

Brief communication (Original)

Long-term outcome of botulinum toxin injection for the treatment of chronic anal fissure: a randomized controlled trial

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Background: Lateral internal sphincterotomy has been accepted as the gold standard for chronic anal fissure. Despite the effectiveness, it carries a risk of fecal incontinence. Non-operative management of chronic anal fissure has been used as alternative treatment.

Objectives: Evaluate the efficacy and long-term outcomes of botulinum toxin injection for the treatment of chronic anal fissure.

Material and method: A prospective randomized controlled trial was conducted on 40 patients diagnosed with chronic anal fissure who were assigned to undergo either botulinum toxin injection or lateral internal sphincterotomy.

Results: The wound-healing rate at 12 weeks and the reduction of post-treatment-resting pressure was significantly better in the sphincterotomy group. Complications and the continence status were not different between the two treatment groups. None of the patients in the sphincterotomy group required additional treatment, while seven patients in the botulinum toxin injection group underwent subsequent sphincterotomy within three years.

Conclusion: The long-term result of botulinum toxin injection for chronic anal fissure was inferior to lateral internal sphincterotomy.

Keywords: Botulinum toxin injection, chronic anal fissure, lateral internal sphincterotomy, long-term outcome

Chronic anal fissure is a painful tear at the anoderm, usually at the midline, accompanied by the spasm of the internal anal sphincter [1]. The principal treatment of chronic anal fissure is to reduce the internal sphincter spasm, which ultimately allows the fissure to heal [2]. Lateral internal sphincterotomy has been accepted as the gold standard. However, this procedure carries a risk of surgical wound complications and anal incontinence [3-6]. Hence, there has been an emerging trend to treat chronic anal fissure with the use of pharmacologic means including a local application of diltiazem and glyceryl trinitrate, and botulinum toxin injection [2, 7]. The

benefit of botulinum toxin injection has been shown for the treatment of various muscle spasm disorders [8] including chronic anal fissure [4-6, 9].

The action of botulinum toxin A temporarily inhibits acetylcholine release into the synaptic gap, which eventually causes muscle relaxation [8, 9]. Despite of the success of botulinum toxin injection for healing of the fissure, long-term outcomes have not been well studied. In this study, we compared the effectiveness and long-term outcomes of the botulinum toxin injection and the lateral internal sphincterotomy for the treatment of chronic anal fissure.

Material and methods

A prospective randomized controlled trial was conducted. This study was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University. Written informed consent was obtained.

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Forty patients diagnosed with chronic anal fissure for more than three months were enrolled. They were computer-generated assigned into two treatment groups, botulinum toxin injection, and lateral internal sphincterotomy. Individuals with previous perianal operation, inflammatory bowel disease, bleeding disorder, and pregnancy were excluded from the study. Data accrued included age, sex, symptom, pain score before and after the treatment, wound healing, continence status, and the need for additional treatment. Resting anal pressure and squeeze pressure, using a five-channel-water-perfusion anal manometry, were recorded before and after the treatment.

For the patients allocated to the botulinum toxin injection, 40 units of botulinum toxin A (Dysport, Beaufour Ipsen Biotech, Paris Cedex, France) were injected to both lateral aspects of the internal sphincter (total dosage of 80 units) using insulin syringe with a 27-gauge needle.

For the patients in the surgery group, lateral internal sphincterotomy was performed. The technique involved an infiltration of 1% xylocain with adrenaline (1:100,000) at the perianal area followed by a small incision (5 millimeter) at the intersphincteric groove on the lateral aspect of the anal verge. The internal sphincter was dissected and divided to the level of the dentate line. Medications after the treatment for both groups included paracetamol, ibuprofen, and bulk

forming agent (Mucilin, Berlin Pharm, Bangkok, Thailand).

Success of the treatment was defined by the healing of the fissure. Continence status was evaluated using the questionnaire of the ability to control flatus, liquid stool, and form stool. The manometric study before and after the treatment was used to compare the result between the treatment groups.

The patients who failed to improve after botulinum toxin injection were subsequently treated with lateral internal sphincterotomy.

Statistical analysis

Data were analyzed using parametric and nonparametric statistics. Chi-square(²)-test was used to compare categorical data while continuous variables were evaluated by Student's *t*-test.

Results

The patient demographics were shown in **Table 1**. Posterior midline location was the most common site of the fissure. We note that the preoperative manometric measurement was not different from demographic one.

Pain score after the treatment at day one was significantly higher in the surgery group ($p=0.005$). However, it was significantly lower at day 7 ($p=0.041$) as shown in **Figure 1**.

Table 1. Demographic data.

Parameter	Lateral sphincterotomy	Botulinum toxin injection	P-value
<i>Sex (M:F)</i>	5:15	6:14	0.723 ^a
<i>Age (mean: SD)</i>	36.6:13.1	31.8:10.1	0.202 ^b
<i>Symptom</i>			
Painful	3	7	0.144 ^a
Painful with bleeding	17	13	
<i>Baseline pain score (mean: SD)</i>	6.70:1.90	6.65:2.03	0.936 ^b
<i>Fissure location</i>			
Anterior	4	1	0.564 ^a
Posterior	14	16	
Anterior and posterior	2	3	
<i>2nd change</i>			
minimal	13	13	1.000 ^a
moderate	3	2	
distinct	4	5	
<i>Manometry (mean: SD)</i>			
Resting pressure	97.0: 24.5	100.9: 24.0	0.614 ^b
Squeeze pressure	178.4: 25.3	179.2: 24.0	0.914 ^b

^aFisher's exact, ^bStudent's *t*-test.

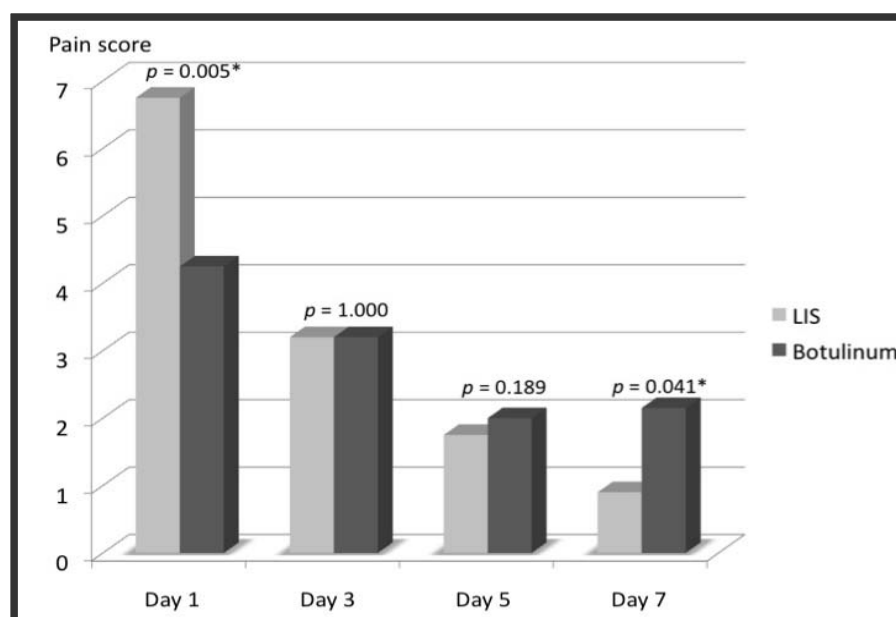


Figure 1. Post-treatment pain score. LIS: lateral internal sphincterotomy, Botulinum: botulinum toxin injection, *Statistical difference by p-value (Student's t-test).

Healing of the fissure at 12 weeks after the treatment was significantly better in the surgery group ($p=0.047$) (**Table 2**). The complications were not different between the treatment groups. Four patients in the surgery group and three in the botulinum toxin injection group developed incontinence, which was not different. All of them were transient. The resting pressure after the treatment was significantly lower in the surgery group ($p=0.002$). For the botulinum toxin injection group, there were five unhealed fissures at the 12-week follow-up and two recurrent fissures at the three-year follow-up. These patients were subsequently treated with lateral internal sphincterotomy. None of the patients in the surgery group required additional treatment.

The significant reduction of the resting anal pressure was demonstrated in the surgery group ($p=0.001$), but not in the botulinum toxin injection group (**Table 3**).

Discussion

Lateral internal sphincterotomy has been accepted as the gold standard for chronic anal fissure with more than 90% success rate reported [3]. Despite of the effectiveness, it carries a risk of fecal incontinence, which ranged from 1% to 30% [3]. Hence, non-operative management of chronic anal fissure including botulinum toxin injection is expected.

However, as shown in this study, the continence status comparing between groups was not different, and all incontinences were temporarily. This is similar to previous reports elsewhere [10, 11]. In addition, good quality of life, especially the continent status after lateral internal sphincterotomy, has been demonstrated [11].

The action of botulinum toxin is reversible and usually last for two to three months after injection. Varying dosage regimens of botulinum toxin has been used, but a single injection of 20 to 25 units of BOTOX (Allergan, Mougins Cedex, France) has been generally recommended for the treatment of chronic anal fissure [4-6]. In the present study, 80 units of Dysport (Beaufour Ipsen Biotech, Paris Cedex, France) were used. Although Dysport (Beaufour Ipsen Biotech, Paris Cedex, France) is different in pharmacology, potency, and other properties to BOTOX (Allergan, Mougins Cedex, France), a conversion factor of 1:3 to 1:5 has been documented for equivalent results [12].

Significant pain score reduction after lateral internal sphincterotomy comparing to botulinum toxin injection has been reported [5]. In the present study, symptomatic improvement after the treatment was demonstrated in both groups. However, significant reduction of the pain score at the postoperative day 7 was shown in the patients treated with sphincterotomy, as shown in **Figure 1**. In addition, the fissure-healing

Table 2. Results of the treatment.

Parameter	Lateral sphincterotomy	Botulinum toxin injection	P-value
Wound healing at 6 week			
Yes	19	15	0.182 ^a
No	1	5	
Wound healing at 12 week			
Yes	20	15	0.047 ^a
No	0	5	
Complication			
None	20	18	0.487 ^a
Bleeding	0	2	
Symptom			
Itching	18	14	0.235 ^a
No itching	2	6	
Continence status			
Good continence	16	17	1.000 ^a
Impair continence (temporary)	4	3	
Flatus	(4)	(1)	
Liquid stool	(0)	(1)	
Formed stool	(0)	(1)	
Post-operative manometry (mean: SD)			
Resting pressure	71.40:19.68	92.70:20.67	0.002 ^b
Squeeze pressure	176.60:26.56	177.55:27.56	0.912 ^b
Accumulated patients requiring subsequent surgery at			
1-year-follow-up	0	5	0.047 ^a
2-year-follow-up	0	7	0.008 ^a
3-year-follow-up	0	7	0.008 ^a

^aFisher's exact, ^bStudent's t-test.**Table 3.** Comparison of resting pressure between pre-treatment and post-treatment.

Resting pressure (mean: SD)	Pre-treatment	Post-treatment	P-value
Botulinum toxin injection group	100.90: 24.00	92.70: 20.67	0.254 ^b
Lateral sphincterotomy group	97.00: 24.52	71.40: 19.68	0.001 ^b

^bStudent's t-test.

rate at 12-week post treatment was significantly better in the sphincterotomy group, which was compatible with previous reports [4, 5].

There has been a trend to progressive recurrence over time in the botulinum toxin treatment [4, 13]. In our study, 15 patients treated with botulinum toxin (75%) had healed fissure in 12 weeks, but two of them developed recurrent fissure in three years. All of unhealed fissures (five patients) and recurrent fissures (two patients) in the botulinum toxin injection

group were subsequently treated with lateral internal sphincterotomy. All of them ultimately had healed fissure.

Significant decline of the resting pressure following lateral internal sphincterotomy has been demonstrated [1, 5]. In this study, the resting pressure reduction after the treatment was significantly better in the sphincterotomy group, while the squeeze pressure after the treatment from both groups was not changed. In addition, we found a significant decline of the resting

pressure after treatment in the sphincterotomy group, as shown in **Table 3**. This phenomenon was not demonstrated in the botulinum toxin injection group. This result is a robust support of the difference in the efficacy between two treatment methods.

In conclusion, the long-term result of botulinum toxin injection for chronic anal fissure was inferior to lateral internal sphincterotomy.

Acknowledgement

This study was supported by Ratchadapisek Sompotch Fund, Thailand. The authors have no conflict of interest to report.

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