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A COMPARISON OF INJECTIONS OF BOTULINUM TOXIN AND TOPICAL NITROGLYCERIN OINTMENT FOR THE TREATMENT OF CHRONIC ANAL FISSURE

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ABSTRACT

Background and Methods Lateral internal sphincterotomy, the most common treatment for chronic anal fissure, may cause permanent injury to the anal sphincter, which can lead to fecal incontinence. We compared two nonsurgical treatments that avert the risk of fecal incontinence. We randomly assigned 50 adults with symptomatic chronic posterior anal fissures to receive treatment with either a total of 20 U of botulinum toxin injected into the internal anal sphincter on each side of the anterior midline or 0.2 percent nitroglycerin ointment applied twice daily for six weeks.

Results After two months, the fissures were healed in 24 of the 25 patients (96 percent) in the botulinum-toxin group and in 15 of the 25 (60 percent) in the nitroglycerin group (P=0.005). No patient in either group had fecal incontinence. At some time during treatment, five patients in the nitroglycerin group had transient, moderate-to-severe headaches that were related to treatment. None of the patients in the botulinum-toxin group reported adverse effects. Ten patients who did not have a response to the assigned treatment — 1 in the botulinum-toxin group and 9 in the nitroglycerin group — crossed over to the other treatment; the fissures subsequently healed in all 10 patients. There were no relapses during an average of about 15 months of follow-up.

Conclusions Although treatment with either topical nitroglycerin or botulinum toxin is effective as an alternative to surgery for patients with chronic anal fissure, botulinum toxin is the more effective nonsurgical treatment. (N Engl J Med 1999;341:65-9.)

ANAL fissure, a split in the skin of the distal anal canal, is a common problem that causes substantial morbidity in people who are otherwise healthy. The incidence of anal fissure is similar in men and women.[1,2] The majority of fissures occur in the posterior midline of the anal canal; multiple fissures or lateral fissures may have other causes, such as Crohn's disease, ulcerative colitis, tuberculosis, infection with the human immunodeficiency virus (HIV), or syphilis.[1-3]

Spasm of the anal sphincter has been noted in association with anal fissure,[4,5] and for many years treatment has focused on alleviating hypertonia of the sphincter. Since 1951, the most common treatment for chronic anal fissure in the United States and Europe has been lateral internal sphincterotomy, as described by Eisenhammer.[6] Although Eisenhammer's technique is simple and effective, the fundamental drawback of this surgery is its potential to cause minor but sometimes permanent alterations in the control of gas, mucus, and occasionally, stool.[1-3,7-9] The American Society of Colon and Rectal Surgeons[10] recommends caution before performing lateral sphincterotomy, particularly in elderly patients or those with diarrhea, irritable bowel syndrome, diabetes, or recurrent fissure after previous surgery.

With medications, it is possible to create the effect of a temporary or reversible sphincterotomy, reducing the sphincter pressure only until the fissure has healed. Two such approaches — injection of botulinum toxin[11,12] and application of nitroglycerin ointment[13,14] — have been used to treat chronic anal fis-

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sure and avoid the risk of permanent injury to the internal anal sphincter. A reduction in the anal pressure for three or more months allows the fissure to heal and thus eliminates the need for surgery. We report the results of a study comparing injections of botulinum toxin with the application of nitroglycerin ointment for the treatment of chronic anal fissure.

METHODS

Patients

Consecutive adults with symptomatic chronic anal fissure were enrolled in the study. The diagnosis was based on the following clinical criteria: evidence of posterior circumscribed ulcer, with a large sentinel tag of skin, induration at the edges, and exposure of the horizontal fibers of the internal anal sphincter; and symptoms (post-defecatory or nocturnal pain, bleeding, or both) lasting for more than two months. Patients with acute fissure, or fissure associated with other conditions (i.e., inflammatory bowel diseases, HIV infection, hemorrhoids, fistula in ano, anal abscesses, or anal or perianal cancer) and those who had undergone previous surgical procedures in the anal canal were excluded. The protocol was reviewed and approved by the institutional committee of the Catholic University of Rome; each patient provided written informed consent.

Study Design

Eligible patients were randomly assigned to one of the two treatment groups according to a computer-generated list. During the trial, the randomization code was not available to the investigators. The code was broken at two months, at which time the patients had completed the first part of the trial. At one and two months of follow-up, one examiner, unaware of the treatment assignments, evaluated the outcome. The outcome in each group was evaluated clinically and by comparing the pressure of the anal sphincter, as measured by anorectal manometry, before treatment with that after treatment.

The end point of the study was complete healing after treatment. The treatment was considered successful if the fissure healed. Persistence of the fissure in the absence of symptoms was considered to be symptomatic improvement.

Base-Line Assessment

All the patients underwent a pretreatment evaluation that included clinical inspection of the fissure and anorectal manometry. Anorectal manometry was performed with the sphincter at rest and after maximal voluntary contraction, and the results were compared with the normal range of values for our laboratory. The resting anal pressure and the maximal squeeze pressure (i.e., the maximal voluntary increase in pressure above the resting pressure) were measured according to a stationary pull-through technique.[15] One and two months after treatment, the patients underwent the same evaluation.

Treatment

Botulinum toxin A (Botox, Allergan, Irvine, Calif.) was diluted in saline to a concentration of 50 U per milliliter. The internal anal sphincter was palpated and injected with a 27-gauge needle while the patient was lying on his or her left side. Each patient received 0.4 ml of solution containing botulinum toxin (for a total of 20 U), administered as two injections of equal volume (0.2 ml), one on each side of the anterior midline of the internal anal sphincter. No sedation or local anesthesia was used during the procedure.

The ointment was prepared from 2 g of 2 percent nitroglycerin (Percutol, Dominion Pharma, Haslemer, United Kingdom), diluted to 100 g with soft paraffin. Treatment consisted of 0.2 percent nitroglycerin ointment applied by fingertip to the anus and the anal canal twice daily for six weeks. Each patient was given a supply of ointment and instructions for applying it to the lower anal canal. In addition, each patient was provided with a dose regulator, which allowed about 1.2 g of ointment to be dispensed for each application.

Clinical Care, Follow-up, and Outcome Measures

At each monthly visit, the patients were asked whether they wanted to continue to participate in the study. If they did not, they were offered lateral internal sphincterotomy. If the fissure persisted at the two-month evaluation, the examiner could decide to offer the patient the alternative pharmacologic treatment. The re-treated patients in the botulinum-toxin group received 0.2 percent nitroglycerin ointment, and those in the nitroglycerin group received a total of 20 U of botulinum toxin injected into the internal anal sphincter on both sides of the anterior midline, as described above. The re-treated patients were then evaluated according to the same protocol one month and two months after the rescue treatment. The patients with healed fissures were followed clinically for at least 11 months.

Statistical Analysis

Analyses were conducted with Statistics for Windows (Statsoft, Tulsa, Okla.). The results are expressed as means ±SD; differences between the treatment groups in manometric data were compared with use of Student's t-test, and differences in percentages were analyzed with use of Fisher's exact test. All P values are two-tailed. P values of less than 0.05 were considered to indicate statistical significance.[16]

RESULTS

Between January and September 1997, 50 consecutive outpatients with chronic posterior anal fissure were enrolled; 25 were randomly assigned to receive injections of botulinum toxin, and 25 were assigned to receive nitroglycerin ointment. All the patients reported severe pain 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. The groups were similar with regard to age, sex, duration of symptoms, and resting and maximal voluntary pressures at base line (Table 1). The internal anal sphincter was easily palpated in all the patients in the botulinum-toxin group. There were no complications during the injection of botulinum toxin or side effects afterward.

Clinical Evaluation

One month after treatment, 22 patients in the botulinum-toxin group and 10 in the nitroglycerin group had healed fissures ($P<0.001$). Ten patients had symptomatic improvement: two in the botulinum-toxin group and eight in the nitroglycerin group. All patients in both groups who had previously reported nocturnal pain no longer had such pain. No patient had bleeding. One patient in the botulinum-toxin group had persistent symptomatic fissure, as compared with seven patients in the nitroglycerin group ($P=0.05$). At the two-month evaluation, 24 patients in the botulinum-toxin group (96 percent) and 15 in the nitroglycerin group (60 percent) had healed fissures ($P=0.005$).

Only patients in the nitroglycerin group had ad-

TABLE 1. BASE-LINE CHARACTERISTICS OF 50 PATIENTS WITH CHRONIC POSTERIOR ANAL FISSURE.*

CHARACTERISTIC	BOTULINUM TOXIN (N=25)	NITROGLYCERIN (N=25)
Age (yr)	45.1±14	39.2±15.5
Sex (M/F)	13/12	12/13
Post-defecatory pain (no. of patients)	25	25
Nocturnal pain (no. of patients)	4	5
Bleeding (no. of patients)	5	4
Duration of symptoms (mo)	9.5±6.8	14.7±10.7
Resting anal pressure (mm Hg)	89.8±21.2	83.4±15.0
Maximal voluntary pressure (mm Hg)	86.9±26.8	79.7±26.1

*Plus–minus values are means ±SD.

TABLE 2. ANAL PRESSURE AFTER THE ASSIGNED TREATMENT.*

TIME	BOTULINUM TOXIN		NITROGLYCERIN	
	RESTING PRESSURE	MAXIMAL VOLUNTARY PRESSURE	RESTING PRESSURE	MAXIMAL VOLUNTARY PRESSURE
	mm Hg			
Base line	89.8±21.2	86.9±26.8	83.4±15.0	79.7±26.1
1 mo	66.2±15†	81.7±29.7	69.5±16.8‡	81.5±23.8
2 mo	64.2±14.9†	83.3±25.2	71.9±17§	86.5±31.3

*Values are means ±SD. All patients were included in all evaluations except for one patient in the nitroglycerin group at the two-month evaluation.

†$P<0.001$ for the comparison with the base-line value.

‡$P=0.004$ for the comparison with the base-line value.

§$P=0.003$ for the comparison with the base-line value, and $P=0.04$ for the comparison with the botulinum-toxin group.

verse effects ($P=0.005$). At some time in the course of treatment, five patients reported moderate-to-severe headaches after application of the ointment. These headaches were transient (30 to 40 minutes) and were relieved with oral analgesia. One of these five patients stopped applying the ointment after 32 days because of severe headache and underwent lateral sphincterotomy. Two patients in the nitroglycerin group reported moderate anal burning. No patient in either group had fecal incontinence.

Anal Manometry

At one month, the mean resting anal pressure in the botulinum-toxin group was 26 percent lower than the base-line value; the maximal voluntary pressure was not significantly changed. In the nitroglycerin group, the mean resting anal pressure was 17 percent lower than the base-line value, and the maximal voluntary pressure was relatively unchanged. The values at one month did not differ significantly between the two groups (Table 2).

At two months, the resting anal pressure was reduced by 29 percent in the botulinum-toxin group and by 14 percent in the nitroglycerin group, as compared with base-line values, and was similar to the one-month value for each group. Resting anal pressure was lower among the patients in the botulinum-toxin group than among those in the nitroglycerin group ($P=0.04$). The maximal voluntary pressure did not differ significantly from base line or from the one-month value for either group.

Follow-up and Long-Term Outcomes

The one patient in the botulinum-toxin group with a persistent fissure was subsequently treated with nitroglycerin ointment. Two months later, the fissure was completely healed. The patients in the botulinum-toxin group were followed for a mean (±SD) of 15.4±4.1 months; during this time, there were no relapses, complications, or side effects.

One patient in the nitroglycerin group underwent lateral sphincterotomy, and nine were treated with botulinum toxin. Two months later, the fissures in all nine of those treated with botulinum toxin had healed. The mean maximal voluntary pressure in these nine patients was similar before they were treated with botulinum toxin (93.9±34.2 mm Hg) and afterward (96.7±30 mm Hg at one month and 96.7±32 mm Hg at two months). During nitroglycerin therapy, the mean resting anal pressure (Fig. 1) did not differ significantly from the base-line value. One month after treatment with botulinum toxin, the resting anal pressure was 23 percent lower than the value obtained during the evaluation that preceded this treatment ($P<0.001$), and at two months, it was 20 percent lower than the pretreatment value ($P=0.003$). The mean follow-up period for the patients in the nitroglycerin group was 16.1±2.6 months; during this time, none of the patients had relapses, complications, or side effects.

DISCUSSION

Spasm of the anal sphincter has been noted in association with anal fissure, and for many years the aim of treatment has been to reduce hypertonia of the sphincter.[1-9] Lateral internal sphincterotomy is a simple and effective surgical procedure that results in a healing rate of 90 to 95 percent.[1-3,9] Its fundamental drawback is that it can cause minor but sometimes permanent alterations in continence.

Two pharmacologic approaches — injections of botulinum toxin and application of nitroglycerin ointment — have been used to treat chronic anal fissure while averting the risk of permanent injury to the in-

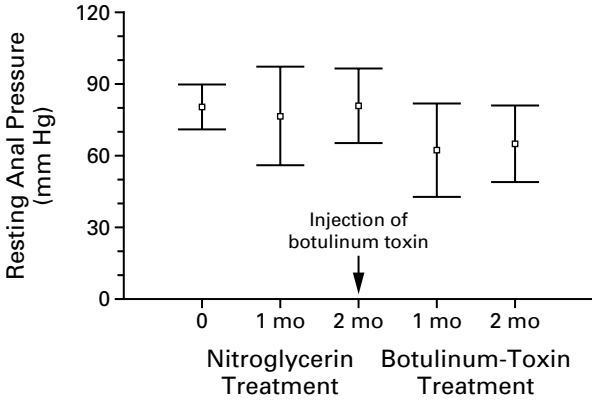

Figure 1. Mean (±SD) Resting Anal Pressure in Nine Patients Initially Treated with Nitroglycerin and Subsequently Treated with Botulinum Toxin.

The mean resting anal pressure was similar at base line and during nitroglycerin therapy (base line, 80.4±9.4 mm Hg; one month, 76.6±20.5 mm Hg; two months, 80.7±15.6 mm Hg) but was reduced after treatment with botulinum toxin (one month, 62.3±19.4 mm Hg; two months, 65±16 mm Hg).

ternal anal sphincter. The use of various topical organic nitrate preparations has been associated with healing rates ranging from 47 to 86 percent,[13,14,17-21] as well as a substantial reduction in pain within five minutes after the application of the ointment. When organic nitrates are degraded, nitric oxide is released.[22] Nitric oxide is an inhibitory neurotransmitter in the internal anal sphincter.[23,24] Recently, a randomized, placebo-controlled trial involving 80 patients showed that 0.5 g of 0.2 percent nitroglycerin ointment applied twice daily healed chronic ulcers in 68 percent of the patients, as compared with a healing rate of 8 percent in the patients who received placebo ointment.[21] After the treatment, manometric studies showed reductions in resting anal pressure and Doppler flow studies showed increases in anodermal blood flow.

Botulinum toxin also causes denervation of the internal anal sphincter. The toxin acts rapidly and prevents the release of acetylcholine by presynaptic nerve terminals.[25] Paralysis occurs within a few hours, and the transmission of neuromuscular impulses resumes after the growth of new axon terminals.[26] Weakening of the muscle is seen clinically for three to four months. Previous studies of chronic anal fissure have demonstrated a healing rate ranging from 60 to 76 percent[12,27] after a single injection of 15 or 20 U of botulinum toxin in the internal anal sphincter. A study of 57 patients treated with 15 or 20 U of botulinum toxin showed that the higher dose was more effective than the lower dose with respect to long-term healing and was not associated with a higher rate of complications.[28]

We found that treatment with either nitrates or botulinum toxin was effective as an alternative to surgery for patients with chronic anal fissure.[29] Furthermore, botulinum toxin was more effective than the topical nitrate. After two months, the fissures were healed in 96 percent of the patients treated with botulinum toxin and in 60 percent of those treated with nitroglycerin ($P=0.005$). Resting anal pressure at two months was significantly lower than the base-line values in both groups and was significantly lower in the patients treated with botulinum toxin than in the patients treated with nitroglycerin.

We injected botulinum toxin into the internal anal sphincter. Botulinum toxin injected into the external anal sphincter is also effective for treating fissure.[11] However, chronic anal fissure is associated with spasm of the internal anal sphincter, and the rationale for injecting botulinum toxin into the external sphincter is therefore unclear. We found that toxin injected into the internal sphincter did not spread to the external sphincter, and we believe that it is easier to inject the toxin directly into the internal anal sphincter. The role of the weakening of the external anal sphincter in the treatment of chronic anal fissure remains uncertain.

Adverse effects of treatment were reported only by the patients who were treated with topical nitrates. When topical nitrate preparations are used, there is a substantial incidence of transient headache (range, 19 to 44 percent).[4,17-21] Headache is particularly evident at higher concentrations of the drug.[22] Anal burning as a result of treatment with nitroglycerin has also been reported. Another potential difficulty is the development of tolerance to the drug,[18,30] a problem that has been well documented with the use of nitrate therapy for cardiovascular disease and has also been reported with its use for anal fissure.[18] In our study, five patients in the nitroglycerin group reported transient headache, which was relieved with oral analgesia. One of these patients stopped applying nitroglycerin ointment because of severe headache. Anal burning was reported by two other patients treated with nitroglycerin. No patient in either group had fecal incontinence.

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CORRECTION

A Comparison of Injections of Botulinum Toxin and Topical Nitroglycerin Ointment for the Treatment of Chronic Anal Fissure

A Comparison of Injections of Botulinum Toxin and Topical Nitroglycerin Ointment for the Treatment of Chronic Anal Fissure . On page 66, five lines from the bottom of the left-hand column, the sentence should read, ``The ointment was prepared from *10 g* of 2 percent nitroglycerin,´´ not ``from *2 g* of 2 percent nitroglycerin,´´ as printed.