International Journal of Colorectal Disease (2025) 40:54
https://doi.org/10.1007/s00384-025-04823-y

RESEARCH

Retrospective analysis on the efficacy of botulinum toxin alone versus combined botulinum toxin and topical diltiazem

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Accepted: 3 February 2025

Abstract

Objective This study aims to compare the short- and long-term outcomes of botulinum toxin (BT) alone versus BT combined with topical diltiazem (TD) in the treatment of chronic anal fissures (CAF).

Design The study is designed as a retrospective analysis, reviewing data from 1296 patients diagnosed with anal fissures who presented to our clinic between 2017 and 2022.

Setting Single center (University hospital).

Patients A total of 217 patients who met the inclusion criteria were analyzed, with 143 receiving BT alone and 74 receiving the combination of BT + TD.

Interventions BT was administered as 100 IU injected into four quadrants. TD was applied twice daily for 10 days immediately following the BT injection.

Main outcome measures Primary outcome measures were fissure healing at 2 months and days to pain-free defecation. Secondary outcome measures were complete healing and recurrence rates at 24 months.

Results There were no significant differences in demographic characteristics and symptom duration between the BT and BT + TD groups. The median time to pain-free defecation was 7 days across the entire series, with no statistical difference between groups. At 2 months, complete healing was observed in 74.4% of patients, with no significant difference between groups: 74.8% for BT and 74.3% for BT + TD. During a median follow-up of 53 (22–101) months, a recurrence rate of 26.3% was observed, and TD showed no effect on complete healing and recurrence rates.

Limitations The most significant limitation of our study is its retrospective design and the absence of a placebo control for TD.

Conclusion The study demonstrates that BT is an effective and safe treatment for CAF, with or without the addition of TD. The combination therapy did not show superior outcomes.

Keywords Anal fissure · Botulinum toxin · Topical diltiazem

Introduction

Anal fissure is a common and painful condition characterized by a tear in the lining of the anal canal. It often presents with symptoms such as pain during defecation and rectal bleeding, significantly affecting the quality of life of those afflicted. Chronic anal fissures (CAF) are when these symptoms last longer than 6 weeks and approximately 40% of patients who present with acute anal fissures progress to CAF [1]. Although the exact pathophysiology is unknown, increased anal tone and decreased anodermal blood flow and local ischemia are the mechanisms held responsible. Based on this pathophysiology, the main aim of CAF treatments has been to relax the internal anal sphincter (IAS). In non-surgical management, glyceryl trinitrate and topical diltiazem (TD) demonstrate similar healing rates, approximately 50–70%, with late recurrence rates between 9 and 18% [2, 3]. Botulinum toxin (BT) shows comparable healing rates of 62–66%, with a recurrence rate of 41% [3, 4]. This

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Published online: 26 February 2025

suggests that about half of the patients require additional treatments.

Lateral internal sphincterotomy (LIS) is considered the gold standard for treating CAF, achieving healing rates over 90%. However, it carries a 30–45% risk of minor fecal incontinence and a 0.4–22% risk of permanent incontinence [5, 6]. While the reported outcomes for healing and recurrence with BT are not as effective as those achieved with LIS, the incontinence rates are significantly lower (0–14%), and any impact on continence is transient [4, 7]. This concern has led to the exploration of adjunctive therapies to enhance BT. A limited number of studies have investigated the combined efficacy of BT and topical treatments, involving small patient cohorts and yielding heterogeneous results [8–10].

This study aims to retrospectively compare the short- and long-term outcomes of BT alone versus BT combined with TD in the treatment of CAF in a single center series.

Methods

This study was approved by institutional ethics committee (Approval number: E-10840098–772.02–786) and registered to clinicaltrials.org (NCT05797220). The prospectively recorded data of 1296 patients who presented to our outpatient clinic with a diagnosis of anal fissure from October 2017, when anal BT treatment began in our clinic, to June 2022, when we switched our BT protocol from 100 to 50 IU, were reviewed.

Our treatment algorithm was as follows: For patients with acute anal fissure and CAF who have not received prior treatment, our first-line recommendation includes a 6-week regimen of TD, a high-fiber diet, laxatives, and warm showers. In patients who do not respond to this initial treatment or experience recurrent anal fissures after the first-line treatment, our second-line approach is the application of BT. Patients with non-healing and recurrent fissure after the first BT injection were offered either a second BT injection or LIS.

The diagnosis of CAF and healing was made in all patients based on history and rectal examination. Anal tone was assessed subjectively by the surgeon. Resolution of all symptoms with complete epithelization or granulation of the fissure examined by the principal investigator (CA) was defined as fissure "healing." Persistence of pain or bleeding regardless of fissure epithelization 2 months after BT injection was defined as "non-healing." The return of the symptoms after complete relief is defined as "recurrence."

Inclusion criteria were patients older than 18 years old with CAF who received 100 IU BT through four quadrants, with or without TD treatment. Previous anal surgery (lateral internal sphincterotomy, hemorrhoidectomy, anal fistula procedures), inflammatory bowel diseases, accompanying anorectal disease (hemorrhoids, anal fistula, abscess), BT injection within 1 year before recruitment, atypical fissures (lateral or multiple; or painless or low-pressure fissures), comorbidities including AIDS, sexually transmitted disease, tuberculosis, leukemia, and pregnancy were exclusion criteria. Since 2022, our BT protocol was adjusted to 50 IU administered through two quadrants, and all patients receiving this updated protocol were excluded from the study. Detailed information about the outcomes and complications of the treatment options was provided to the patients, and written consent was obtained for the procedures and the use of their data in research.

Botulinum toxin application

The procedures were performed at outpatient clinic without anesthesia. Lyophilized 100 IU BT Type-A (BOTOX, Allergan, CA, USA) was applied after diluted with 1 cc saline. A 26-G injector was used to inject 25-unit toxin in every four quadrants, to the alignment of clock 12, 3, 6, and 9 to internal anal sphincter.

Topical diltiazem cream

After BT injection, topical 2% diltiazem hydrochloride 20 Mg/G rectal gel (Locafen, Ilko Ilac, Konya, Türkiye) was prescribed, applied two times per day starting immediately after BT injection for 10 days (two doses of 1 g each per day). No selection criteria were used when recommending this treatment; it was randomly suggested to some patients during the 2021–2022 period, as the surgeon believed it might enhance the efficacy of BT. In patients who received a second BT injection, TD administration was performed in the same manner as during the first injection.

Outcome measures

Primary outcome measures were fissure healing at 2 months and days to pain-free defecation.

Secondary outcome measure was complete healing and recurrence rates at 24 months.

Follow-up

All patients were examined in the outpatient clinic on the 3rd and10th days and at 1 and 2 months post-procedure. Symptoms, fissure epithelization, complications (hematoma/ecchymosis, abscess, incontinence), and adherence to TD treatment were evaluated. The examination was performed by inspection alone, without the use of anoscopy. Incontinence was not routinely scored; the Cleveland Clinic Incontinence Score (CCIS) was used to assess the severity only when the patient reported any symptoms.

At the end of the 2 months, patients with complete healing were advised to return to the clinic if they experienced any symptoms. All patients were contacted by phone at 6, 12, 24, 48, and 60 months to inquire about recurrence. Patients who reported symptoms during the phone inquiry were invited for an examination.

Statistical analysis

Data obtained in this study were statistically analyzed using the SPSS version 26.0 (SPSS, Statistical Package for Social Sciences, IBM Inc., Armonk, NY, USA) software. Variables are expressed as mean and standard deviation or median and range. Chi-square or Fisher exact tests were used in comparisons between categorical variables. The suitability of continuous variables to normal distribution were evaluated with histograms and probability graphs and Kolmogorov–Smirnov and Shapiro–Wilk tests, *t*-test, and Mann–Whitney *U* and Kruskal–Wallis tests were used in comparisons. A value of $p < 0.05$ was considered statistically significant.

Results

Among 1296 patients with CAF, 457 had BT injection and 217 those fulfilling inclusion criteria were included in the analysis (Fig. 1). Botulinum toxin was administered alone to 143 (65.9%) patients, while a combination of BT and TD was given to 74 (34.1%) patients. Mean age was 34.4 ± 10.6 and 157 (72.4%) patients were female. Demographic

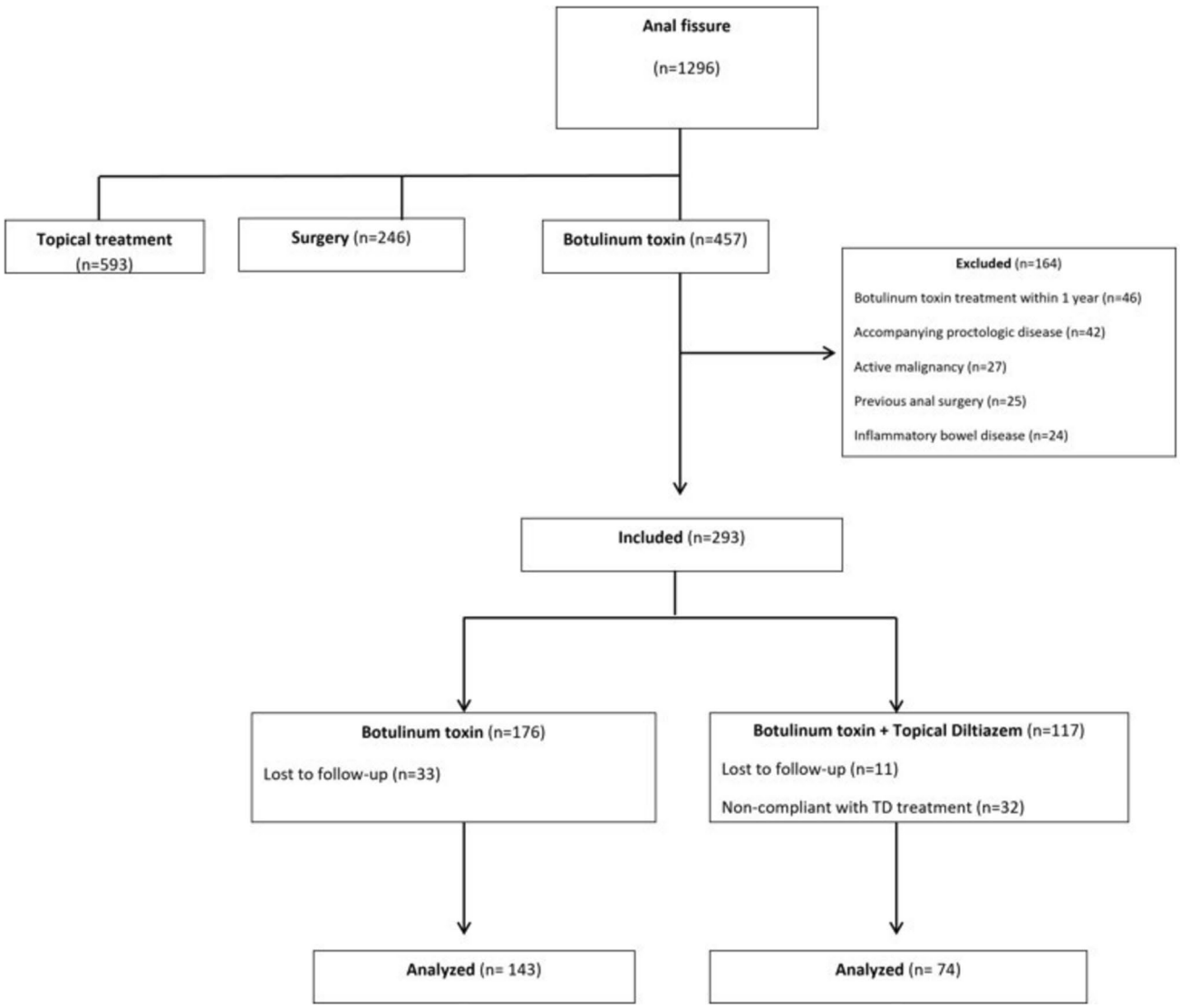

Fig. 1 Flow diagram of the study

characteristics and symptom duration were similar between BT and BT + TD groups (Table 1).

The median time to pain-free defecation was 7 (3–27) days across the entire series and was similar in both groups ($p = 0.088$). Two months after the BT injection, complete healing was observed in 162 (74.7%) patients: 107 (74.8%) in BT group and 55 (74.3%) in BT + TD group ($p = 530$) (Table 2).

Of the 55 (25.3%) non-healing patients, 27 received a repeat BT injection and 28 underwent LIS. The number of non-healing patients after first BT injection was 36 (25.2%) in BT group and 19 (25.7%) in BT + TD group, with no statistically significant difference between the groups ($p = 530$) (Table 2). Among those who received a repeat BT injection, 11 (5.1%) patients still did not respond to the treatment and offered LIS.

There were no major complications in the series. Complications included temporary minor incontinence in six (2.7%) patients (mean CCIS: 3.4 ± 1.1), one abscess managed on an outpatient basis with drainage and three hematomas that resolved with conservative management. There were no differences regarding complications between the two groups (Table 2).

During a median follow-up of 53 (22–101) months, 57 (26.3%) recurrences were observed as well as 11 (5.1%) non-healing after BT injections. Patients in BT + TD group had significantly shorter median follow-up when compared to BT group (25 vs 89 months, $p < 0.001$) (Table 3). Eventually, 149 (68.7%) patients had complete healing with BT treatment and 60 (27.6%) underwent LIS. Topical diltiazem showed no effect on complete healing and recurrence rates (Table 3).

Table 1 Demographic and clinical characteristics of the patients and comparison between groups

n (%)	Total (*n* = 217)	BT (*n* = 143)	BT + TD (*n* = 74)	*p*
Age (years, mean ± SD)	34.4 ± 10.6	34.6 ± 11.1	34 ± 9.6	0.706
Gender				0.099
Female	157 (72.4%)	108 (75.5%)	49 (66.2%)	
Male	60 (27.6%)	35 (24.5%)	25 (33.8%)	
Symptom duration (month, median, range)	6 (2–36)	6 (2–36)	6 (2–27)	0.258

TD topical diltiazem, *SD* standard deviation

Table 2 Primary outcome measures and complications

n (%)	Total (*n* = 217)	BT (*n* = 143)	BT + TD (*n* = 74)	*p*
Pain-free defecation (days, median, range)	7 (3–27)	7 (3–27)	8 (3–27)	0.088
Fissure healing at 2 months	162 (74.7%)	107 (74.8%)	55 (74.3%)	0.530
Non-healing after 1st BT injection	55 (25.3%)	36 (25.2%)	19 (25.7%)	0.530
Non-healing after 2nd BT injection (*n* = 27)	11 (5.1%)	9 (6.3%)	2 (2.7%)	0.083
Incontinence	6 (2.7%)	4 (2.8%)	2 (2.7%)	-
Abscess	1 (0.4%)	1 (0.6%)	0	-
Hematoma	3 (1.3%)	2 (1.4%)	1 (1.3%)	-

TD topical diltiazem, *BT* botulinum toxin

Table 3 Long-term healing and recurrence rates

n (%)	Total (*n* = 217)	BT (*n* = 143)	BT + TD (*n* = 74)	*p*
Follow-up (months, median, range)	53 (22–101)	89 (22–79)	25 (22–29)	< 0.001
Overall healing after BT				0.129
Complete healing	149 (68.7%)	102 (71.3%)	47 (63.5%)	
Non-healing	11 (5.1%)	9 (6.3%)	2 (2.7%)	
Recurrence	57 (26.3%)	32 (22.4%)	25 (33.8%)	
LIS	60 (27.6%)	35 (24.5%)	25 (33.8%)	0.099

TD topical diltiazem, *BT* botulinum toxin, *LIS* lateral internal sphincterotomy

Discussion

This retrospective analysis compared the efficacy of BT alone versus a combination of BT and TD in treating CAF and indicated that while both treatment modalities are effective, the addition of TD did not significantly enhance the healing rates or reduce recurrence compared to BT alone. The primary outcome of fissure healing at 2 months was similar between the two groups, with approximately 74% of patients achieving complete healing. The median time to pain-free defecation was also comparable, indicating that the addition of TD does not expedite symptomatic relief.

The first study evaluates the combination of BT and TD randomized patients into two groups: partial LIS ($n = 50$) and BT + TD ($n = 49$) [8]. Over a 1-year follow-up, the overall healing rates were 65% in the BT + TD group and 94% in the partial LIS group ($p < 0.001$). However, for patients with CAF lasting ≤ 12 months, both groups achieved a 100% healing rate. The complete healing rate in our series was 63.5% at the end of a 24-month follow-up. Due to the small number of patients, we did not conduct an analysis based on the duration of symptoms. In a previous study of ours, we demonstrated that BT had lower recurrence rates in patients with shorter duration of symptoms [11]. Although these studies do not provide information about the primary effect of TD, they may guide further research in selecting the appropriate patient group for BT.

In their double-blind randomized trial, Herreros et al. [9] evaluated the effects of BT followed by either TD or placebo gel over 12 weeks, involving 25 patients in the TD group and 30 in the placebo group. They observed complete healing in 37.1% of the TD group and 31.4% of the placebo group ($p = 0.61$). The TD group reported better symptomatic relief, with significantly lower anal pain and bleeding scores at 12 weeks compared to the placebo group ($p < 0.05$). Both groups experienced a significant reduction in anal pressures, and approximately 30% of participants reported minor and temporary incontinence, with no significant difference between the groups. At 24 months, the relapse rate was 69.2% in the TD group and 54.5% in the placebo group ($p = 0.67$). The study's complete healing and recurrence rates appear poor compared to other literature and our findings. The small cohort size and patient loss during follow-up along with the 20 IU dose of BT used in the trial should be noted. Also, complete healing was determined by video assessment in this study and scarring might be wrongly judged as persisting fissure. Unlike this study, we found similar durations of pain-free defecation between the two groups. While the incontinence rate in this study was 30%, it was less than 3% in our study. This rate might be misleading, as we did not actively inquire about incontinence unless reported by the patients.

In studies combining topical treatments with BT, the duration of topical application varies between 4 to 12 weeks [8–10]. Our hypothesis when applying TD was to utilize its sphincter-relaxing effect during the initial 10-day period before BT takes full effect. In our algorithm, after first topical treatment failure, we directly proceed to BT without reattempting topical treatments due to the extended duration of therapy and challenges with patient adherence. Therefore, we do not believe that extending the treatment beyond 10 days would have altered the outcomes. There are no recommendations in current guidelines regarding the combination of BT with topical treatments as well as the duration of TD application [12].

In a recent meta-analysis of medical management options for CAF, healing rates are 50–65% for BT, 78% for TD, 66% for nitrates, and 47–81% for nifedipine [13]. Recurrence rates were 23% for BT, 15% for TD, 9.5–41% for nitrates, and 7.4% for nifedipine. Adverse events were seen in 5.3% after BT, 11% after TD, 38–58% after nitrates, and 6% after nifedipine. Adverse events in our series were seen in 4% of the patients. During the median follow-up period of 53 (22–101) months, recurrence was observed in 26.3% of patients, with no significant difference between the BT and BT + TD groups. However, considering that we started the BT + TD application in 2021, the follow-up period for the TD group is significantly shorter, and recurrence may increase in this group as the follow-up period extends. In any case, it is clear that additional TD treatment does not improve recurrence rates.

Limitations

The most significant limitation of our study is its retrospective design and the absence of a placebo control for TD. Additionally, when assessing pain-free defecation post-procedure, patients were only asked on which day they experienced pain-free defecation; the visual analogue scale (VAS) was not used. Incontinence was also not routinely assessed using a valid scale. Another weakness is that TD was applied randomly to some patients for a certain period starting from 2021 without specific criteria, which could introduce significant bias. Therefore, the follow-up period for two groups was not even. Any potential adverse events in particular to TD were not questioned.

Conclusion

Our study demonstrates that BT is an effective and safe treatment for CAF, with or without the addition of TD. The combination therapy did not show superior outcomes. Future research should focus on identifying patient subgroups that may benefit from adjunctive therapies and exploring other potential combinations to optimize CAF management.

Author contribution Cigdem Arslan: Conception and design of the study, the acquisition of the data, analysis, and interpretation of the data, writing the manuscript. Emre Karagoz: The acquisition of the data, analysis, and interpretation of the data Caglar Pekuz: The acquisition of the data, analysis, and interpretation of the data Yasemin Yildirim: The acquisition of the data, analysis, and interpretation of the data Mustafa Oncel: Conception and design of the study, revising the work critically, final approval of the version to be published.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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