

# Botulinum toxin injection versus lateral internal sphincterotomy for the treatment of chronic anal fissure: randomized prospective controlled trial

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## Abstract

**Purpose** Lateral internal sphincterotomy has been the gold standard treatment for chronic anal fissure, but it still carries the risk of permanent damage of the anal sphincter, which has led to the implementation of alternative treatment like botulinum toxin injection. The aim of this randomized prospective controlled trial was to compare the efficacy and morbidity of botulinum toxin injection and lateral internal sphincterotomy in the treatment of chronic anal fissure.

**Methods** Fifty consecutive adults with chronic anal fissure were randomly treated with either lateral internal sphincterotomy or botulinum toxin (BT) injection with 50 U BT into the internal sphincter. The complications, healing and recurrence rate, and incontinence score were assessed 2, 3, 6, 12 months after the procedure.

**Results** Inspection at the 2-month visit revealed complete healing of the fissure in 11 (44 %) of the patients in the BT group and 22 (88 %) of the patients in the lateral internal sphincterotomy (LIS) group ( $p=0.001$ ). At the 3-month

visit, there was no significant difference between the two groups in healing. The overall recurrence rate after 6 months in the BT group was higher than in the LIS group ( $p<0.05$ ). In the 3-month follow-up, the LIS group had a higher rate of anal incontinence compared to the BT group ( $p<0.05$ ). The final percentage of incontinence was 4 % in the LIS group ( $p>0.05$ ).

**Conclusions** The treatment of chronic anal fissure must be individualized depending on the different clinical profiles of patients. Botulinum toxin injection has a higher recurrence rate than LIS, and LIS provides rapid and permanent recovery. However, LIS carries a higher risk of anal incontinence in patients.

**Keywords** Chronic anal fissure · Botulinum toxin injection · Lateral internal sphincterotomy · Anal incontinence

## Introduction

Anal fissure remains one of the most common proctologic problems which cause severe sharp pain on defecation, occasionally accompanied by bleeding [1–3]. The pain associated with chronic anal fissure (CAF) leads to proportionate worsening of quality of life and tends not to heal without intervention [4, 5]. Breaking the vicious cycle of spasm, ischemia, and pain in CAF is accomplished with surgical or medical procedures. Today, lateral internal sphincterotomy (LIS) remains the gold standard for treatment of chronic anal fissure. This operation has been successful in more than 90 % of cases and has rates of recurrence smaller than 10 % [6–8]. However, it carries the risk of permanent complications [1] like fecal incontinence in up to 30 % of

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patients [9]. This has led to the studies and implementation of other alternative medical treatments, mainly botulinum toxin injection [10–14] and organic nitrate preparations [15–17]. Of these, botulinum toxin injection seems to be an optimal non-operative therapy with similar healing rates [18] but lowest rate of recurrence [12] and fewest side effects [19], and studies have shown no permanent damage to the continence mechanism that was detected in patients treated with botulinum toxin [20–22].

The aim of this randomized prospective controlled study was to compare the efficacy and morbidity of botulinum toxin injection and lateral internal sphincterotomy in the treatment of chronic anal fissure.

## Materials and method

### Patients

Between January 2007 and January 2009, 50 consecutive adults with chronic anal fissure were included in our study. All the patients diagnosed by medical history (bleeding and/or pain during or after defecation for at least 3 months) and physical examination including digital anal examination and anoscopy. Conservative treatment (high-residue diet, warm sitz baths, and analgesics) had failed in these patients. The diagnosis of the chronic anal fissure was based on the following criteria: evidence of posterior or anterior circumscribed ulcer with a sentinel tag of skin, indurations at the edges, and exposed internal sphincter fibers. The exclusion criteria were complicated fissure (fistula, stenosis, abscess, and symptomatic hemorrhoids), large sentinel pile, associated disease (inflammatory bowel disease, tuberculosis, malignancy, prior pelvic radiotherapy, and any immunosuppressive condition), allergy to local anesthetics, and patients who had undergone previous surgical procedure in the anal canal.

This study was done in Ayatollah Taleghani Hospital, Shahid Beheshti University of Medical Science and was approved by the ethics committee of Ayatollah Taleghani Hospital. An informed consent was signed by each patient before participating in the study.

### Study design

The patients were categorized into two groups by the computer randomization program: group 1 underwent surgical sphincterotomy ( $n=25$ ) and group 2 underwent chemical sphincterotomy with botulinum toxin ( $n=25$ ).

### Lateral internal sphincterotomy

All the procedures were performed by the same surgeon using a similar method in the lithotomy position. Lateral

internal sphincterotomy was done under spinal anesthesia. The lateral anal region was exposed with an anal retractor through a 1.5 to 2-cm circumferential incision placed outside the anal verge. Internal and external sphincters were separated using the intersphincteric plane, and the internal sphincter was assessed under direct vision and about 50 % of the sphincter was incised. The skin incision was either closed with interrupted sutures or was left open, and skin tags were removed as a routine.

### Botulinum toxin injection

Botulinum toxin injection was performed under local anesthesia (xylocaine gel 5 %). A 100-U vial of type A lyophilized botulinum (BOTOX, Allergan, CA) stored at  $-20\text{ }^{\circ}\text{C}$ , diluted with saline to 50 U/ml on the day of injection. With a so-called insulin syringe (26-G needle), 25 U was injected into each side of the sphincter. In patients with posterior fissure, BT was injected on each side of the anterior midline, and in patients with anterior fissure, BT was injected on each side of the posterior midline.

### Postoperative follow-up

In both groups, conservative treatments including high-residue diet and warm sitz baths were recommended to control constipation and decrease pain and bleeding. At the time of admission, documents regarding age, gender, symptoms (pain, bleeding, and constipation), duration of symptoms, and physical examination findings (skin tag, site of fissure) were collected. Early complications were collected at 1 week visit. Postoperative follow-ups regarding degree of fissure healing, different types of incontinence, and relapse of the fissure were collected at 2 weeks and 2, 3, 6, 12 months follow-up visits. All the patients were examined by the same surgeon at the outpatient department of Ayatollah Taleghani Hospital. Complete healing was considered as complete re-epithelialization of fissure and absence of symptoms. Partial healing was defined as initiation of epithelialization and reduction of symptoms. Persistence of fissure whether associated with symptoms or not were considered as recurrent fissure. The validated Cleveland Clinic scoring system was used for assessment of continence severity. The system gives points for each degree of incontinence, whether gas (1–3), liquid stool (4–6), solid stool (7–9), or the requirement of wearing a pad (1–3) according frequency (occasionally,  $>1/\text{week}$  or daily), respectively. The Cleveland score is the sum of those points: 0=perfect continence, 1–7=good continence, 8–14=moderate continence, 15–20=severe incontinence, and 21=completely incontinent [23, 24]. The treatment was considered successful if the CAF was healed completely within 2 months after treatment. Unhealed fissures were considered as failure of treatment. According to Table 1, the two groups were

**Table 1** Characteristics and symptoms of patients and anal examination results before treatment

	Group 1 ( <i>n</i> =25) lateral internal sphincterotomy	Group 2 ( <i>n</i> =25) toxin botulinum
Mean age (year)	36.4±8.5	34.8±8.1
Gender (men/women)	8 (32 %)/17 (68 %)	11 (44 %)/14 (56 %)
Symptoms duration (months)	9.07±4.8	11.4±4.8
Site of fissure		
Posterior midline	20 (80 %)	19 (76 %)
Anterior midline	5 (20 %)	6 (24 %)
Skin tag	18 (72 %)	17 (65.4 %)
Pain	23 (92 %)	22 (88 %)
Bleeding	21 (84 %)	19 (76 %)
Constipation	14 (56 %)	16 (64 %)
Pruritus	11 (44 %)	8 (32 %)

almost similar in characteristics and symptoms, and there was no significant difference between them in anal exploration before treatment.

#### Statistical analysis

The data are analyzed with the aid of the SPSS 11.5 computer program, and continuous variables are expressed as means ± SD. Statistical significance of CAF healing and incontinency, etc. in the two groups is analyzed with the chi-square test and 95 % confidence interval. Probability values of less than 0.05 were considered significant. Considering the power of our study as 0.7 and effect size as 0.5, the sample size was calculated as 25 patients in each group.

#### Results

Early complications occurring after procedures were hematoma in 1 (4 %) patient and also self-limited hemorrhage in 2 (8 %) patients in the surgical sphincterotomy group. There were no anal abscesses, perianal fistulae, urinary retention, and hemorrhoid thrombosis in our patients.

There was complete healing of fissure in seven patients (28 %) in the BT group and ten patients (40 %) in the LIS group at the 2-week visit, and partial healing was found in five patients (20 %) of each group. Inspection at the 2-

month visit revealed a statistically significant higher rate of complete healing in the LIS group than in the BT group ( $p=0.001$ ). According to the healing classification in our study, nine and one patient in the BT and LIS group had a partial healing, respectively. Considering partial healing as a start of the healing process, there was no significant difference in the rate of healing between the two groups, and the data analysis at the 3-month visit showed no significant difference between the two groups ( $p>0.05$ ) (Table 2).

In patients in whom the symptoms duration had been present for longer than 12 months in both groups, fissures were significantly less likely to heal ( $p=0.028$  in BT group,  $p=0.014$  in LIS group). There was no relationship found between the other preoperative clinical variables analyzed and healing.

Evaluation of the persistence or recurrence of the fissures after 6 months revealed a significantly higher rate of recurrence in the BT group than in the LIS group ( $p=0.005$ ). Significant differences in overall healing were found after 12 months follow-up; 12 patients (48 %) in the BT group and 23 patients (92 %) in the LIS group ( $p=0.001$ ). Fissures were less likely to relapse in patients with symptom duration less than 12 months in the LIS and the BT group ( $p=0.003$  in the BT group,  $p=0.014$  in the LIS group). There was no relationship found between the other preoperative clinical variables and recurrence.

Inspection of patients in the BT group at 2 weeks after treatment revealed a complete healing in seven patients

**Table 2** Healing rate and incontinence in the two groups

Follow-up visits	Healed fissures		<i>p</i>	Incontinence		<i>p</i>
	BT group	LIS Group		BT group	LIS group	
2 months	11 (44 %)	22 (88 %)	0.001	3 (12 %)	12 (48 %)	0.005
3 months	20 (80 %)	23 (92 %)	>0.05	0	5 (20 %)	<0.05
6 months	13 (52 %)	22 (88 %)	0.005	0	4 (16 %)	<0.05
12 months	12 (48 %)	23 (92 %)	0.001	0	1 (4 %)	>0.05

(28 %), partial healing in five patients (20 %), and no healing in 13 patients (52 %). Of the patients in whom no healing was found in the 2-week visit, ten patients had a recurrent or persistent fissure at the end of the study (76 %). There was a significant higher rate of recurrence in patients with unhealed fissures at 2-week visit than patients with partial or complete healing ( $p=0.023$ ).

In the 3-month follow-up, moderate incontinence (Cleveland Clinic scoring system (8–14)) was present in five patients (20 %) in the LIS group and none of the patients in the BT group suffered anal incontinence ( $p=0.018$ ). Six months after LIS, anal incontinence has resolved in one patient, spontaneously. At the end of the study, after 12 months, only one patient from the LIS group (4 %) reported occasional incontinence to gas or liquid stool (Cleveland Score, <7) (Table 2). Occurrence of anal incontinence after LIS was significantly higher in age >40 years ( $p=0.022$ ) (Table 3).

## Discussion

Since botulinum toxin injection was introduced as a potential treatment for anal fissures in 1993 [25], various studies compared the efficacy of this treatment to surgical methods in the treatment of fissures [26–29]. Because of different results and unclear conclusions, there is still controversy on whether BT injection is a suitable substitute for LIS in treatment of CAF.

Some studies suggest chemical sphincterotomy methods like BT injection as a first choice in treatment of CAF because they are relatively less expensive and less invasive than surgery [30, 31], and there were studies with results suggesting that BT injection has an equal healing rate compare with LIS [32]. The best healing results in the short-term follow-up have been (>80 %) in the studies about the use of

BT in the treatment of anal fissures [13, 33]. However, longer follow-up in some other studies shows a progressive recurrence over time with lower rate of healing than initial reports and relapse of anal fissure in 55 % of patients at 3 years [27] and 41.5 % at 42 months [34]. This could be related to the fact that relaxation of smooth internal anal sphincter produced by the botulinum toxin is not permanent, and the clinical efficacy lasts only for 2–3 months after injection [35]. In our study, there was also a progressive rate of recurrence of fissure in the BT group which starts at 19.2 % in 3 months and reaches 50 % in 12 months. The end point of our study was 12 months because according to Arroyo et al. [27], recurrence occurs mainly between 6 and 12 months so later relapses is not expected. The recurrence rate of surgical sphincterotomy was 8 % and not progressive. Studies suggested that some clinical factors like posterior localized fissure and short duration of symptoms (<12 months) are predictive factors for a favorable outcome in BT toxin treatment in CAF [34, 36]. In our study, we found duration of symptoms as a clinical parameter related to a higher rate of recurrence. In the BT group, the mean duration of symptoms was 11 months and in the LIS group it was 9 months. This difference could be responsible for the higher rate of recurrence for patients treated with BT. Therefore, we believe that LIS seems to be a better option for these patients as a first therapeutic option considering higher probability of recurrence with BT treatment in the long term follow-up.

Different studies have used varying dosage regimens of botulinum toxin but in most of them a single injection of 20–30 U was employed [18, 28, 29]; however, there was studies that have suggested higher doses (up to 50 U) provide a higher success rate (up to 96 %) without a significant rising in complications or side effects [37]. In this study, we used 50 U and it did not cause any rise in complication rate. In addition, the site of injection of BT toxin is an important parameter in success rate of BT

**Table 3** Correlation between the healing of fissure, incontinence, and fissure recurrence and preoperative variables following botulinum toxin injection and surgical sphincterotomy

	BT group				LIS group			
	Total	Healed Fissures (n=11)	Incontinence (n=0)	Fissures recurrence (n=12)	Total	Healed fissures (n=22)	Incontinence (n=5)	Fissures recurrence (n=3)
Age, years								
<40	18	8	0	9	16	15	1	2
>40	7	3	0	3	9	7	4	1
Male/female	11/14	3/8	0	6/6	8/17	7/15	2/3	1/2
Duration, months								
<12	12	8	0	2	16	16	2	0
≥12	13	3	0	10	9	6	3	3
Anterior/posterior fissure	6/19	1/10	0	3/9	5/20	4/18	0/5	1/2
Skin tag	17	6	0	9	18	17	5	2

treatment. According to the study of Maria et al. [13], to reduce the resting pressure of anal sphincter efficiently, we injected BT into the internal anal sphincter on each side of fissure.

By analyzing the immediate complication rate (hemorrhage, hematoma, anal abscess, fistula, urinary retention, and hemorrhoid thrombosis), there was no significant difference between two groups. In our study, the rate of incontinence after 12 months was 4 % in the LIS group while there was no incontinence in the BT group. Although the difference was not statistically significant, considering the specific impacts of incontinence on quality of life [38], the LIS advantages in treatment of the CAF will be nullified. An age of >40 was the only pretreatment factor associated with an increase in incontinence. Based on these findings, Botox therapy might be considered as the first therapeutic approach in patients with high surgical risks or those who avoid surgery or in cases with high risk of future incontinence (age greater than 40, women with multiple vaginal deliveries, inflammatory bowel diseases, prior anal surgery, prior incontinence, etc.) despite the higher rate of recurrence and reoperation, cause BT injection is relatively safe and leads to no detriment to continence. In addition, BT treatment represents a simple outpatient procedure without anesthesia or incision which makes it a relatively less expensive and less invasive procedure than LIS. These advantages make BT injection an effective alternative for treatment of chronic anal fissure. On the other hand, BT injection was performed in a blind manner and dislocation of this injection is inevitable while LIS is performed under direct vision so it is a more reproducible procedure.

In our study, we found that in the BT group, patients with no healing at 2-week visit tend to relapse or not heal during follow-up, and the recurrence rate is relatively lower in patients who have been healed at 2-week visit. Based on these results, we suggest that patients who remained unhealed 2 weeks after the BT injection seems to need other procedures like LIS to achieve better results.

Although all the patients underwent conservative management before recruitment to this study, there is always a possibility that fissures can be healed without any intervention. Using a control group could eliminate this problem, and this can be a limitation of current study and should be focused in the future studies.

## Conclusion

The treatment of chronic anal fissure must be individualized depending on the different clinical profiles of the patients. Botulinum toxin injection has a higher recurrence rate than LIS, and LIS provides rapid and permanent recovery. However, LIS carries a higher risk of anal incontinence in patients.

**Conflicts of interests** None.

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