pressure was 15% lower than the baseline ($P = .04$).

Examinations revealed complete healing in 55 patients from group I and 65 patients from group II ($P = .04$). Symptomatic improvement was noted in 15 patients from group I and 10 patients from group II ($P = .2$). Persistence of a symptomatic fissure occurred in only 5 patients from group I ($P = .02$ vs group II). Resting anal pressure values ($P = .3$) and maximum voluntary pressure values ($P = .2$) did not differ between the groups.

Two-month evaluation. In group I, 67 patients (89%) had a healing scar ($P = .01$ vs 1-month evaluation). A relapse of the fissure was observed in 6 patients (8%) who had a healing scar at 1 month; 2 other patients (3%) never healed. The mean resting anal pressure was the same compared with the 1-month value ($P = .6$) and was 30% lower than the baseline value ($P < .001$). The maximum voluntary squeeze did not differ significantly from the baseline ($P = .9$) and 1-month ($P = .5$) values.

In group II, 72 patients (96%) had a healing scar ($P = .04$ vs 1-month evaluation). A persistent fissure was present in 3 patients who had no other symptoms. Compared with pretreatment, post-defecatory and nocturnal pain had disappeared in all patients. Resting pressure was 35% lower than the baseline values ($P < .001$) and did not vary from 1-month values ($P = .4$). Maximum voluntary pressure did not differ from the baseline or 1-month values (each $P = .3$). Resting anal pressure and maximum voluntary pressure were not different ($P = .6$) when compared with those from group I.

Follow-up and long-term outcomes. The 8 patients from group I with persistent fissures underwent retreatment at 2 months. All patients received 30 units of botulinum toxin (0.6 mL) in the same site of the first injection. Examinations at 1 month after retreatment revealed a healing scar in 5 patients. Two months after retreatment, complete healing was observed in all 8. Patients with healed scars were followed up for an average of 21 ± 5 months. During this time, no relapse occurred and no complications or side effects were reported.

At 2 months, 3 patients in group II were retreated with 50 units (1 mL) in the same site of the first treatment. One month later, a healing scar was present in all 3 patients. Follow-up averaged 23 ± 4 months; during this time no relapse of anal fissure, complications, or side effects occurred.

Table I. Baseline characteristics of 150 patients with chronic anal fissure

<i>Characteristics</i>	<i>Group I (75 patients)</i>	<i>Group II (75 patients)</i>	<i>P value</i>
Age (y)	43 ± 15	45 ± 14	.4
Ratio of men to women	42:33	38:37	.5
Duration of symptoms (mo)	12 ± 12	13 ± 12	.5
Symptoms (number of patients)			
Post-defecatory pain	75	75	
Nocturnal pain	12	20	
Post-defecatory bleeding	21	20	
Resting pressure (mm Hg)	93 ± 21	99 ± 21	.09
Maximum voluntary pressure (mm Hg)	86 ± 37	90 ± 47	.5

Table II. Anal pressures before and after treatment in both groups of patients

<i>Time</i>	<i>Group I</i>		<i>Group II</i>	
	<i>Resting pressure</i>	<i>Maximum voluntary pressure</i>	<i>Resting pressure</i>	<i>Maximum voluntary pressure</i>
Baseline	93 ± 21	86 ± 37	99 ± 21	90 ± 47
1 mo	65 ± 16*†	83 ± 33*	67 ± 17*†	77 ± 35*‡
2 mo	65 ± 15*†	86 ± 32*	65 ± 18*†	83 ± 40*

Values are means ± SD. Data are expressed in mm Hg. All patients were included in all evaluations.

*Resting anal pressure and maximum voluntary pressure did not differ between groups.

† $P < .001$ versus baseline value (by the Student *t* test).

‡ $P = .04$ versus baseline value (by the Student *t* test).

DISCUSSION

Botulinum toxin can be used to treat anal fissures.^{9-13,16-23} Our results confirmed that botulinum toxin injected into the internal sphincter on each side of the anterior midline is effective in treating anal fissures and avoiding permanent complications. In the current study, all patients were treated with the active drug and healed after 1 or 2 successive treatments.

In a double-blind study, a success rate of 76% was achieved after a single treatment of 20 units.⁹ A prospective comparison between 2 dose regimens (15 and 20 units) showed negligible side effects and no complications; symptomatic improvement was achieved in both groups of patients, but the healing rate was higher in the group that received 20 units.¹⁰ We have also demonstrated that fissure healing is induced more effectively by botulinum toxin treatment than glyceryl trinitrate and that hypertonia of the internal anal sphincter is also alleviated more effectively.¹¹ Compared with the baseline values, resting pressure was reduced by 26% in toxin-treated patients and by 17% in nitrate-treated patients 1 month after treatment. Two months after treatment, resting anal pressure was reduced by 28% in the botulinum toxin group and 14% in the glyceryl trinitrate group.¹¹ Recently, it has also been noted that topical isosorbide dinitrate potentiates the effect of botulinum toxin in patients with refractory chronic fissures.²⁴

In our current study, the healing rate was higher than in previous studies (Table III). However, in

these studies, botulinum toxin was injected close to the fissure in the posterior aspect of the internal anal sphincter.^{9,10} We have shown that, at a fixed dose of 20 units, choosing a different injection site could improve the clinical outcome and induce a greater decrease in resting anal pressure.¹² Choosing an injection site different from the site of the fissure was based on the concept that fibrosis of the internal sphincter is more prominent in the zone of the anal fissure than in other sites in the smooth muscle.²⁵ Furthermore, the fibrous tissue in the lateral site of the internal anal sphincter in patients with chronic anal fissures was greater than in healthy subjects.²⁵ The fibrosis may reduce compliance of the internal sphincter and block the action of botulinum toxin. In patients with posterior chronic anal fissures, anterior injection was more effective in inducing healing than posterior injection. Anorectal manometry showed that resting anal pressure was significantly lower compared with pretreatment values in both groups. However, resting pressure was significantly lower in patients who received injections in the anterior site compared with patients who received posterior injections.¹² A healing rate of 96% was found in 25 patients treated with 20 units of botulinum toxin injected in the anterior site of the internal anal sphincter.¹¹

The therapeutic efficacy of different doses of botulinum toxin in chronic fissures has been reported recently. The healing rate does not differ significantly when the total dose and the number of

Table III. Comparison of published results on the treatment of patients with chronic anal fissures with botulinum toxin

Author	Patients Nr	Dose of toxin (U)	Healing rate at 6 to 8 weeks (%)	Temporary incontinence (%)	Recurrence (%)	Complications (%)
Gui et al ¹⁶	10	15 B	70	10	20	10
Jost and Schimrigk ¹⁷	12	5 B	83	0	8	0
Jost et al ¹⁸	54	5 B	78	6	6	11
Mason et al ¹⁹	5	Nr D	60	0	0	0
Jost ²⁰	100	5 B	82	7	6	0
Espi et al ²¹	36	10/15 B	65/81	0	0	0
Maria et al ⁹	25	20 B	88	4	0	0
Maria et al ¹⁰	57	15/20 B	44/68	0	0	0
Minguez et al ²²	69	10-21 B	48-70	0	37-52	0
Jost and Schrank ²³	50	20/40 D	76/80	4/12	4/8	0
Brisinda et al ¹¹	25	20 B	96	0	0	0
Maria et al ¹²	50	20 B	74	0	0	0
Current study	150	20/30 B	89/96	3.4	4	0

Nr, Not reported; B, botox; D, Dysport.
Plus-minus values are mean ± SD.

injection sites are varied. The healing rate was 83% in patients treated with 10 units, 78% in those treated with 15 units, and 90% in the group treated with 21 units. Between-group comparison did not reveal significant differences.²² The injections were administered through the intersphincteric groove in the direction of the internal anal sphincter; however, 1 month after treatment, the mean squeeze pressure was reduced more than resting pressure, which suggests the diffusion of the toxin to the external sphincter.

In the current study, we investigated the influence of different dosage regimens injected anteriorly in the internal anal sphincter on the clinical outcome of patients with posterior chronic anal fissures. Fissure healing and symptomatic improvement were achieved in both groups of patients. At 1 month after injection, complete healing was present in 55 patients (73%) in group I and 65 patients (87%) in group II. A symptomatic fissure persisted in only 5 patients (7%) in group I. A symptomatic improvement was noted in 15 patients from group I and 10 patients from group II. Two months after injection, 67 patients (89%) in group I had a healing scar, 72 patients (96%) in group II had a healing scar, and 3 patients in group II had a persistent fissure without any symptoms. These results confirm that higher doses lead to a higher success rate without increase in complications or side effects. Resting anal pressures were significantly lower than pre-treatment values in both groups. Although the maximum voluntary pressure was unchanged in group I, it was significantly lower than the pre-treatment value of group II, which was probably related to the diffusion of the toxin to the

external sphincter. Five of these patients reported mild incontinence of flatus that lasted 2 weeks after treatment and disappeared spontaneously. Diffusion of toxin in the tissues is a dose-dependent phenomenon. Histochemical staining of acetylcholinesterase suggested that higher doses produced a biologic effect throughout the entire muscle, whereas smaller doses produced a gradient down the length of the muscle studied.²⁶ Diffusion of the toxin outside the targeted muscles, the so-called "toxin jump," may be responsible for side effects associated with the use of botulinum toxin.²⁷

Botulinum toxin exerts its effects on the peripheral nerve endings at the neuromuscular junction, which results in a flaccid paralysis due to the irreversible, selective multiphasic blockade of acetylcholine.²⁸ However, botulinum toxin is also capable, within the autonomic nervous system, of blocking nerve endings where acetylcholine is the primary neurotransmitter. Furthermore, in the ileums of pigs, botulinum toxin does not block nonadrenergic noncholinergic responses,²⁹ which are mediated in part by nitric oxide. O'Kelly et al³⁰ demonstrated that relaxation of the internal anal sphincter occurs through nitrergic enteric neurons. Based on this evidence, it seems conceivable that botulinum toxin may bring about a local increase in the release of nitric oxide.³¹ This increase may be related to dosage regimens of toxin. The inactivation of neuromuscular junctions produces a drastic degradation of post-synaptic acetylcholine receptors due to the loss of synaptic activity.^{32,33} It seems conceivable that with increasing doses of botulinum toxin, the degree of dener-

vation at the injection site increases. Moreover, biologic effects of the botulinum toxin appear to be dose-related^{26,27}; the larger the dose, the more homogenous the effect throughout the muscle.

In conclusion, botulinum toxin injected anteriorly into the internal anal sphincter is effective in treating patients with anal fissures and avoids permanent complications. Higher doses injected anteriorly account for an earlier and higher success rate, with little increase in complications or side effects.

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