

Botulinum Toxin Injections in the Internal Anal Sphincter for the Treatment of Chronic Anal Fissure

Long-Term Results After Two Different Dosage Regimens

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Objective

To investigate the effects of two different dosage regimens of botulinum toxin to induce healing in patients with idiopathic anal fissure.

Summary Background Data

Chronic anal fissure is maintained by contraction of the internal anal sphincter. Sphincterotomy, which is successful in 85% to 95% of patients, permanently weakens the sphincter and therefore might be associated with anal deformity and incontinence.

Methods

Fifty-seven consecutive outpatients were evaluated. Type A botulinum toxin was injected into the internal anal sphincter.

Results

Patients were divided into two treatment groups based on the number of botulinum toxin units injected. Patients in the first

group were treated with 15 units and retreated with 20 units. Patients in the second group were treated with 20 units and retreated with 25 units. Two months after treatment, 10 patients in the first group and 23 patients in the second group had a healing scar. Symptomatic improvement was observed in 13 patients in the first group and in 24 patients in the second group. Statistical analysis showed that resting anal pressure varied from baseline values as a function of treatment; in contrast, the treatment had no effect on maximum voluntary pressure. Long-term healing was achieved in 13 patients in the first group and in all patients in the second group who underwent a complete treatment.

Conclusions

Botulinum toxin is safe and effective in the treatment of anal fissure. It is less expensive and easier to perform than surgical treatment. No adverse effects resulted from injections of the toxin. The higher dosage is effective in producing long-term healing without complications.

An anal fissure is a split in the skin of the distal anal canal. It is a common problem that causes significant complications in a young and otherwise healthy population, with a roughly equal incidence in both sexes.¹ Although its prevalence is not known, anal fissure is believed to be underdiagnosed. An epidemiologic survey conducted in 1994 among Italian proctologic clinics revealed that 10% of 15,161 consecutive outpatients were affected by anal fis-

sure.² Most fissures occur in the posterior midline of the anal canal, but 10% of fissures in women and 1% in men occur in the anterior midline. Multiple fissures or fissures in the lateral position arouse suspicion of other diseases, including Crohn's disease, ulcerative colitis, tuberculosis, human immunodeficiency virus infection, or syphilis.³

Most acute fissures heal spontaneously, but some progress to form a chronic ulcer in the anal canal and show great reluctance to heal without intervention. Although there is no strict temporal definition of chronicity, it is suggested that any patient with symptoms for more than a few weeks will usually have a chronic fissure.¹

The pathogenesis of this condition is not yet fully ex-

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plained.⁴ Anal fissure can be caused by constipation or straining, because a hard fecal bolus can crack the anal canal. The posterior commissure is less perfused than the rest of the anal canal; it seems that local ischemia may play an important part in the pathogenesis. Chronic anal fissure is maintained by contraction of the internal anal sphincter (IAS), triggered by the excruciating pain.⁵

Management plans revolve around breaking the vicious circle of anal pain and spasm by dilatation of the IAS. This can be attempted either conservatively (anal dilators, anal anesthetic locations, manipulating dietary fiber) or surgically (anal dilatation, sphincterotomy). Conservative treatment tends to be protracted and ineffective, and significant recurrence and complication rates accompany both surgical procedures.⁶ Sphincterotomy permanently weakens the sphincter and therefore may be associated with anal deformity, incontinence, and infections.^{1,6}

Chemical denervation with botulinum toxin (BTX) is a versatile tool for targeted weakening of striated muscles.⁷ The toxin may also weaken smooth muscle in the gastrointestinal tract.^{8,9} The advantage of using BTX injections in the IAS in patients with anal fissure is that the ensuing reduction in anal pressure for 3 or more months should allow the fissure to heal, thus removing the need for surgery.

In previous studies,^{10,11} we have observed that anal fissure may be effectively treated with IAS infiltrations of BTX. In the present study, we investigated the effects of two different dosage regimens of BTX (15 or 20 units) to induce healing in patients with idiopathic anal fissure. We also evaluated the complications and the long-term results in both groups.

METHODS

Study Patients

Patients with a chronic anal fissure who were scheduled for treatment at the Department of Surgery of the Catholic University of Rome's Hospital Agostino Gemelli were eligible for inclusion in this study. The diagnosis of chronic anal fissure was based on the presence of typical clinical features: a posterior anal fissure with a large sentinel tag of skin, with induration at the edges of the fissure and the exposure of the horizontal fibers of the IAS; symptoms persisted for more than 2 months. Exclusion criteria included acute fissure, fissure resulting from inflammatory bowel disease, fissure associated with hemorrhoids, fistula in ano, abscesses, or anal and perianal cancer. Patients who underwent previous anal surgery procedures were excluded from the study. Patients with human immunodeficiency virus infections were also excluded. Each patient provided written informed consent for the study.

Baseline Assessment

The patients were assessed using clinical evaluation, anoscopy, and anorectal manometry. Anorectal manometry

was performed at rest and after maximum voluntary contraction; the results were compared with the normal range for our laboratory.^{10,11}

Surgical Technique

Type A BTX (Botox; Allergan, Irvine, CA) was diluted in saline to 50 U/ml. The IAS was easily palpated and injected using a 27-gauge needle, with the patient lying on the left side. No sedation or local anesthesia was used during the procedure. BTX was injected into the IAS on either side of the fissure.

Clinical Care, Follow-up, and Outcome Measures

All patients were advised to eat foods with a high fiber content and received a prescription for laxatives. No patient was treated with topical anesthetic agents before or during the study.

The patients were studied 1 and 2 months after treatment by clinical evaluation, anoscopy, and anorectal manometry. At the 2-month evaluation, the treating physician (GM) could decide to retreat the patient should the fissure persist. Retreated patients were then evaluated using the same protocol 1 and 2 months after the second treatment. At each visit the patients were asked whether, despite any local pain, they wanted to stay in the study. If not, they were offered lateral internal sphincterotomy.

The healed patients were followed clinically until December 1996. Results were evaluated clinically and by comparing the strength of the internal and external anal sphincters, as measured by anorectal manometry. The study end points were evaluation of complete healing and symptomatic improvement after BTX injections. Success was considered to be healing of the fissure; symptomatic improvement was considered to be a persistent anal fissure in the absence of symptoms.

Statistical Analysis

Statistical analysis was performed using Statistica for Windows version 4.5 (Statsoft, Tulsa, OK). The data were analyzed by standard statistical methods; results were expressed as mean $\pm$ standard deviation. Differences between manometric data were compared using Student's *t* test for paired and unpaired samples; differences between percentages were analyzed using Fisher's exact test. Probability values of less than 0.05 were considered significant.

RESULTS

Fifty-seven consecutive outpatients with chronic idiopathic anal fissure were studied. Patients were divided into two treatment groups based on the number of BTX units injected. Group A patients were treated with 15 units (0.3

Table 1. RESULTS IN PATIENTS TREATED WITH 15 BTX-A UNITS (GROUP A)

	Healing Scar	Symptomatic Improvement	Persistent Symptomatic Fissure
1 month	5	7	11
2 months	10	3*	10*

* A rescue treatment with 20 BTX-A units was proposed in these patients; 8 of them refused and underwent surgery; the other 5 received a rescue treatment. Two months after the rescue injection, a complete healing was observed in three patients.

ml) and, if the fissure persisted, were retreated with 20 units (0.4 ml). Group B patients were treated with 20 units (0.4 ml) and retreated with 25 units (0.5 ml).

Baseline Assessment

Group A comprised 23 patients (10 men, 13 women) with a mean age of 44.60 ± 17.24 years (range 20 to 82 years). They had been symptomatic for an average of 10.08 ± 7.92 months (range 3 to 36 months). All had postdefecatory pain lasting more than 2 hours; six had nocturnal pain. Resting pressure was 94.13 ± 35.02 mmHg and maximum voluntary squeeze pressure was 65.86 ± 33.63 mmHg.

Group B comprised 34 patients (18 men, 16 women) with a mean age of 41.38 ± 13.19 years (range 19 to 64 years). They had been symptomatic for an average of 13.32 ± 12.72 months (range 2 to 48 months). All had postdefecatory pain lasting more than 2 hours; 10 had nocturnal pain. Resting pressure was 110.58 ± 30.24 mmHg and maximum voluntary squeeze pressure was 83.67 ± 40.32 mmHg.

The two groups were comparable in terms of age ($p = 0.42$), gender distribution ($p = 0.33$), duration of symptoms ($p = 0.28$), resting pressure ($p = 0.063$), and maximum voluntary pressure ($p = 0.086$) at anorectal manometry.

One-Month Evaluation

Inspection 1 month after the injection (Table 1) revealed a healing scar in five group A patients ($p = 0.024$ vs. baseline assessment). Compared with pretreatment records, postdefecatory pain had disappeared in 12 patients ($p = 0.00001$) and was reduced in 5 patients. Nocturnal pain had disappeared in all six patients who had previously reported it. Resting pressure was 67.60 ± 26.10 mmHg and maximum voluntary squeeze pressure was 54.34 ± 28.05 mmHg. Compared with baseline, only resting pressure (Fig. 1) was reduced ($p = 0.0056$).

Inspection 1 month after the injection (Table 2) revealed a healing scar in 17 group B patients ($p = 0.00001$ vs. baseline assessment). Postdefecatory pain had disappeared

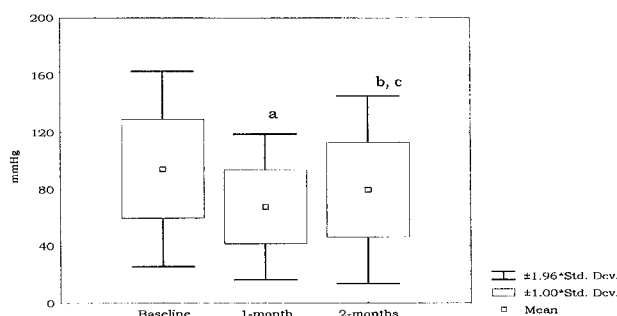


Figure 1. Resting anal pressure in group A patients. a: $p = 0.0056$ vs. baseline; b: $p = 0.053$ vs. 1-month value; c: $p = 0.13$ vs. baseline.

in 24 patients ($p = 0.00001$) and was reduced in 4. Nocturnal pain had disappeared in the 10 patients who previously reported it. Resting pressure was 80.14 ± 22.61 mmHg and maximum voluntary squeeze pressure was 72.20 ± 35.67 mmHg. Compared with baseline, resting pressure (Fig. 2) was significantly reduced ($p = 0.000014$), but maximum voluntary pressure was unchanged ($p = 0.21$).

Inspection revealed complete healing in 5 group A patients and in 17 group B patients ($p = 0.029$). Overall symptomatic improvement was observed in 12 group A patients and in 24 group B patients ($p = 0.12$).

Two-Month Evaluation

In group A, 10 patients (43.47%) had a healing scar ($p = 0.0003$ vs. baseline and $p = 0.1$ vs. the 1-month evaluation; see Table 1). Resting anal pressure (see Fig. 1) was increased (79.56 ± 33.57 mmHg) compared with the 1-month value and did not differ from baseline ($p = 0.13$). Maximum voluntary squeeze pressure (58.04 ± 30.40 mmHg) did not differ significantly from baseline ($p = 0.14$) or from the 1-month value ($p = 0.20$).

In group B, 23 patients (67.64%) had a healing scar ($p = 0.00001$ vs. baseline and $p = 0.1$ vs. the 1-month evaluation; see Table 2). In two patients who had a healing scar at 1 month, a relapse of the fissure was observed. Compared

Table 2. RESULTS IN PATIENTS TREATED WITH 20 BTX-A UNITS (GROUP B)

	Healing Scar	Symptomatic Improvement	Persistent Symptomatic Fissure
1 month	17	7	10
2 months	23	1*	10*

* A rescue treatment with 25 BTX-A units was proposed in these patients; 4 of them refused and underwent surgery; the other 7 received a rescue treatment. Two months after the rescue injection, a complete healing was observed in all retreated patients.

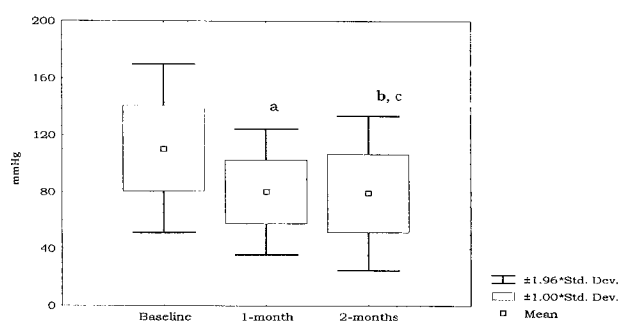


Figure 2. Resting anal pressure in group B patients. a: $p = 0.000014$ vs. baseline; b: $p = 0.000031$ vs. baseline; c: $p = 0.86$ vs. 1-month value.

with pretreatment records, postdefecatory pain had disappeared in 24 patients ($p = 0.00001$) and was reduced in 4. Nocturnal pain was not reported. Resting anal pressure was 79.11 ± 27.72 mmHg and maximum voluntary squeeze pressure was 73.85 ± 35.25 mmHg. Resting pressure (see Fig. 2) was significantly reduced ($p = 0.000031$) from baseline and did not vary from 1-month values ($p = 0.86$). Maximum voluntary pressure did not differ significantly from baseline ($p = 0.28$) or from the 1-month value ($p = 0.84$).

Ten group A patients and 23 group B patients had a healing scar ($p = 0.061$). Symptomatic improvement was observed in 13 group A patients and in 24 group B patients ($p = 0.20$).

Follow-up and Long-Term Outcomes

A rescue treatment was proposed to the remaining 13 patients in group A. Eight of them refused, were excluded from the study, and underwent surgery. The other five, all of whom reported postdefecatory pain, received 20 units BTX each (see Table 1). Inspection 1 month after rescue treatment revealed a healing scar in one patient; in three patients, postdefecatory pain had disappeared. Resting pressure was 68 ± 10.95 mmHg and maximum voluntary squeeze pressure was 77 ± 32.71 mmHg. Two months after the rescue injection, complete healing was observed in three patients.

The healed patients were followed for an average of 24.76 ± 6.26 months (range 12 to 34 months). During this time, no relapse occurred in any of them. No complications or side effects were reported during injection or follow-up of this group of patients, with the exception of one who had mild flatus incontinence 1 month after treatment with the rescue dose; incontinence lasted a week and spontaneously disappeared.

Twenty-three group B patients were healed and were not retreated; four patients refused rescue treatment and were excluded from the study. Seven patients were reinjected with the rescue dose of BTX (25 units). Inspection 1 month after the second injection revealed a healing scar in four patients, who also reported disappearance of postdefecatory

pain. Two months after the rescue injection, all patients had a healing scar; postdefecatory pain had disappeared in all healing patients.

The healed patients were periodically evaluated. Follow-up averaged 19.27 ± 7.19 months (range 8 to 31 months). During this time, no relapse of anal fissure occurred. No complications or side effects were reported during treatment or follow-up of this group of patients.

In the patients who underwent a complete treatment, fissure healing was observed in 13 of 15 patients (86.66%) in group A and in all patients (30 cases) in group B ($p = 0.10$).

DISCUSSION

Spasm of the anal sphincter has been noted in association with anal fissure, and therapeutic approaches, such as anal dilation and lateral sphincterotomy, have generally been aimed at overcoming this spasm.¹ Since 1838,¹² the popularity of anal stretch for the treatment of anal fissure has waxed and waned. Surgeons have been attracted to the procedure by its extreme simplicity and because it can be easily performed without any special equipment.¹ However, the technique is difficult to standardize and has been criticized for causing uncontrolled tearing of the sphincter. Several studies have reported rapid and effective symptomatic relief after the procedure. The recurrence rate of the fissure was reported to be 2.2% to 56.5%, and tended to be higher with longer follow-up.¹ Impaired continence (incontinence of flatus or soiling of underclothes) occurred in 0% to 39.2% of patients; fecal incontinence was reported in up to 16%.¹ Patients who have impaired continence after anal dilatation have low resting anal pressures and low voluntary squeeze pressures.^{13,14} Of 12 men who had fecal incontinence after anal dilatation, 11 were noted to have disruption of the IAS using anal endosonography.¹³ Nielsen et al.¹⁵ performed anal endosonography on 20 consecutive patients 2 to 6 years after anal dilatation and reported sphincter defects in 11 of the 18 continent patients, 4 of whom had fragmentation of the IAS.

The current recommended surgical treatment for chronic anal fissure is lateral internal sphincterotomy. It may be performed under local or general anesthesia. Surgery for anal fissure is associated with several complications, most of which can be prevented by the use of judicious surgical technique and, of course, by familiarity with anorectal anatomy.¹⁶ However, the incidence of complications was relatively high: flatus control problems occurred in 35% and soiling in 22%. Abcarian et al.⁵ found a flatus incontinence rate in 30% of patients after lateral sphincterotomy and in 40% of patients after the posterior procedure. In a retrospective study of 1313 patients who underwent closed or open lateral sphincterotomy, Oh et al.¹⁶ observed, as a late complication, 21 cases of flatus or liquid incontinence and 18 cases of recurrence of anal fissure. Pernikoff et al.¹⁷ reported a 2% incidence of major complications and an 8%

incidence of incontinence. These results are from unselected series of patients. However, Sultan et al.,¹⁸ in a prospective study of the extent of IAS division at sphincterotomy using anal endosonography, suggested that more of the IAS than intended was divided, especially in multiparous women, who may already have an unrecognized obstetric-related sphincter injury. We agree that these patients were acutely decompensated by the internal sphincterotomy. An anal canal ultrasound study is mandatory in multiparous women without continence problems in whom internal sphincterotomy is planned because, in the presence of an already existing sphincter defect, this procedure may result in severe fecal incontinence. Corby et al.¹⁹ showed that postpartum anal fissure is associated with reduced anal canal pressures; in this condition, further surgical damage to the anal sphincter mechanism clearly risks incontinence. Obviously, performing anal endosonography in a patient with an anal fissure may not be easy; however, surgeon awareness, patient education, and special measures such as local injection of BTX may help these high-risk patients. A further endosonographic study²⁰ examining patients with persistent anal fissure after lateral internal sphincterotomy found that in five of seven patients, no defect could be detected in the IAS, although defects in the external anal sphincter were observed at a site consistent with the position of the previous sphincterotomy.

In view of the above reports, the American Society of Colon and Rectal Surgeons²¹ recommended caution before performing lateral sphincterotomy in patients with diarrhea, irritable bowel syndrome, or diabetes, and in elderly patients. They also recommended that before further surgery for fissure is contemplated, resting anal pressure should be recorded and the anal sphincter complex visualized by endoanal ultrasonography in patients with recurrent fissure after previous surgery.

Preliminary results of small series suggest that two new therapies that produce reversible reduction of sphincter pressure may be effective in allowing healing of anal fissure. A chemical sphincterotomy was found after application of topical nitroglycerin ointment.¹ Eighty-three percent of anal fissures were healed after 2 weeks of treatment with nitroglycerin 0.3% ointment in a small pilot study.²² A significant reduction in pain, as assessed by linear analog pain score, was observed within 5 minutes of application of the ointment and after defecation. In another study, topical glyceryl trinitrate ointment applied twice daily cured 18 of 21 patients with chronic anal fissures after 6 weeks.²³ Local application of isosorbide dinitrate reduces anal pressure and improves anodermal blood flow; this dual effect resulted in a healing rate of 67% at 6 weeks. Many patients experienced transient headache (range 19% to 44%) when using topical nitrate preparations, and an anal burning sensation has also been reported; however, there has been no report of incontinence during treatment.¹ It has been suggested that tachyphylaxis may develop, but this has not proved to be a problem in practice. Watson et al.²⁴ reported, at 6 weeks, a

fissure healing rate of 33%, with persistent or recurrent fissure in 44% of patients and failure to complete treatment in 23% of patients. They observed that treatment may not produce fissure healing because of a shorter duration of action of topical glyceryl trinitrate in patients with fissures compared with controls. A better understanding and a protocol to address the potential problems of tachyphylaxis, short duration of action, and side effects will be needed.²⁵

Chemical denervation is also possible with BTX. It is one of the most lethal biologic toxins; it acts rapidly and strongly binds to presynaptic cholinergic nerve terminals.⁸ Paralysis occurs within a few hours. Transmission of neuromuscular impulses resumes after the growth of new axon terminals, and clinical weakening of muscle is seen for 3 to 4 months. BTX has been used to weaken striated muscle in the treatment of disorders such as blepharospasm and spasmodic torticollis; it may also weaken smooth muscle in the gastrointestinal tract.⁷⁻⁹ It has also been used to weaken the external anal sphincter²⁶ and puborectalis muscle in constipated patients with Parkinson's disease²⁷ or in persons with severe constipation resulting from anismus.²⁸ However, because the effects of the toxin wear off within 3 months of administration, repeated injections are necessary to maintain any clinical improvement. The advantage of using BTX injections in the IAS in patients with anal fissure is that the ensuing reduction in anal pressure for 3 or more months should allow the fissure to heal, thus eliminating the need for surgery. Further, any complications of the treatment, such as incontinence (one case of mild flatus incontinence in present experience), could be expected to settle as the effects of the toxin wear off, unlike the permanent sphincter damage that can follow surgery.⁶

Small uncontrolled trials using BTX to treat anal fissure have been reported. Jost and Schimrigk^{29,30} treated 12 patients with chronic anal fissure and increased basal sphincter tone who had not responded to conservative treatment with BTX injected into the external sphincter. At 3 months, the fissure was healed in 10 of 12 patients, and manometry showed a reduction in maximum voluntary squeeze pressure. The significance that the weakening of the external anal sphincter has in healing chronic anal fissure remains controversial, and long-term results are not yet available.

We injected BTX in the IAS of 10 patients with chronic anal fissure.¹⁰ Pain was absent in 5 patients and was reduced in 4 at the first review at 1 week; pain had disappeared at 1 month in 7 of 10 patients. Resting anal pressure, as expected, was significantly lower than pretreatment values; maximum voluntary squeeze pressure was unaffected. Healing was seen in eight patients at 2 months. One of two patients with relapse was successfully treated with further BTX.

We also observed, in a double-blind, placebo-controlled study, that a dose of 0.4 ml diluted BTX (50 units/ml) injected into the IAS on either side of the fissure reduces the resting anal pressure, treats anal fissure, and avoids permanent complications.¹¹ In the present study, a low incidence

of side effects and a lack of complications were observed. Symptomatic improvement was achieved in both groups. The higher dosage is more effective to induce fissure healing. Anorectal manometry showed that resting anal pressures, as expected, were significantly lower than pretreatment values in both groups; maximum voluntary pressures were unchanged. Compared with baseline, resting pressures at 2 months were reduced by 28.4% in group B and by 15.5% in group A; these data suggest that the higher dosage is more effective in long-term weakening of the IAS without producing complications.

In conclusion, the use of BTX appears to be a promising approach for the treatment of anal fissure, particularly in patients at high risk for incontinence. It is less expensive and easier to perform than surgical treatment and does not require anesthesia. No adverse effects or permanent sphincter damage resulted from the injections of the toxin. The higher dosage is safe and more effective in inducing long-term fissure healing without producing complications.

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