A randomized trial of botulinum toxin vs lidocain pomade for chronic anal fissure

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Abstract

Purpose : **As lateral sphincterotomy and anal dilatation causes complications, a reversible chemical sphincterotomy method has been recently proposed as an alternative treatment in patients with anal fissure. In this study, the effect of botulinum toxin causing temporary paralysis in internal anal sphincter was compared with that of lidocaine in patients with chronic anal fissure.**

Method : **A total of 62 outpatients were randomly assigned to receive botulinum toxin or lidocaine pomade. The patients were evaluated before and after two months of treatment with physical examination and anal manometry. Pain and nocturnal pain were scored.**

Results : **In an evaluation period of two months, in 24 of 34 patients of botulinum group (70.58%), and in six of 28 patients of lidocaine group (21.42%) showed complete epithelization (p = 0.006). All patients who had previously reported nocturnal pain became symptom free in botulinum group and in four patients of lidocaine group. Pain following defecation disappeared in 24 patients of botulinum group and in 20 patients of control group (p = 0.959). There was no adverse effect in both groups. While resting anal pressure and maximum voluntary pressure were significantly low in botulinum toxin group, both parameters did not change in lidocaine group.**

Conclusions : **Botulinum toxin is a reliable and effective method for patients with chronic anal fissure. It can be applied easily without any anesthesia and instrumentation. It is cheaper in comparison with surgical methods and it can be a good alternative treatment in patients with risk of incontinence.** (Acta gastroenterol. belg., **2002**, 65, **187-190**).

Key words : anal pressure, botulinum toxin injection, chemical sphincterotomy, chronic anal fissure.

Introduction

Anal fissure, a linear ulcer of the distal anal canal, is characterized by painful defecation, rectal bleeding and anal spasm (1). It is one of the most common and painful anal diseases (2). Ischemia of the posterior commissure of the anal canal, exacerbated by hyper tonicity of the internal anal sphincter (IAS) plays an important role in the pathophysiology. Local ischemia of (less perfuse) posterior commisure produces a triggering mechanism (3,4,5).

To reduce spasm, posterior or lateral internal sphincterotomy (LIS) is the most commonly employed methods in the treatment of chronic anal fissure. However, they are not entirely free from complications and worrisome incidences of anal incontinence (5.3-35.1%) were reported (6). Therefore The American Society of Colon and Rectal Surgeons recommends caution before performing lateral sphincterotomy, particularly in elderly patients or those with diarrhoea, irritable bowel syndrome, diabetes or recurrent fissure after previous surgery (7).

Recent studies led to a better understanding of the pathogenesis of anal fissure and to an increasing use of new therapeutic options like reversible chemical sphincterotomy. Reversibility of the chemical effect prevents the occurrence of permanent complications (8,9,10).

Botulinum toxin (BTX) produces denervation in striated muscles. The toxin may also weaken smooth muscles in the gastrointestinal tract (11). It causes a reduction in anal pressure for 3 or more months allowing the fissure to heal, thus removing the need for surgery (9,10, 12).

In previous studies, we have observed that anal fissure may be effectively treated with IAS injections of BTX. The purpose of this study is to investigate the effects of BTX injections in patients with chronic anal fissure when compared traditional therapy as a lidocaine pomade application.

Patients and method

Patients

62 outpatients with chronic anal fissure were enrolled 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 indurations at the edges of the fissure and the exposure of the horizontal fibers of the IAS, and persistence of symptoms for at least two months. Exclusion criteria included acute fissure, fissure resulting from inflammatory bowel disease, fissure associated with hemorrhoids, fistula in ano or anal cancer, previous anal surgery history.

Study Design

Informed consent was obtained from each patient who entered this study. Patients were randomly assigned

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to one of two treatment groups according to a computer-generated list (created on the Microsoft quick BASIC compiler runtime version 4.50 by biostatistics department). 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 treatment was considered successful if the fissure healed. Persistence of the fissure in the absence of symptoms was considered to be symptomatic improvement.

Baseline Assessment

The patients were assessed using clinical evaluation, anoscopy and anorectal manometry. The patients were reevaluated two months following the first examination by clinical evaluation, anoscopy and anorectal manometry. Resting anal pressure and maximum voluntary squeeze pressure were determined.

Treatment

Topical pomade with lidocaine (Anestol® pomad, Ilsan LTD., Istanbul, Turkey) was applied twice daily and after each defecation at least four weeks by fingertip to the anus and into the anal canal**.** Type A BTX (Botox®, Abdi Ibrahim LTD., Istanbul, Turkey) was diluted in saline to 50 U/ml. The IAS was palpated and 25 IU BTX was injected into the IAS on either side of the fissure using a 27-gauge needle, with the patient in knee to elbow position. No sedation or local anesthesia was used during the procedure.

All patients were advised to eat foods with high fiber content. Topical pomade with lidocaine was applied to patients in-group I (28 patients) and 25 IU BTX were injected to internal anal sphincter in-group II (34 patients).

Statistical analysis

Differences between age and symptom durations of the two groups were compared using Student's t test. Differences between healing ratios and postdefecatory pain of the two groups were compared using two sides Z test. Differences between resting anal pressure and maximal voluntary squeeze pressure were analyzed by paired samples T-test ; results were expressed as mean ± standard deviation. Probability values of less than 0.05 were considered significant.

Results

Six patients were excluded from lidocaine group because of three patients rejected the second anal manometry, two patients did not applied the pomade appropriately and two patients give-up the therapy. These patients were not evaluated in this study.

In baseline assessment, remaining 28 patients (18 women, 10 men) constituted the lidocaine group.

Table I. — **The characteristics of the patients included in the study**

	Lidocaine	BTX
Age (year)	39 ± 14	36 ± 15
Gender (F/M)	18/10	16/18
Period of symptoms (month)	11 ± 6	12 ± 8
Nocturnal pain	10/28	12/34
Postdefecatory pain	28	34
Number of patients	28	34

Their average age and the period of symptoms were **39 ± 14** years (21-69) and **11 ± 6** months (2-27). All of the patients experienced postdefecatory pain and 10 had nocturnal pain. Their anal sphincter resting pressure and maximum voluntary squeeze pressure were **83 ± 19** mmHg (60-125) and **81 ± 23** mmHg (50-120) respectively.

34 patients (16 women, 18 men) were injected with BTX. Their average age and the period of symptoms were **36 ± 15** years (20-74) and **12 ± 8** months (3-36), respectively. Their anal sphincter resting pressure was **86 ± 15** mmHg (60-115) and maximum voluntary squeeze pressure was **105 ± 19** mmHg (70-135). All the patients in this group experienced postdefecatory pain, and 12 had nocturnal pain. There was no significant difference between the two groups in view of age and symptomatic period ($p = 0.770$ and $p = 0.723$ respectively) (Table I). In an evaluation period of two month, in the lidocaine group, nocturnal pain disappeared in four patients, and postdefecatory pain in 20 patients. In six of the patients (21.42%) epithelization was seen. As for the BTX group, all of the patients were free from nocturnal pain. Postdefecatory pain, disappeared in 24, decreased in six and showed no change in four patients. In 24 patients (70.58%) epithelization was complete. In the remaining 10 patients (29.41%) epithelization was partial and evaluated as unsuccessful.

In the lidocaine group, anal resting pressure and maximum voluntary squeeze pressure decreased to **81 ± 21** and **80 ± 22** respectively ($p = 0.365$, $p = 0.984$). These values were not significant. In BTX group, resting pressure and maximum voluntary squeeze pressure decreased to **71 ± 13** and **95 ± 19**, respectively ($p = 0.0001$, $p = 0.003$) (Table II).

When compared two groups, healing ratios (epithelization) were found significantly high in the BTX group ($p = 0.006$), however postdefecatory pain not changed statistically ($p = 0.959$).

Discussion

Anal dilatation can be easily performed without any special equipment. However, it is difficult to standardize and causes uncontrolled tearing of the anal sphincter. In addition, recurrence rate of the fissure was reported to be 2.2% to 56.5%. Incontinence of flatus or soiling of underclothes occurred in 0% to 39.2% of patients ; fecal incontinence was reported in up to 16% (13). Most of

Table II. — **Summary of results before and after treatment**

	Before treatment	After treatment
Lidocaine		
• MARP (mmHg)	83 ± 19	81 ± 21
• MVP (mmHg)	81 ± 23	80 ± 22
• Nocturnal pain	10/28	6/28
• Postdefecatory pain	28/28	8/28
• Epithelization	0/28	6/28
BTX		
• MARP (mmHg)	86 ± 15	71 ± 13
• MVP (mmHg)	105 ± 19	95 ± 19
• Nocturnal pain	12/34	0/34
• Postdefecatory pain	34/34	10/34
• Epithelization	0/34	24/34

MARP : maximum anal resting pressure, MVP : maximum voluntary squeeze pressure.

the patients who had fecal incontinence after anal dilatation were noted to have disruption of the IAS following anal endosonography (14,15). For these reason, lateral internal sphincterotomy (LIS) technique has been widely preferred for the surgical treatment of chronic anal fissure. However, the incidence of complications was relatively high : flatus control problems occurred in 35% and soiling in 22% (6,10,16).

Sultan and co-workers reported that IAS division formed before the sphincterotomy in most of the multiparious women because of previous obstetric trauma (17). In the presence of an already existing sphincter defect, this procedure may result in severe faecal incontinence.

Reversible reduction of sphincter pressure by new chemical therapies may be effective in allowing fissure healing. Recently glycerine trinitrate as a donor of nitric oxide, nifedipine and diltiazem as a calcium-canal blocker and botulinum toxin causing anal sphincter denervation have been used successfully (8,10,18-23).

Uncontrolled trials using BTX to treat anal fissure have been reported. BTX strongly binds to presynaptic cholinergic nerve terminals and causes paralysis within a few hours. Transmission of neuromuscular impulses resumes after the growth of new axon terminals and clinical weakening of muscle is seen for 3-4 months. During this period, IAS is functionally denervated and atrophied and it allows the fissure to heal, thus eliminating the need for surgery (4,9,10,24).

Maria *et al.* reported that 15 IU and 25 IU BTX injections cause 44% and 67% recovery rate, respectively (10). Brisinda *et al.* found that 50 IU BTX injection results in 96% recovery in a period of 2-month (9). Jost and Schimring also showed recovery in 3 months as 83% (17). In recent studies, BTX was used in patients with recurring fissure and 73% of patients became pain-free within the first week, and in 63% of patients fissures were healed in three months (25). It was reported that, The comparison between anterior side and posterior of BTX injections in patients with posterior anal fissure revealed that anterior injection of internal anal sphincter resulted in improved lowering of resting anal pressure and produced an earlier healing scar (26).

In our study, epithelization was seen in six of 28 the patients (21.42%) in lidocaine group and in 24 of 34 patients (70.58%) in BTX group following two months ($p = 0.006$). Postdefecatory pain disappeared in 20 and 24 patients and did not change in eight and four patents in lidocaine group, and in BTX group respectively ($p = 0.959$). Nocturnal pain disappeared in all patients in BTX group, and decreased in four and did not change in six patients in lidocaine group. Anal sphincter resting pressure and maximum voluntary squeeze pressure did not decrease significantly in lidocaine group ($p = 0.365$, $p = 0.984$), whereas a significant decrease was detected in BTX group ($p = 0.0001$, $p = 0.003$).

In conclusion, BTX injection into anal sphincter is highly effective when compared to lidocaine application exempt from postdefecatory pain. BTX injection is easier to perform than surgical treatment and does not require anesthesia **and perhaps the best treatment of chronic anal fissure in patients resistant to topical application of diltiazem and with high risk of incontinence with surgical leiomyotomy.**

References

1. LUND N.J., ARMITAGE N.H. Use of glyceryl trinitrate ointment in the treatment of anal fissure. *Br. J. Surg.*, 1996, **83** : 776-7.
2. GARCIA-AGUILAR J., MONTES C.B., PEREZ J.J., JENSEN L., MADOFF R.D., WONG W.D. Incontinence after lateral internal sphincterotomy: anatomic and functional evaluation. *Dis. Colon. Rectum*, 1988, **41** : 423-7.
3. BROWN A.M., ROZWADOWSKI J.V. Histopathology of the internal anal sphincter in chronic anal fissure. *Dis. Colon. Rectum*, 1989, **32** : 680-6.
4. NEUFELD D.M., PARAN H., BENDEHAN J., FREUND U. Outpatient treatment of anal fissure. *Eur. J. Surg.*, 1995, **161** : 435-8.
5. SCHOUTEN W.R., BRIEL J.W., AUWERDA J.J. Relationship between anal pressure and anodermal blood flow: the vascular pathogenesis of anal fissures. *Dis. Colon. Rectum*, 1994, **37** : 664-9.
6. KHUBCHANDANI I.T., REED J.F. Squeal of internal sphincterotomy for chronic fissure in ano. *Br. J. Surg.*, 1989, **76** : 431-4.
7. ROSEN L., ABEL M.E., GORDON PH., DENSTMAN F.J., FLESHMAN J.W., HICKS T. Practice parameters for the management of anal fissure. The Standards Task Force American Society of Colon and Rectal Surgeons. *Dis. Colon. Rectum*, 1992, **35** : 206-8.
8. LODER P.B., KAMM M.A., NICHOLLS R.J., PHILIPS R.K.S. "reversible chemical sphincterotomy" by local application of glyceryl trinitrate. *Br. J. Surg.*, 1994, **81** : 1386-9.
9. BRISINDA G., MARIA G., BENTIVOGLIO A.R., CASSETTA E., GUI D., ALBANESE A. A comparison of injections of botulinum toxin and topical nitroglycerin ointment for the treatment of chronic anal fissure. *N. Engl. J. Med.*, 1999, **341** : 65-9.
10. MARIA G., BRISINDA G., BENTIVOGLIO A.R., CASETTA E., GUI D., ALBANESE A. Botulinum toxin injections in the anal sphincter for the treatment for chronic anal fissure. *Ann. Surg.*, 1998, **228** : 664-9.
11. ALBANESE A., COLOSIMO C., CARRETTA D., DICKMANN A., BENTIVOGLIO A.R., TONALI P. Botulinum toxin as a treatment blepharospasm, spasmodic torticolllis and hemi facial spasm. *Eur. Neurol.*, 1992, **32** : 112-7.
12. PASRICHA P.J., RAVICH W.J., HENDRIX T.R., SOSTRE S., JONES B., KALLOO A.N. Intrasphincteric botulinum toxin for the treatment of achalasia. *N. Engl. J. Med.*, 1995, **332** : 774-8.
13. LUND J.N., SCHOLEFIELD J.H. A etiology and treatment of anal fissure. *Br. J. Surg.*, 1996, **83** : 1335-44.
14. SPEAKMAN C.T.M., BURNETT S.J.D., KAMM M.A., BARTRAM C.I. Sphincter injury after anal dilatation demonstrated by anal endosonography *Br. J. Surg.*, 1991, **78** : 1429-30.

15. NIELSEN M.B., RASMUSSEN O.O., PEDERSEN J.F., CHRISTIANSEN J. Risk of sphincter damage and anal incontinence after anal dilatation for fissure in ano. *Dis. Colon. Rectum*, 1993, **36** : 677-80.
16. LEWIS TH., CORMAN M.L., PRAGER E.D., ROBERTSON W.G. Long-term results of open and closed sphincterotomy for anal fissure. *Dis. Colon. Rectum*, 1988, **31** : 368-71.
17. SULTAN A.H., KAMM M.A., NICHOLLS R.J., BARTRAM C.I. Prospective study of the extent of internal anal sphincter division during lateral sphincterotomy. *Dis. Colon. Rectum*, 1994, **37** : 1031-3.
18. ALTOMARE D.F., RINALDI M., MILITO G., ARCANA F., SPINELLI F., NARDELLI N. *et al.* Glyceryl trinitrate for chronic anal fissure-healing or headache? *Dis. Colon. Rectum*, 2000, **43** : 174-84.
19. COOK T.A., HUMPHREYS S., MORTENSEN M.C. Oral nifedipine reduces resting anal pressure and heals chronic anal fissure. *Br. J. Surg.*, 1999, **86** : 1269-73.
20. JONAS M., NEAL K.R., ABERCROMBIE J.F., SCHOLEFIELD J.H. A randomized trial of oral vs. topical diltiazem for chronic anal fissures. *Dis. Colon. Rectum*, 2001, **44**: 1074-8.
21. CARAPETI E.A., KAMM M.A., PHILLIPS R.K. Topical diltiazem and bethanechol decrease anal sphincter pressure and heal anal fissure without side effects. *Dis. Colon. Rectum*, 2000, **43**: 1359-62.
23. KNIGHT J.S., BIRKS M., FAROUK R. Topical diltiazem ointment in the treatment of chronic anal fissure. *Br. J. Surg.*, 2001, **88** : 553-6.
24. JOST W.H., SCHIMRIGK K. Therapy of anal fissure using botulinum toxin. *Dis. Colon. Rectum*, 1994, **37** : 1321-4.
25. JOST W.H., SCHRANK B. Repeat botulinum toxin injections in anal fissure: in patients with relapse and after insufficient effect of first treatment. *Dig. Dis. Sci.*, 1999, **44** : 1588-9.
26. MARIA G., BRISINDA G., BENTIVOGLIO A.R., CASETTA E., GUI D., ALBANESE A. Influence of botulinum toxin site of injections on healing rate in patients with chronic anal fissure. *Am. J. Surg.*, 2000, **179** : 46-50.