



The Effect of 3-Way Low-Dose Botox Toxin Treatment on Recurrence Rates in Chronic Anal Fissures

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Botox toxin treatment is an effective method in chronic anal fissures. Although the risk of anal incontinence is very low in botox toxin treatment, the recurrence rates are very high. Therefore, it is necessary to develop new application methods that can reduce the recurrence rates. In our study, 3-way botox toxin treatment method was compared with one-way treatment in order to determine which method was more effective.

Methods: Patients performed botox toxin treatment for chronic anal fissure in the single center between 2017 and 2021 were retrospectively studied. The rates of recurrence and anal incontinence after one-way(Group A) and 3-way(Group B) low-dose botox toxin treatment were compared. Visual analog scale and Cleveland Clinic Incontinence Score tests were performed before and after botox treatment. Results were compared statistically.

Results: Early relapse rate was 28.5% in Group A, in Group B 9.0%.

At the end of the 2-year follow-up, the total recurrence rate was 38.0% in Group A, 22.7% in Group B. Temporary anal incontinence rate was 4.7% in Group A, and 6.8% in Group B.

There was no persistent anal incontinence in either group. The difference between the early relapse rates between Group A and Group B was statistically significant ($p < 0.05$). The difference

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between anal incontinence rates according to Cleveland Clinic Incontinence Score was not statistically significant between the patients with GP A and Gp B ($p > 0.05$).

Conclusion: 3-way low-dose botox toxin treatment is a more effective treatment method for preventing early recurrence than one-way treatment in chronic anal fissures.

Keywords: Anal fissure; chronic; botox toxin; treatment.

1. INTRODUCTION

Anal fissures are very common, painful proctological diseases that negatively affect daily life. The lifetime cumulative incidence is up to 11% [1]. The most important etiological factor is constipation [2,3]. According to a hypothesis suggested by Meegdenburg [4], trauma is the first factor in the formation and development mechanisms of chronic anal fissures (CAF)s. It has been reported that [4], post-traumatic pain and related increase in internal sphincter pressure cause local ischemia and result in CAF. The authors reported that [4], CAF-induced mucosal damage also caused spasm in the external sphincter.

A number of treatment methods are used in CAFs. Topical local analgesic and corticosteroid creams are generally used for conservative medical treatment (MT). Internal lateral sphincterotomy (ILS), fissurectomy, and anal dilatation are the most commonly used surgical treatment methods[1].

Chemical substances that cause temporary paralysis in external and internal anal sphincters; BT are glyceryl trinitrate (GT) and calcium channel blockers [5].Botox toxin creates temporary paralysis and decreases muscle tone by preventing the release of acetylcholine in the internal sphincters in chronic anal fissures.

The treatment method scheme with botox toxin treatment (BT) in CAFs has not yet been fully standardized. In the literature, there are studies that give conflicting results regarding the amount of BT and application site in CAFs.

Therefore, in this study we compared the recurrence and anal incontinence rates in patients who performed 1-way and 3-way low-dose BT into the internal and external sphincters.

In a previous prospective preliminary study, we found that patients who underwent low-dose 3-way BT had statistically lower rates of early relapse compared to patients who received 1-way therapy [6].

Therefore, in this study; we retrospectively re-evaluated the results by increasing the number of our cases and the duration of follow-up.

2. PATIENTS AND METHODS

2.1 Patients

In our study, we compared the recurrence and anal incontinence rates after treatment in 2 different CAF patient groups with similar characteristics and clinical features, but with different methods of BT performed. The cases included in our study were, had not been operated due to chronic anal fissure before, not respond to medical treatment, admitted to our hospital (Muğla Yücelen Hospital) between September 2017- March 2021 with symptomatic chronic anal fissure. 1-way or 3-way BT therapy was applied by same surgeon to these patients in the internal and external sphincter. The patients included in our study were followed up for at least 24 months and the longest 43 months after CT treatment.

In the cases included in our study, the results of the first 2-year follow-up were evaluated.

Patients had surgery for CAF prior to BT, pregnant CAF patients, or with chronic inflammatory bowel disease, were excluded from the study. Low-dose BT patients were divided into two groups as 1-way (Group A) and 3-way (Group B) patients.

2.2 Methods

The patients were asked to evaluate their pain on the horizontal 100 mm Visual analog scale(VAS) and mark 0 if there is no pain and 100 if there is very severe pain. The differences between pre- and post-treatment VAS values were evaluated statistically and it was concluded that improvement was achieved in those with significant differences.

The presence of anal incontinence before and after treatment was evaluated by Cleveland clinic incontinence score(CCIS). CCIS 1-2; mild anal

incontinence, CCIS 3-4; moderate anal incontinence, CCIS 5 and above; was accepted as severe anal incontinence.

Intestinal cleansing was performed with glycerol + sodium citrate rectal tube 1 hour before BT injection. BT was performed under intravenous general anesthesia in patients.

For analgesia, 100 mg pethidine HCL was administered intramuscularly.

A total of 30 units of BT were injected with a 28 gauge needle at the posterior direction into the internal and external sphincters in patients with Group A(Gp A).

In patients with Group B(Gp B); a total of 30 units of BT were injected laterally and posteriorly into the internal and external sphincters with a 28 gauge needle.

2.3 Follow-up

The patients included in our study were followed up for at least 24 months and the longest 43 months after CT treatment. In the cases included in our study, the results of the first 2-years follow-up were evaluated.

Differences between VAS values before and after treatment were determined periodically.

Patients with no significant difference between VAS test results and cases without wound healing were considered to be recurrence. CCIS values were determined periodically after treatment in all patients.

2.4 Statistical Analysis

SPSS (Statistical Package for the Social Sciences) 23.0 package program was used for statistical analysis of the data. Categorical measurements in numbers and percentages, if

continuous measurements were summarized as mean and standard deviation (median and minimum-where necessary).

Chi-square test and Fischer's precision test were used to compare categorical variables. Shapiro-Wilk test was used to determine whether the parameters in the study showed normal distribution. Independent student's t-test in normal distribution parameters by controlling the distributions in the comparison of continuous measurements between the groups, Mann whitney u tests were used for the parameters that did not show normal distribution.

Statistical significance level was taken as 0.05 in all tests.

3. RESULTS

3.1 Characteristics of Patients

26 of the patients in Gp A were female, 16 were male, the average age 33.9, 27 of the patients with Gp B were female and 17 were male, the mean age was 32.3.

When the groups were compared in terms of age and sex, the difference was not statistically significant ($p > 0.05$).

The demographic characteristics of our patients are given in Table 1.

3.2 Symptoms and Signs of Patients

The most common symptom in patients is pain, the most common location of the fissure was posterior. Before treatment, the CCIS was 0 in all patients.

The distribution of the symptoms and clinical features of in Gp A and Gp B patients was shown in (Table 2).

Table 1. Distribution of demographic characteristics of our patients in Gp A and Gp B

		Gp A (n: 42)	Gp B (n: 44)	p
		n(%)	n(%)	
Sex	Female	26 (61.9)	27 (61.3)	0,441
	Male	16 (38,0)	17 (38.6)	
		Gp A	Gp B	p
		mean±ss	mean±ss	
Age		33,90±5,27	32,32±4,60	0,805

Gp A: Group A; Gp B: Group B

Table 2. Distribution of symptoms and signs in Gp A and Gp B cases

	Gp A	%	Gp B	%	Total	%	p
Pain	42	100	44	100	86	100	>0.05
Bleeding	16	38.0	16	36.3	32	37.2	>0.05
Constipation	38	90.4	39	88.6	77	89.5	>0.05
CAF site							
Posterior	36	85.7	38	86.3	74	86.0	>0.05
Anterior	6	14.2	5	11.3	11	12.7	>0.05
Bilateral	2	4.7	3	6.8	5	5.8	>0.05

Gp A: Group A; Gp B: Group B

The recurrence rate in both groups after 2 years of follow-up is 30.2%.

The total recurrence rate in Gp A and Group B patients was 38.0% and 22.7% respectively.

Recurrence rates in the first week was 28.5 in Gp A, 9.0% in Gp B.

There was no significant difference between inadequate treatment the two groups in terms of total recurrence rates($p>0.005$)(Table 3) (Fig. 1).

However, early recurrence (insufficient treatment) rates were found to be significantly higher in Gp A patients compared to Gp B patients($p<0.05$) (Table 3) (Fig. 1).

In both groups, 61.5% of relapses occurred in the first week as early recurrence after BT treatment. It was determined that 75.0% of relapses in Gp A and 40.0% in Gp B were early relapse (insufficient treatment).

Table 3 shows the recurrence rates occurring in both groups.

When the cases with significant difference in VAS values before and after treatment were compared between the two groups; it was observed that the number of cases with difference was significantly higher in GpB than Gp A ($p<0.05$) (Table 4).

Table 4 shows the distribution of patients with significant difference in VAS values before and after treatment in Gp A and Gp B.

The rate of temporary anal incontinence occurring in both groups was 5.8%. Anal incontinence in Gp A after BT appeared as CCIS 2 in 2 patients and completely resolved at 3 months. Anal incontinence in Gp B was observed as CCIS 2 in 2 patients, CCIS 3 in 1 patient, and completely resolved in the 3rd month.(Table 4) (Fig. 2). There was no statistically significant difference between post-treatment CCIS values in both groups($p>0.05$).

Table 5 shows the rates of anal incontinence occurring in both groups.

Table 3. Recurrence rates in botox treatment groups

Times of recurrence		Gp A (n: 42)	Gp B (n: 44)	p
		n(%)	n(%)	
First week	No	30 (71.5)	40 (91.0)	0,038
	Yes	12 (28,5)	4 (9.0)	P<0.05
First month	No	29 (69.1)	38 (86.4)	0.182
	Yes	13 (30.9)	6 (13.6)	
Third month	No	29(69.1)	38 (86.4)	0.182
	Yes	13 (30.9)	6 (13.6)	
Sixth month	No	28 (66,7)	37 (84.0)	0,193
	Yes	14 (33,3)	7 (16.0)	
First year	No	27(63,3)	35 (79,6)	0,223
	Yes	15(35,7)	9 (20.4)	
Second year	No	28 (66.6)	34 (80.9)	0,246
	Yes	14 (33.4)	10 (19.1)	p>0.05
Total recurrence				

Gp A: Group A; Gp B: Group B

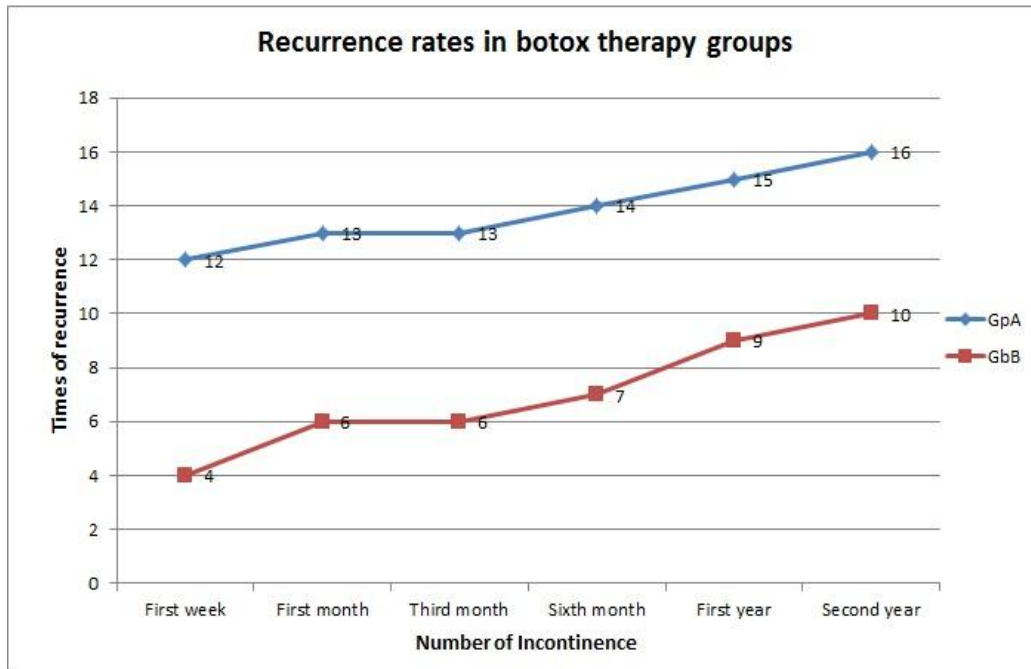


Fig. 1. Shows the recurrence rates occurring in both groups

Table 4. The distribution of patients with significant difference in VAS values before and after treatment in Gp A and Gp B

Follow-up	Group A (mm)	Group B(mm)	p
First week	-8.4(9.4)	-26.7(24.2)	0.034 (p<0.05)
First month	-16.5(23.6)	-15.5(24.7)	0.724
Third month	-18.2(27.2)	-22.6(26.1)	0.462
Sixth month	-16.4(26.1)	-17.2(27.0)	0.382
First year	-18.2(30.1)	-18.5(26.2)	0.936
Second year	-16.2(25.2)	-16.5(25.8)	0.456

Table 5. Anal incontinence rates in botox treatment groups

Times of anal incontinence		Gp A (n: 42)	Gp B (n: 44)	p
		n(%)	n(%)	
First week	No	40 (95,3)	41(93,2)	0,524
	Yes	2 (4.7)	3 (6,8)	
First month	No	40 (95,3)	41 (93,2)	1.000
	Yes	2 (4.7)	3 (6,8)	
Third month	No	42 (100,0)	44 (100,0)	1.000
	Yes	0 (0,0)	0 (0,0)	
Sixh month	No	42 (100,0)	44 (100,0)	1,000
	Yes	0 (0,0)	0 (0,0)	
First year	No	42 (100,0)	44 (100,0)	1,000
	Yes	0 (0,0)	0 (0,0)	
Second year	No	42 (100,0)	44 (100,0)	1,000
	Yes	0 (0,0)	0 (0,0)	

Gp A: Group A; Gp B: Group B

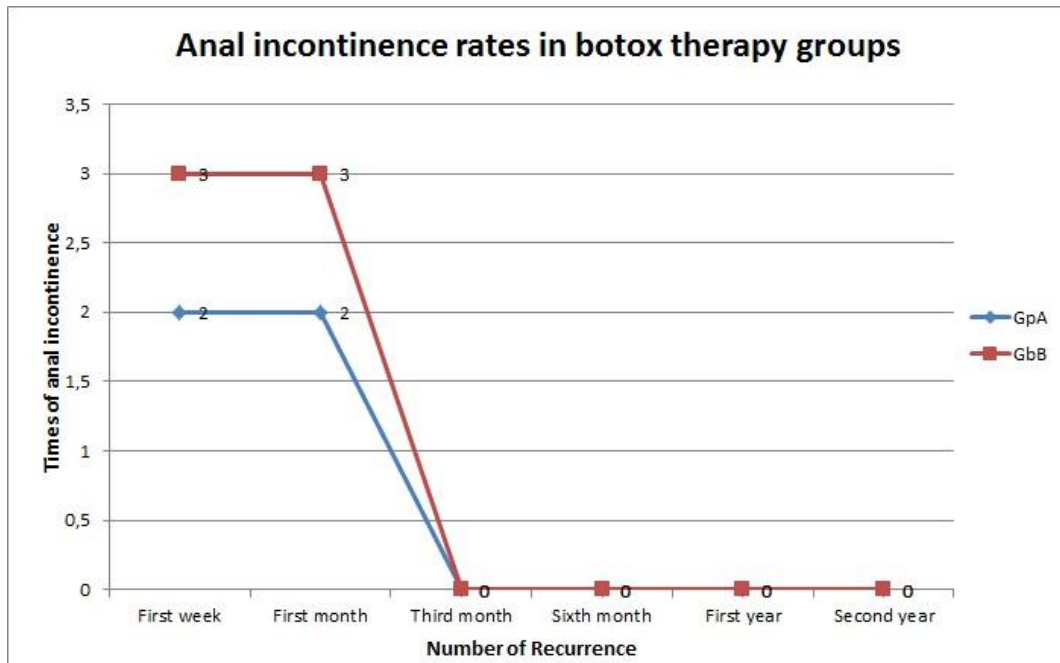


Fig. 2. Shows cases of anal incontinence in Gp A and Gp B

A hematoma occurred in one patient in Gp A after BT, but it was completely recovered after 2 weeks.

4. DISCUSSION

BT has been used in the treatment of CAFs for many years. Maria et al. [6] divided CAF patients into 2 groups. In the first group of patients, saline was injected into the internal sphincter. In the second group of patients; BT was applied. The pain disappeared significantly in patients performing BT compared to the other group [7].

Salem et al. [8] reported that invasive methods in the treatment of CAF are expensive and complication rates are high, and that combined drug therapy is effective, cheap, and has low complication rates. They recommended the combined topical application of nifedipine + lidocaine hydrochloride + betamethasone for 6 weeks [8].

The biggest dilemma in the treatment of CAFs after medical therapy is whether to use surgical methods or non-surgical invasive methods such as BT.

In a study by Topal et al. [9], it was reported that the treatment method in patients with CAF should be selected according to the results of the

measurement of rectal sphincteric pressures. The authors stated that according to the results of this study, it is appropriate to perform internal lateral sphincterotomy (ILS) in only 20% of patients with CAF [9].

In a study by Dinç et al. [10] 60 CAF patients were divided into 2 groups; ILS was performed to the first group and BT was applied to the other group [10]. 3.4% recurrence was observed in cases with ILS and 32% in cases with BT [10]. According to the CCIS in 2 of ILS cases there was gas incontinence and moderate faecal incontinence in 1 ILS patient (3 patients in total) [10]. Another study by Nelson [11] compared the results obtained in patients undergoing ILS and BT. They reported that it should be preferred because patients with ILS have lower recurrence rates [11].

Ebinger et al. [1] performed a metaanalysis of a large CAF series of 3268 cases. As a result of their studies, they reported that ILS was more effective, but the risk of anal incontinence was higher in these patients were followed for at least 2 months [1]. Fitzdowse and colleagues performed fistulotomy and BT in 20 anal fissures and fistula cases [12], and followed patients on average for 10.5 weeks. They reported that symptoms disappeared in all cases. Brisinda et al [13] reported that BT is a useful treatment

method for overactive sphincteric diseases in the gastrointestinal tract by inhibiting neuromuscular transmission.

Meegdenburg manometricly demonstrated that [4], local ischemia occurring in CAFs also causes spasm in the external sphincter. He stated that, when ILS is performed, anal-external sphincter reflex will disappear and therefore anal incontinence will develop more frequently after ILS [4]. For this reason, they reported that, ILS is not an appropriate operation in CAFs and that BT is a more effective treatment method because it resolves spasm in skeletal muscles [4].

In a study by Sahebally et al. [14], 393 CAF cases were divided into 2 groups; BT was applied to one group, and GT applied to the second group. They compared wound healing and recurrence rates. As a result of their studies, they reported that wound healing rates were the same in both groups, but that side effects were less common in the group with BT.¹⁴

Another dilemma in BT is the dosage and method of treatment.

Ravindran et al. in a retrospective study of 158 CAF cases; reported that relapse rates were lower in high-dose (80-100 IU) BT patients than in low-dose (20-40 IU) patients, and there was no anal incontinence in long-term follow-up in both groups [15]. Lin et al. in a meta-analysis performed in 1158 CAF cases, they reported that a low BT dose was as effective as a high dose in wound healing, and that low dose administration paradoxically reduced the risk of recurrence and incontinence [16]. Barberiu et al. administered 25 IU toxins in 126 cases where they performed BT and followed the patients for at least 5 years [3]. They achieved complete or partial recovery in 64.8% of the cases and did not report stool leakage [3].

Barnes et al. reported transient anal incontinence in 7% of 102 cases followed for a mean of 33 months undergoing fissurectomy +100 IU BT, and none of them recurred [17].

Bobkiewitz et al. reported that the effect of BT was not dose-dependent in a meta-analysis on 1577 CAF cases [18]. The authors reported that low-dose BT is as effective as high-dose, and also more cost-effective [18].

In a study conducted by Azadzoi et al it was reported that cavernous nerve can be easily

injured in operations such as transurethral prostatectomy, external sphincterotomy or electrocautery applications performed in the region close to the prostate apex and membranous urethra, and erectile dysfunctions may occur [19].

Therefore, it may be considered risky to perform BT anteriorly or circumferentially, especially in male patients.

In the literature, the long-term recovery rates after the first BT treatment range between 64.8-77.0% [3,9,14,20,21].

In our study, the long-term recovery rate was found to be 77.3 in the 3-way treatment cases (Table 3). According to these results, 3-way low-dose BT is one of the most appropriate methods in CAFs.

In a study of 101 CAF patients undergoing BT by DAT, it was reported that the main cause of early relapses was inadequate treatment, the most common symptom of relapses was pain, relapses were not associated with the dose of BT, and low-dose BT was as effective and cost-effective as high-dose BT [22].

According to the results we obtained in our study, cases with significant difference in VAS values before and after CT in patients with Gp A were found to be statistically lower than Gp B ($p < 0.05$)(Table 5).

Although we applied the same dose of BT in total, performing BT treatment in 3 directions on the internal and external sphincters significantly decreased the recurrence rates in the first week (Table 3-4), (Fig. 1).

It has been revealed that when the insufficient treatment rates are reduced with this method, a more effective BT will be provided. The possible reason for the higher rates of insufficient treatment in low-dose 1-way BT compared to Gp B may be that the toxin cannot reach the sphincters sufficiently.

Although the recurrence rate in Gp B was lower in the 2 year follow-up of the patients, the difference was not statistically significant ($p > 0.05$) (Table 3) (Fig. 1).

3-way low-dose BT method also did not increase anal incontinence rates ($p > 0.05$) (Table 5) (Fig. 2). According to the findings of our study, CCIS 2

in 2 cases in GpA, CCIS 2 in 2 cases and CCIS 3 anal incontinence in one case were observed in Gp B. However, the difference between incontinence rates was not statistically significant ($p > 0.05$).

The anal incontinence rates found in our study were similar to the rates in the literature [10,14].

Therefore, we can say that 3-way low-dose BT therapy does not increase the rates of anal incontinence after treatment.

According to the results of studies on the treatment of chronic anal fissures, the most effective treatment method is still surgical methods [1,3,11,21].

In chronic anal fissures, after BT (at the first control of the patient after application), the patient's pain does not significantly decrease, meaning early relapse or, more accurately, inadequate treatment [22].

This is largely due to the inability of BT to reach the anal sphincters sufficiently. As can be seen from the results obtained in our study, with 3-way low-dose BT treatment, BT reaches more regions in both internal and external sphincters and this risk is eliminated.

An other important advantage of BT therapy over ILS operations is that permanent sphincter failure almost never occurs [3,10,15,16,21,22]. However, due to the high risk of anal incontinence of surgical methods and higher treatment costs, medical treatment and BT can be tried primarily in these cases [8,10,16,18,22].

The limitation of our study is that our study was not prospective and anal manometric measurements were not performed before and after treatment in patients.

The difference of our study compared to similar studies is that, for the first time in the literature, it has been shown that the 3-way low-dose internal and external sphincter BT method reduces the early recurrence (insufficient treatment) rates more than the 1-way treatment method.

5. CONCLUSION

Low-dose BT therapy applied to 3-way internal and external sphincters is a more effective method to prevent early relapses (inadequate treatment) than 1-way low-dose therapy.

3-way BT does not increase the rates of permanent anal incontinence, it is more cost effective than surgical interventions.

However, more studies are needed in order to be able to give more definite conclusions on this issue.

CONSENT

Written consent was obtained from all patients in the study.

ETHICAL APPROVAL

GAU Health Sciences Ethical Commite Approval
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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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