

# A New Botox Therapy Method in Chronic Anal Fissüre

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## Research article

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# Abstract

## Background

Botox toxin treatment(BT) is an effective method in chronic anal fissures(CAF).

However, there are different suggestions regarding the application place and method of BT in the literature. Our aim in this study is to reveal the most appropriate application site and method in BT for CAFs.

## Methods

For this purpose, 2 groups were randomly selected from patients who admitted to our hospital with CAF complaints. In our study, we performed the BT application in different places in different amounts in both groups. After the treatment, we evaluated the recurrence and anal incontinence scores of the patients in certain periods and compared them with each other. The follow-up period for our patients were at least 12 months.

## Results

The recurrence rate was found to be 33.3% in patients in Group A (Gp A) and 19.3% in patients in Group B (Gp B). Patients in Gp A had a statistically significant higher recurrence rate (inadequate treatment) compared to patients in Gp B at the first control, which was performed at first week after treatment( $p<0.05$ ). Anal incontinence rate 3.3% in Gp A, 6.4% in Gp B. The difference between anal incontinence rates according to Cleveland Clinic Incontinence Score (CCIS) was not statistically significant between patients with GP A and Gp B ( $p>0.05$ ).

## Conclusion

3-way BT in internal and external anal sphincters in CAFs, is an effective and low-risk treatment method.

## Introduction

Anal fissures are very common painful proctologic diseases that affects daily life in many uncomfortable and inconvenient ways. The cumulative lifetime incidence is up to 11% throughout life [1]. The most important etiological factor is constipation[2,3]. According to a hypothesis featured by Meegdenburg, trauma is the first factor in the process of formation and development mechanism of CAFs[4]. It has been stated that post-traumatic pain and related internal sphincter pressure increasement are leading to local ischemia and ending up with CAF. The authors reported that CAF-induced mucosal damage also caused spasm in the external sphincter.

A number of treatment methods were applied in CAFs. Topical local analgesic and corticosteroid creams are commonly used as conservative medical treatment (MT). Internal lateral sphincterotomy (ILS),

fissurectomy and anal dilatation are the most commonly used surgical management methods.

Chemical substances that cause temporary paralysis of the external and internal sphincters are; BT, glyceryl trinitrate (GT), and calcium channel blockers[5].

The treatment method scheme has not been standardized yet in CAFs.

There are publications in the literature that give contradictory results regarding the application site and amount of BT therapy in CAF.

In the treatment of BT in CAFs, in case of lowering the pressure in both internal and external sphincter with low dose, reducing the risk of anal incontinence, maximum treatment rate is likely to be achieved.

For this reason, in our study, in order to find the most effective application place and amount in BT application, we performed a newly developed method in a patient group and compared with other group.

## **Materials And Methods**

### **Patients**

Our study was carried out on 61 patients with CAF in Mugla Ortaca Yucelen Hospital between 2017 and 2020. Inclusion criteria were symptomatic anal fissures which had persisted for 6 weeks or longer and failed to respond conservative MT with medical measures. Exclusion criteria were pregnancy, a history of inflammatory bowel disease, or an allergy to BT.

We included patients who admitted to our hospital with CAF complaints in group A and B in random order. We performed BT with separate methods in Group A (Gp A) patients (n = 30) and Group B (Gp B) patients (n = 31).

### **Methods**

The day before BT treatment for patients in both groups, visual analogue scalas (VAS) test with a 100 mm scale to measure the degree of pain sensations and Cleveland Clinic Incontinence Score (CCIS) tests were performed to measure whether there is anal incontinence.

Bowel cleansing was performed with glycerol + sodium citrate rectal tube 1 hour before BT injection. 100 mg petidine HCL was given intramuscularly for analgesia.

We injected a total of 30 units BT in patients Gp A by using 28 gauge needles, only in the posterior direction and only into the internal sphincter.

We injected 5 units, a total of 30 units BT, into the internal and external sphincters in lateral and posterior directions in Gp B patients by using 28 gauge needles.

Patients were discharged on the same day and our follow up period was 12 months at least. Follow up visits were realized at the 1st week, 1st month, 3rd month, 6th month and 12th month.

When the patients came to the controls, VAS and CCIS tests were performed again and they were evaluated to ascertain whether gas-stool incontinence, pain and bleeding were present. Patients with CAF recurrence and anal incontinence have been identified.

Anal incontinence revealed during the control examination of the patients was rated according to the CCIS.

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 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.

## Results

18 of our patients in Group A were female, 12 were male, and the mean age was; 36.9. 17 of the patients in Gp B were female and 14 were male, and the mean age was; 36.3. When the groups were compared in terms of age and sex, the difference was not statistically significant ( $p > 0.05$ ).

Demographic characteristics of our patients were given in (Table 1).

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

		<b>Gp A</b>	<b>Gp B</b>	<b>p</b>
		<b>(n: 30)</b>	<b>(n: 31)</b>	
		<b>n(%)</b>	<b>n(%)</b>	
Sex	Female	18 (60,0)	17 (54,8)	0,441
	Male	12 (40,0)	14 (45,2)	
		<b>Gp A</b>	<b>Gp B</b>	<b>p</b>
		<b>mean±ss</b>	<b>mean±ss</b>	
Age		36,90±5,77	36,32±4,80	0,805
Gp A: Group A				
Gp B: Group B				

The most common anatomic location of CAF was the posterior location, the most common complaint was pain in GpA and Gp B patients.

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

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

	Gp A	%	Gp B	%	Total	%
Pain	30	100	31	100	61	100
Bleeding	12	40.0	10	32.2	22	36.0
Constipation	23	70.6	21	67.7	44	72.1
CAF site						
Posterior	24	80.0	25	80.6	49	80.3
Anterior	4	13.3	3	9.6	7	11.4
Bilateral	2	6.5	3	9.6	5	8.1
Gp A: Group A						
Gp B: Group B						

In the controls performed in patients after BT treatment: in Gp A, CAF did not heal or recur in 10 patients, predominantly at 1st week, and 1 patient developed gas-stool incontinence according to CCIS. In patients in Gp B, it was determined that CAF did not improve or recurred in 6 patients mainly in 1st week, and 2 patients developed anal incontinence with gas incontinence and gas-stool incontinence according to CCIS. The recurrence rate in patients with Gp A was 33.3%, and 19.3% in Gp B, respectively.

Patients in Gp A had a statistically significant higher recurrence rate (inadequate treatment) compared to patients in Gp B at the first control, which was performed at first week after treatment( $p>0.05$ )(Figure 1).

Although relapse rates were higher in Gp A at the end of one-year follow-up, the difference was statistically insignificant( $p>0.05$ ) (Table 3).

Recurrence rates in Gp A and Gp B patients were shown in (Table 3).

Table 3  
Analysis of groups in terms of relapse differences

Relapse or inadequate treatment		Gp A (n: 30)	Gp B (n: 31)	p
		n(%)	n(%)	
1st week	No	22 (73,3)	29 (93,5)	<b>0,035</b>
	Yes	8 (26,7)	2 (6,5)	
1st month	No	20 (66,7)	25 (80,6)	0,171
	Yes	10 (33,3)	6 (19,4)	
3rd month	No	20 (66,7)	25 (80,6)	0,171
	Yes	10 (33,3)	6 (19,4)	
6rd month	No	19(63,3)	25 (80,6)	0,111
	Yes	11(36,7)	6 (19,4)	
1st year	No	19 (63,3)	25 (80,6)	0,111
	Yes	11 (36,7)	6 (19,4)	
Gp A: Group A				
Gp B: Group B				

Gas-stool leakage started in 2nd day after the treatment in a patient with Gp A and ended in the third month. In a patient with gas - stool leakage in Gp B, complaints started in the 2nd day after the treatment and ended in the 3rd month. Gas leakage in the other patient in Gp B started 3rd day after treatment and ended in 3 months.

When analyzed anal incontinence rates according to CCIS in patients:

The differences between the complication findings observed in the first week and first month were not statistically significant ( $p > 0.05$ ). In the third month, sixth month and first year findings, it was observed that the existing complications improved, and it was found that the distribution between the groups showed homogeneity

( $p > 0.05$ )(Table 4).

Table 4  
Distribution of anal incontinence (CCIS) findings in groups

Anal incontinence(CCIS)		Gp A (n: 30)	Gp B (n: 31)	p
		n(%)	n(%)	
1st week	No	29 (96,7)	29 (93,5)	0,513
	Yes	1 (3,3)	2 (6,5)	
1st month	No	29 (96,7)	29 (93,5)	0,513
	Yes	1 (3,3)	2 (6,5)	
3rd month	No	30 (100,0)	31 (100,0)	1,000
	Yes	0 (0,0)	0 (0,0)	
6rd month	No	30 (100,0)	31 (100,0)	1,000
	Yes	0 (0,0)	0 (0,0)	
1st year	No	30 (100,0)	31 (100,0)	1,000
	Yes	0 (0,0)	0 (0,0)	

## Discussion

BT has been used for many years in the treatment of CAFs. Maria et al. divided CAF patients into 2 groups. Saline was injected into the internal sphincter in the first group of patients and BT applied to the 2nd group. Pain was eliminated significantly in patients undergoing BT compared to the other group[6].

Salem et al. reported that invasive methods are expensive and complication rates are high in CAF treatment and combined drug therapy was effective, inexpensive and complication rates are low[7]. They suggested applying nifedipine + lidocaine hydrochloride + betametazone as a combined topical drug for 6 weeks.

MT was given previously to all of our patients, but no remarkable results were obtained.

The biggest dilemma in the treatment of CAFs following medical treatment is whether surgical methods or non-surgical invasive methods such as BT and GT should be applied. In a study by Topal et al. it was reported that the treatment method to be selected in patients with CAF should be given according to the measurement of rectal sphincteric pressures. According to their results, they stated that it was appropriate to perform internal lateral sphincterotomy (ILS) in only 20% of patients with CAF[8].

In a study by Dinç et al. 60 CAF patients were divided into 2 groups; ILS was performed to the first group and BT was applied to the other group. 3.4% recurrence was observed in cases with ILS and 32% in cases with BT. 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)[9]. Another study by Nelson 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[10].

Ebinger et al. 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 who were followed for at least 2 months[1]. Fitzdowse and colleagues performed fistulotomy and BT in 20 anal fissures and fistula cases, and followed patients on average for 10.5 weeks. They reported that symptoms disappeared in all cases[11]. Brisinda et al. reported that BT is a useful treatment method for overactive sphincteric diseases in the gastrointestinal tract by inhibiting neuromuscular transmission[12].

Meegdenburg manometricly demonstrated that local ischemia occurring in CAFs also causes spasm in the external sphincter. He stated that when ILS is performed, anal-external sphincter continuity reflex will disappear and therefore anal incontinence will develop more frequently after ILS. 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 Sahabaly et al., 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[13].

In our study, we preferred to apply BT because ILS had high incontinence rates.

Another dilemma in cases where BT is performed is related to which dose and where to perform. In a retrospective study conducted in 158 CAF cases, Rovindon et al. reported that recurrence rates were lower in patients who underwent high dose (80–100 IU) BT compared to those who performed low dose (20–40 IU), and there was no anal incontinence in long-term follow-up in either group[14]. Lin and al. reported that a low BT dose was as effective as a high dose in wound healing in a metaanalysis performed on 1158 CAF cases, and low dose administration paradoxically reduced the risk of recurrence and incontinence[15]. Barberiu et al. applied 25 IU toxin in 126 cases where they performed BT and followed the patients for at least 5 years. They achieved complete or partial recovery in 64.8 % of cases and reported no stool leakage[3]. Barnes et al. reported a mean of 33 months in 102 cases with fissurectomy

+100 IU BT, 7% reported that they had transient anal incontinence, and no recurrence was observed in any of the cases[16]. Bobkiewitz et al. reported that the effect of BT was not dose-dependent in a meta-analysis on 1577 CAF cases[17].

In our study, we performed a total of 30 IU (low dose) BT. BT treatment in Gp B was carried out into both anal sphincters and 6 localizations in 3 directions.

Our reason in this application, in CAF pathophysiology; is that it plays a role not only in internal anal sphincters but also in the elevation of external sphincter pressure [4].

We thought that if the pressure in both sphincters decreased, the possibility of CAF recovery might increase. The reason why we do BT on internal and external sphincters at 6 different points; since we apply BT at low doses, it is able to greatly decrease both sphincter pressures. To the best of our knowledge, this model has been applied for the first time in the literature.

Recurrences seen in the first weeks after BT in CAFs actually mean inadequate treatment, not recurrence. According to the results we obtained in our study regarding the place of application of BT therapy, lowering the pressure in both external and internal sphincters positively affects the treatment rates. Because in the controls in the first week after treatment, insufficient treatment rates were found statistically lower in patients with Gp B compared to Gp A ( $p < 0.05$ ). At the same time, this application does not increase anal incontinence rates ( $p > 0.05$ )(Table 4).

However, although the recurrence rates were lower in Gp B after one-year follow-up of patients, the difference was statistically insignificant ( $p > 0.05$ ) (Table 3) (Figure 1).

In a study by Azadzo et al., it has been reported to have impaired erectile

function in the destruction of the cavernous nerve from the pelvic plexus in males[18]. In patients with Gp B, we did not inject BT in the anterior direction, as the cavernous nerve is very close to the anal sphincters anteriorly.

As a result of the treatment, CAF and pain resolved in 25 of 31 cases in Gp B(80.7 %). The efficiency rate we obtained in our cases is slightly above the literature findings. According to CCIS, temporary gas incontinence was observed in 1 case, temporary gas and stool incontinence in 1 case (6.4 %). In Gp A, according to CCIS, there was gas-stool leakage in 1 case (3.2%). However, the difference between incontinence rates was statistically insignificant( $p > 0.05$ ).

Whatleus et al. applied high dose (100 IU) BT into anal sphincter in 62 cases

circumferentially. They reported 70% success rates after 3 months of follow-up[19]. Since there is a risk of cavernous nerve damage and erectile dysfunction in male patients, we do not think this application is suitable[18].Pilkington et al. divided the CAF patients into 2 groups. They performed 50 IU unilaterally in

the first group and 50 IU bilaterally in the second group. According to the results of this study, they reported that unilateral 50 IU BT was sufficient to prevent recurrence and efficacy[20].

Recurrence usually occurs within the first month after BT treatment of CAFs.

In fact, these cases are probably not recurrence but inadequate treatment.

In our cases, the most inadequate treatment findings were detected both in Gp A and Gp B in the first week after treatment(Table 3).Daf et al. stated in their study on 101 patients that the most important symptom of relapse cases was that the pain did not pass and that this occurred during the first patient control[21].

Our study has some limitations; the follow-up time of patients is not very long. Our number of cases is not very high.

The superiority of our study over other studies; comparatively, 3-way low-dose BT treatment into both internal and external sphincters was performed by us for the first time in the literature.

## **Conclusion**

In CAF, BT should be tried first, since there is a lower risk of anal incontinence in cases where medical treatment cannot be responded to. Low dose BT in 3 directions both internal and external sphincters is an effective and low-risk method in CAF patient. However, in order to speak more precisely, more studies are needed on this subject.

## **Abbreviations**

CAF: Chronic anal fissure

MT: Medical therapy

GT: Glyceril trinitrate

BT: Botox toxine therapy

ILS: Internal lateral sphincterotomy

VAS: Visual analogue scalas

CCIS: Cleveland Clinic Incontinence Score

## **Declarations**

## **Ethics approval and and consent to participate**

All procedures were conducted in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Written informed consent was obtained from all individual participants included in the study.

This study was approved by the Muğla Sıtkı Koçman University Health Sciences Ethics Committee with the reference number: 20112.

## **Consent for publication**

Not Applicable.

## **Availability of data and material**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## **Competing interests**

The authors have no conflicts of interest to declare.

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Not Applicable

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## **Contributions**

HA and AB initiated study conception and design. AB performed the data collection and acquisition of data. HA and AB performed the data analysis. AB and HA interpreted the data. HA wrote the manuscript. HA edited the manuscript. HA had a role in critical revision. All authors have read and approved the manuscript.

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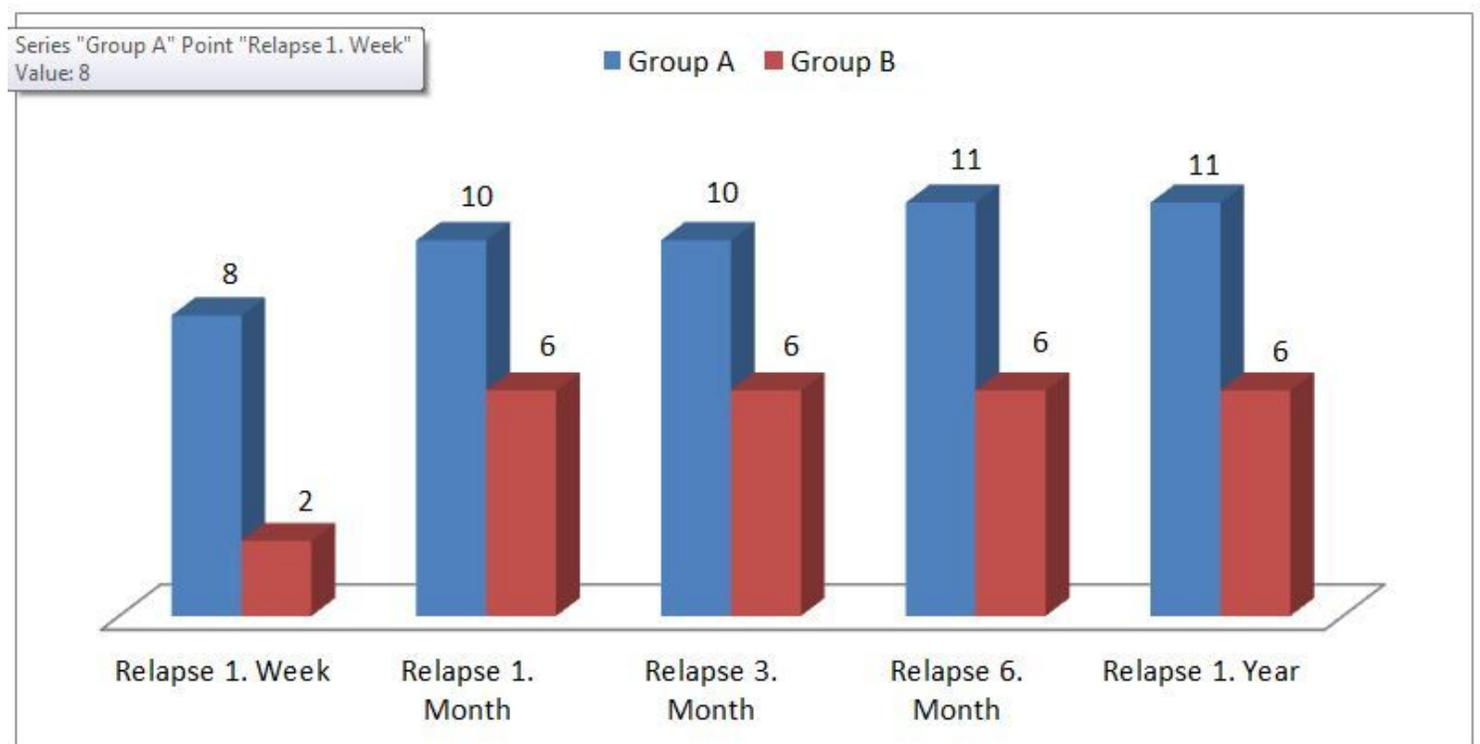
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## Figures



## Figure 1

The distribution of differences between the groups and recurrence findings