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## Botulinum toxin injection versus lateral internal sphincterotomy in the treatment of chronic anal fissure: a non-randomized controlled trial

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### Abstract

**Background:** Although lateral internal sphincterotomy is the gold-standard treatment for chronic anal fissure, intrasphincteric injection of botulinum toxin seems to be a reliable new option. The aim of this non-randomized study is to compare the effect of lateral internal sphincterotomy and botulinum toxin injection treatments on the outcome and reduction of anal sphincter pressures in patients with chronic anal fissure.

**Methods:** Patients with chronic anal fissure were treated with either botulinum toxin injection or lateral internal sphincterotomy by their own choice. Maximal resting pressure and maximal squeeze pressure measurements were performed before and 2 weeks after treatments by anal manometry. Patients were followed for fissure relapse during 14 months.

**Results:** Twenty-one consecutive outpatients with posterior chronic anal fissure were enrolled. Eleven patients underwent surgery and ten patients received botulinum toxin injection treatment. Before the treatment, anal pressures were found to be similar in both groups. After the treatment, the maximal resting pressures were reduced from  $104 \pm 22$  mmHg to  $86 \pm 15$  mmHg in the surgery group ( $p < 0.05$ ) and from  $101 \pm 23$  mmHg to  $83 \pm 24$  mmHg in the botulinum toxin group ( $p < 0.05$ ). The mean maximal squeeze pressures were reduced from  $70 \pm 27$  mmHg to  $61 \pm 32$  mmHg ( $p > 0.05$ ) in the surgery group, and from  $117 \pm 62$  mmHg to  $76 \pm 34$  ( $p < 0.01$ ) in the botulinum toxin group. The fissures were healed in 70 percent of patients in the botulinum group and 82 percent in the surgery group ( $p > 0.05$ ). There were no relapses during the 14 months of follow up.

**Conclusion:** Lateral internal sphincterotomy and botulinum toxin injection treatments both seem to be equally effective in the treatment of chronic anal fissure.

### Background

Increases in resting anal pressure are documented in

patients with chronic anal fissures (CAF) and it has been considered as a major pathophysiologic factor. Therapies

that reduce anal sphincter pressures have been used to achieve fissure healing. Lateral internal sphincterotomy (LIS) is the most common treatment for CAF [1] and can be effective in more than 90 percent of cases but needs general or local anesthesia [2]. The fundamental drawback of this surgery is its potential to cause gas, mucus or occasionally stool incontinence which is permanent in 8 to 30 percent of patients and may be associated with abscess and anal deformity [3-8].

Intrasphincteric injection of botulinum toxin (BT) is a reliable and effective new option in the treatment of uncomplicated CAF. This method has been described initially by Jost and Schmirgk [9], and was found to be an effective treatment in comparison with placebo [10]. Furthermore, BT was more effective than topical nitrate, which constitutes another therapeutic option [11], and no permanent damage to the continence mechanism was detected in patients treated with BT [10,12,13]. The aim of this non-randomized, prospective and controlled study was to compare the therapeutic efficacy of BT injection and LIS in CAF and their effect on the reduction of anal sphincter pressures.

## Methods

### Patients

Consecutive adults with symptomatic CAF were enrolled into the study. The diagnosis of CAF was based on the following 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 (IAS); symptoms (post-defecatory or nocturnal pain, bleeding, or both) lasting for more than two months. Criteria for exclusion from the study were complicated fissure and important secondary changes, i.e., cicatricial deformation, large sentinel pile and subfissural infiltration. Patients were fully informed about the effect and possible side effects of LIS and BT injection. This study was approved by the institutional review board of PTT Hospital.

### Study design

This study was designed in a non-randomized fashion. Treatment arms were decided according to the patients' will. All the patients underwent a pre-treatment evaluation which included clinical inspection of the fissure and anorectal manometry.

### Anal manometry

Anal sphincter manometry was performed on the CAF patients before and at the 3rd week of the treatment. Manometry was carried out by a pre-calibrated, water perfusion system using a catheter with 8 holes 0.5 cm apart (Andorfer Inc. Wisconsin, USA). Manometric data was stored and analyzed with computer software (Smartgraph

Rev.3.40, Sandhill Scientific Inc., Highlands Ranch, Colorado, USA). Anal digital examination was not performed before manometry to avoid the effects of anal dilatation on sphincter pressures. All patients were studied after a bowel preparation with enema (Fleet Enema, C.B. Fleet Co. Inc. USA). Patients were placed comfortably in the left lateral position. After the insertion of the catheter into the rectum, maximal resting pressure (MRP) and maximal squeeze pressure (MSP) measurements were done. MRP was defined as the average of maximal pressures obtained from all holes by stationary pull-through technique. MSP was defined as the mean of differences between the mean pressures obtained by voluntary squeezing for 5 seconds and resting pressures when all of the holes were within the anal canal. Patients were instructed to squeeze their anus as much as they could without squeezing their abdominal and buttock muscles throughout the entire period of MSP measurement in order to record actual sphincter pressures and to prevent pressure interactions.

### Lateral internal sphincterotomy

LIS was performed under general or spinal anesthesia in the lithotomy position by a technique through a circumferential incision placed laterally to the skin outside the anal verge. The anoderm and inter sphincteric groove were dissected, and then the sphincter was divided under direct vision. The wound was either left open or was closed with interrupted sutures.

### Botulinum-toxin injection

Botulinum toxin (Botox, Allergan, Ireland) was diluted with saline to 40 U/ml and 10 U was injected on both sides of the fissure (total dose 20 U and volume 0.5 ml) by a so-called insulin syringe with a short, thin needle (10 mm, 26 gauge needle, 1 mL, Hayat, Turkey). After injection, conservative measures, such as sitting baths and/or anal tampons for the period of healing (at least for the first weeks) were recommended.

The primary end points of the study were complete healing of the CAF and complications after treatment. The treatment was considered successful if the fissure healed with a scar two months after the treatment (evaluation for treatment efficacy). Unhealed fissures were considered as treatment failure and dropped from follow up. Complications were described as incontinence (soiling, flatus and feces), abscess and thrombosed hemorrhoids. The secondary end point of the study was relapse of the fissures. The patients with healed fissures were followed clinically for at least 12 months. In the follow up period, patients were re-examined by inspection and re-evaluated for symptoms at 6th and 12th months (evaluation for fissure relapse).

**Table 1: Clinical characteristics of both groups on entry into the study.**

Baseline characteristics	BT (n = 10)	LIS (n = 11)
Age (years)	41 ± 11	39 ± 10
Sex (female/male)	4/6	7/4
Symptom duration (months)	10 ± 6	11 ± 6
Maximal Resting Pressure (mmHg)	101 ± 23	104 ± 22
Maximal Squeeze Pressure (mmHg) †	70 ± 27	117 ± 62

† p > 0.05 for the comparison between the two groups (by Mann-Whitney test).

**Table 2: Comparisons of anal pressures before and after assigned treatment.**

Groups	Maximal resting pressure (mmHg)			Maximal squeeze pressure (mmHg)		
	Before treatment	After treatment	P	Before treatment	After treatment	P
BT	101 ± 23	83 ± 24	<0.05	117 ± 62	76 ± 34	<0.01
LIS	104 ± 22	86 ± 15	<0.05	70 ± 27	61 ± 32	>0.05

BT = Botulinum toxin injection. LIS = Lateral internal sphincterotomy. p > 0.05 for the comparisons between the two groups (BT vs. LIS).

### Statistics

The results are expressed as mean ± SD. Manometric data were compared between the groups by using Student t-test and Mann-Whitney test according to the differences between SDs of the data. Differences in percentages were analyzed with use of Fisher's exact test. Probability values of less than 0.05 were considered significant.

### Results

Twenty-one consecutive outpatients with posterior CAF were enrolled. Eleven patients underwent LIS and ten patients underwent BT. The two groups were similar with regards to age, sex, duration of symptoms, MRP and MSP (Table 1). There were no complications during or after BT injection.

The MRP (104 ± 22 mmHg and 101 ± 23 mmHg for LIS and BT injection group respectively, p > 0.05) and the MSP (70 ± 27 mmHg and 117 ± 62 mmHg for LIS and BT injection group respectively, p > 0.05) were found to be similar between LIS and BT group before treatment. After treatment, the MRP was reduced to 86 ± 15 mmHg in the LIS (p < 0.05) and to 83 ± 24 mmHg in the BT group (p < 0.05). MSP was reduced to 61 ± 32 (p > 0.05) in the LIS group and to 76 ± 34 (p < 0.01) in the BT group (Table 2).

Inspection at 2 months after treatment revealed a healing scar in 7 (70 percent) patients in the BT group and 9 (82 percent) in the LIS group (p > 0.05). Two of three patients whose fissures were not healed with BT injection under-

went LIS at 1 and 2 months after BT treatment. The other patients had an asymptomatic fissure and refused surgical treatment. All of the patients who had an unhealed fissure at 2 months after treatment were dropped from the follow up in this study.

No fissure relapse was observed at the 6<sup>th</sup> and 12<sup>th</sup> month during follow up period in the two treatment groups. The patients in the botulinum toxin injection group and LIS group were followed for mean of 14 ± 1 months and 14 ± 1 months respectively. There were no relapses, complications, or side effects during this follow up period.

### Discussion

We have shown that LIS and BT injection treatment modalities have had similar effects on internal anal sphincter pressures, have similar fissure healing rates and no recurrence in long-term follow-up. We can suggest that LIS and BT injection treatment are equally effective in the treatment of CAF patients.

Increase in resting anal pressure is documented in patients with chronic anal fissure, which exceeds 30 mm Hg or more when compared with healthy controls and is associated with a decrease in posterior anal blood flow [14,15]. Any prolonged increases in pressure may cause ischemic damage by decreasing blood flow to the sphincter muscle and overlying epithelium [14]. As a consequence, therapies that reduce IAS pressure have been used for fissure healing. Many chronic fissures do not heal with aggressive

local measures and are considered for lateral sphincterotomy. Although surgery is effective, fissure healing and relapse rates are quite variable. After lateral sphincterotomy the healing rates range from >90 percent [16] to 78 percent [17], and the recurrence rates range between 1.3 and 13.1 percent [2,7,18]. These variations could be due to the type of surgical technique (open *vs.* subcutaneous sphincterotomy) or the length of the sphincterotomy incision. Fissure healing rate is relatively low (82 percent) after LIS procedure in this study, which may be related to a more conservative approach in sphincterotomy in order to prevent anal incontinence. Neither significant incontinence nor relapse was observed during 14 months follow-up period.

Botulinum toxin injection into anal sphincter is another therapeutic approach which have been used to treat chronic anal fissure and avoid the risk of permanent injury to the anal sphincter [9,10,13]. Although chemical denervations with botulinum toxin have been mostly used for weakening of striated muscles, it has also been found to weaken smooth muscle in the gastrointestinal tract [19,20]. The toxin acts rapidly and prevents the release of acetylcholine by presynaptic nerve terminals. Paralysis occurs within a few hours, and the transmission of neuromuscular impulses resumes after the growth of new axon terminals [19,21]. On the third day after the injection, the EAS tone was obviously reduced [9]. Chemical denervation produced by the toxin is not permanent and the clinical efficacy lasts for 2–3 months [18]. In anal fissure, however, the duration of action of the toxin roughly corresponds to the time required to reduce the resting pressure of the anal sphincter and allows enough time for healing.

In the present study the healing rate of 70% in the BT group is similar to that in previous studies [9,10,12,13]. We observed significant decrease in both IAS and EAS but interestingly, Gui et al. [13] and Maria et al. [10] did not observe any effect of BT on EAS after injection to IAS. They concluded that toxin injected to the IAS had not spread into EAS [11]. This suggestion may not be valid and could be related with type II error bias. We think that after the injection into IAS, spread of the toxin through the EAS is possibly due to the small thickness of IAS and the proximity of EAS to the IAS. It is also well known that a diffusion gradient crossing even the bone and fascia spreads to a distance of 30–45 mm from the injection point [22]. The other reason of this controversy between our results and the others' may also be related to the volume of the toxin. We used a higher volume (0.5 mL) than Maria et al (0.4 mL) and this might have diffused beyond the target muscle and might have weakened the adjacent muscles [22,23]. The change in resting pressure was not mentioned by Jost and Schimrigk in their initial studies where

they injected BT into the EAS [9,12]. In this study, we did not try to inject BT specifically into the IAS or EAS. We also observed that if the toxin was applied on both sides of the fissure it spread into the EAS and IAS, and we believe it is easier to inject the toxin in this manner. In conclusion, the target muscle for injection of BT seems to be irrelevant.

After therapy with BT, higher recurrence rates are expected, because the sphincter tone is only temporarily reduced. However, we and others have shown that relapse rates after BT injection was very low [10-13]. Recently, posteriorly localized fissures, significant reduction in maximum squeeze pressure and short duration of symptoms (<12 months) were suggested as predictive factors for a favorable outcome in botulinum toxin treatment in CAF [24]. All of our patients had posterior anal fissure and short symptom duration (mean 10 months), and significant reduction of maximally squeeze pressure (-34%) was achieved in the botulinum toxin group. These positive predictive factors could be related with the good outcome of our patients treated with BT.

Theoretically BT injection can produce anal incontinence. BT produces a significant and global reduction in mean resting pressure of the anal canal, but also induces a significant increase in manometric asymmetry of the anal canal [19]. However, incontinence has been a negligible complication of BT treatment. EAS is an important component of continence. Toxin injection produces sufficient weakness of this muscle, but does not completely block voluntary control which is enough for incontinence prevention [25].

The therapeutic success rate of BT seems to be related with injection site and toxin dose. We injected the BT on each site of the fissure, mainly to the posterior of the anal sphincter. However it was suggested that anterior injection of BT could better reduce the resting pressure of the anal sphincter (88 percent *vs.* 60 percent) which could be due to the fibrotic base of the fissure or ischemic degeneration of the myenteric plexus of posterior sphincter [26]. In addition the dose of BT is important. We used 20 units in this study. However, it was suggested that higher doses (up to 50 units) provide a higher success rate (up to 96 percent), without a significant rise in complications or side effects [27].

In a recent randomized, prospective study comparing BT with LIS for CAF, it has been suggested that the healing effect of BT appears slowly and wanes with longer follow-up, whereas LIS provides a faster, more stable and permanent effect [28]. The success rate of the BT group fell to 75.4 percent, whereas it remained stable in the LIS group (94 percent) at 12 months. In conclusion, the authors suggested that BT injection is inferior to LIS in the treatment

of CAF. However they reported 16 percent rate of anal incontinence of varying degrees after surgery, compared with a 0 prevalence in the BT group ( $p < 0.001$ ) within the same follow-up period. If anal incontinence is considered as a failure of LIS, the advantage of this treatment will disappear [29].

In conclusion, BT injection is effective in the treatment of CAF. It is relatively less invasive than surgery and the complication rate seems negligible. However BT injection treatment may provide temporary remissions. Larger scale, randomized controlled studies with long term follow up are needed before making firm conclusions about the advantages of this treatment modality over the conventional methods.

### Authors' contributions

AG: carried out the anorectal manometry, participated in the design of the study and to the writing of the manuscript. KM: carried out LIS surgery and BT injections, participated in the design of the study. YG: carried out LIS surgery and BT injections and the coordination of the study. Nİ: performed the statistical analysis and contributed to the writing of the manuscript. CK: participated in the design of the study and to the writing of the manuscript. NBU: participated in the design of the study. NT: participated in the design of the study and to the writing of the manuscript.

### List of abbreviations

CAF: Chronic Anal Fissure

LIS: Lateral Internal Sphincterotomy

BT: Botulinum Toxin

IAS: Internal Anal Sphincter

EAS: External Anal Sphincter

MRP: Maximal Resting Pressure

MSP: Maximal Squeezing Pressure

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