



Clinical Trial Combining Botulinum Toxin A Injection and Fissurectomy for Chronic Anal Fissure: A Dose-Dependent Study

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Abstract

Background Anal fissure is a common surgical disease that is usually treated conservatively. The golden surgical treatment for anal fissure is lateral internal sphincterotomy, but it may result in multiple complications. Therefore, other treatment methods have recently been introduced, and one of them is the injection of botulinum toxin A (BTA) and fissurectomy. In the present study, we aim to evaluate the effectiveness of the combination of fissurectomy and BTA injection in the treatment of chronic anal fissure by single surgeon.

Materials and Methods The present is a non-randomized prospective cohort study conducted by a single surgeon in Saudi Arabia. Our sample was composed of 116 female patients, with mean age of 36.57 ± 11.52 years, who presented to our Surgical Outpatient Clinic with chronic anal fissure between October 2015 and July 2020, and were treated with BTA injection combined with fissurectomy. They were followed up for 1, 2, 3, 4, and 8 weeks, and after one year to evaluate the efficacy and safety of the treatment. The main outcomes analyzed were symptomatic relief, complications, recurrence, and the need for further surgical intervention.

Results The treatment with BTA injection combined with fissurectomy was effective and safe in 115 patients (99.1%) at 1 year of follow-up. A total of 5 patients experienced recurrence at 8 weeks, which resolved completely with pharmacological sphincterotomy, and 12 patients experienced minor incontinence, which disappeared later.

Conclusion In total, 70 units of BTA injection combined with fissurectomy is a suitable second-line treatment of choice for chronic anal fissure, with a high degree of success and a low rate of major morbidity.

Keywords

- ▶ anal fissure
- ▶ chronic
- ▶ botulinum toxin
- ▶ sphincterotomy

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Introduction

Anal fissure is a common surgical disease that is usually treated conservatively, and spasms of the internal anal sphincter play a major role in its pathogenesis. The golden surgical treatment is lateral internal sphincterotomy, but patients submitted to the procedure may develop postoperative complications in terms of gas or stool incontinence.^{1,2} Therefore, other treatment modalities have recently been introduced, and one of them is the injection of botulinum toxin A (BTA) and fissurectomy.^{3,4} In the present study, we aim to evaluate the effectiveness of the BTA injection and fissurectomy for the treatment of chronic anal fissure.

Materials and Methods

The present is a prospective study (nonrandom simple sampling) with a series of 116 patients who presented to our Surgical Outpatient Clinic at Riyadh, Saudi Arabia with anal fissure between October 2015 and July 2020. The inclusion criterion was all patients with chronic anal fissure, which was defined as: posterior or anterior fissure with clinical evidence of an increased anal resting tone per physical exam with persistent symptoms, including pain and bleeding after defecation, for more than eight weeks, despite the conservative treatment. The exclusion criteria were the presence of concomitant anal abscesses or fistulas, fissures associated with different pathologies such as inflammatory bowel disease, history of use of medications that could interfere with BTA, such as aminoglycosides, baclofen or diazepam, and pregnant women.

The goal of the study was the evaluation of complete healing after BTA injection combined with fissurectomy, comparing the dose-dependent efficacy and complications regarding 50 units, 70 units, and 100 units of BTA. The treatment was considered successful if the patients experienced an absence of symptoms. The secondary variables were the latency of the effect, defined as the interval between the day of the treatment and the onset of symptomatic relief, follow-up, the rate of incontinence, and the time until resolution (in days) in terms of the different doses of BTA.

Baseline Assessment and Operative Technique

All patients underwent a pretreatment evaluation, including a clinical examination. The whole sample was submitted to the conservative treatment (sitz bath, stool softener, and pharmacological treatment with diltiazem), underwent the same evaluation performed at baseline. All the patients were operated by the main author (Alsaleh) of the present study.

The procedure was performed as a day-case surgery. Under laryngeal mask airway anesthesia, with the patient in the lithotomy position, 50, 70, or 100 units of BTA (Botox, Allergan, Dublin, Ireland) were diluted in 1 mL of normal saline. The solution injected into the internal anal sphincter using a small 27-gauge needle. The injection was divided in half: half of the amount was divided once more, and administered at 3 o'clock nad 9 o'clock, and the other half was injected around the fissure. Fissurectomy was performed

with a sharp by removing the edges of the fibrotic fissure and unhealthy granulation tissue at the base in all patients.

Clinical Care, Follow-up and Outcome Measures

All patients were sent home on laxative and oral analgesia within 24 hours of the procedure, and they were advised to take regular warm sitz baths, to maintain a high-fiber diet, and to increase their fluid intake. All patients were evaluated in the outpatient clinic approximately in postoperative weeks 1, 2, 4, and 8. In each postoperative visit, the symptoms were reviewed in terms of pain (onset and degree of improvement), PR bleed, and presence of incontinence (gas, liquid, or stool). The healed patients were followed up clinically until 1 year postoperatively, when their history was taken and they underwent a physical examination.

Statistical Analysis

Descriptive statistics for the study sample were expressed as frequencies and relative frequencies (percentages) for the categorical variables, while means and standard deviations were used to express the numerical variables. The Chi-squared test and the Fisher exact test were used to assess the following correlations: between incontinence and the location of the fissure; age and complete resolution of symptoms; the dose of BTA with age and the time the pain started to improve and completely disappeared (in term of 7, 14, 21, and 28 days); age and time of resolution of symptoms; these tests were also used to compare the groups. The statistical analysis was performed using the Statistical Package for the Social Sciences (IBM SPSS statistics for Windows, IBM Corp., Armonk, NY, United States) software, version 26.0, and values of $p < 0.05$ were considered statistically significant.

Results

The sample was composed of 116 female patients between 20 and 70 years of age (mean: 36.57 years; standard deviation [SD]: ± 11.52 years). The baseline characteristics are shown in **Table 1**. The 3 groups (those who received 50, 70, or 100 units) were comparable in terms of age and the duration of symptoms.

No immediate complications were observed during the procedure. The latency of the effect lasted from 7 to 14 days in 48.2% of the patients. The relationship between age and the time until the resolution of symptoms, which was not statistically significant ($p < 0.05$) is shown in (**Table 2**).

There was a significant correlation between the improvement in pain and the dose of BTA: pain started to improve more rapidly with 50 units in less than 7 days, and with 70 units in less than 2 weeks; however, there was no relationship between the dose of BTA and complete disappearance of pain (**Table 3**).

Neither was there any relationship between the site of the fissure and incontinence, nor between the complete resolution of symptoms (in days) and overall incontinence or the types of incontinence (**Table 4**). About half (18.96%) of the patients had skin tags in which they were excised. After 21 days, the patients who had recurrent symptoms received

Table 1 Demographic and clinical variables of the study sample

Demographic and clinical variables	50 ± 10 units of botulinum toxin A: N(%)	70 ± 10 units of botulinum toxin A: N(%)	100 units of botulinum toxin A: N(%)	Total number of patients
Age				
• 20–40 years	27(58.7)	43(76.8)	5(35.7)	75(64.65)
• 41–60 years	17(37.0)	12(21.4)	7(50.0)	36(31.03)
• > 60 years	2(4.3)	2(3.6)	1(7.1)	5(4.3)
Mean age (± standard deviation)	37.44 (± 12.0)			
Location of the fissure				
• Posterior	34(73.9)	40(71.4)	8(57.1)	84(72.4)
• Anterior	7(15.2)	4(7.1)	1(7.1)	12(10.4)
• Posterior and anterior	5(10.9)	12(21.4)	3(21.4)	20(17.0)
• Skin-tag excision	10(21.7)	11(19.6)	1(7.1)	22(19.1)
Postoperative diltiazem				
• Yes	2(4.3)	3(5.4)	0(0.0)	5(4.3)
• No	44(95.7)	53(94.6)	14(100.0)	111(96.5)

Table 2 Correlation between age and time until the resolution of symptoms

Age (years)	< 7 days: N(%)	7–14 days: N(%)	15–21 days: N(%)	> 21 days: N(%)	Chi-squared test	p-value
20–40	2(2.7)	45(60.8)	11(14.8)	16(21.6)	3.55	0.0753
41–60	2(5.5)	17(47.2)	8(19.4)	10(27.7)		
> 60	0(0.0)	2(40.0)	1(20.0)	2(40.0)		
Total	4	64	20	28		

Table 3 Correlations regarding the dose of Botox and age and the time pain started to improve and completely disappeared in terms of 7, 14, 21, and 28 days

Pain improvement and age distribution of the population	50 ± 10 units of botulinum toxin A: N(%)	70 ± 10 units of botulinum toxin A: N(%)	100 units of botulinum toxin A: N(%)	Chi-squared test	p-value
Time until the pain started to improve					
• < 7 days (76 cases)	10(13.1)	59(77.6)	7(9.2)	13.4328	0.0366*
• 7–14 days (34 cases)	6(17.6)	22(64.7)	6(17.6)		
• 15–21 days (1 case)	0(0.0)	0(0.0)	1(100)		
• > 21 days (5 cases)	1(20.0)	4(80.0)	0(0.0)		
Time until the pain completely disappeared					
• < 7 days	4(8.69)	5(8.92)	0(0.0)	1.2617	0.973
• 7–14 days	27(58.69)	33(76.74)	8(57.14)		
• 15–21 days	6(13.04)	3(6.97)	1(7.14)		
• > 21 days	1(2.17)	2(3.57)	0(0.0)		
Age in years					
• 20–40	27(58.7)	43(76.8)	5(35.7)	7.617	0.106
• 41–60	17(37.0)	12(21.4)	7(50.0)		
• > 60	2(4.3)	2(3.6)	1(7.1)		

Note: * Statistically significant ($p < 0.05$).

Table 4 Correlations regarding incontinence and location of fissure, age, and complete resolution of symptoms (in days)

Location of the fissure and age distribution	No incontinence: N(%)	Gas incontinence: N(%)	Liquid incontinence: N(%)	Chi-squared test	p-value
Location of the fissure					
• Posterior	77(91.6)	7(8.33)	0	13.2947	0.0509
• Anterior	9(75.0)	3(25.0)	0		
• Posterior-anterior	18(90.0)	0(0.0)	2(10)		
Age in years					
• 20–40	58(67.44)	1(10)	0	33.7434	0.00441*
• 41–60	25(29.06)	6(60)	2(100)		
• > 60 years	3(3.48)	3(30.0)	0(0.0)		

Note: *Statistically significant ($p < 0.05$).

diltiazem for 1 month in total 5 patients with the complete resolution of symptoms after 1 month. None of these 5 patients has received 100 units of BTA. Symptomatic improvement was observed in 115 patients (99.1%) in 1 year of follow-up. Only one patient showed recurrence after 6 months; the postdefecation bleeding disappeared in every other patient who had previously reported it at 4 weeks.

Most patients (104; 89.6%) did not experience postprocedure incontinence, while 10 (8.6%) of them had gas incontinence, and 2 (1.72%) had the liquid type, but none had stool incontinence. All 116 (100%) patients recovered in 1 month, and the mean time until the relief of the symptoms of postdefecatory pain after the injections was of 7 to 14 days. However, 5 patients experienced recurrence, which treated by pharmacological sphincterotomy (diltiazem 2%).

There was a statistical correlation between incontinence and age: there were fewer cases of incontinence among younger patients (► **Table 4**). However, no relationship was observed between the site of the fissure and incontinence, neither between the complete resolution of symptoms (in days) and overall incontinence or the types of incontinence (► **Table 4**). When comparing the 3 groups (50, 70 and 100 units), there was superior result with the use of 70 units: complete resolution of symptoms in 7 to 14 days by 76.74% of the patients in this group; for the groups who received 50 and 100 units, this rate was of 58.96% and 57.14% respec-

Table 5 Clinical characteristics and dose of botulinum toxin A

Clinical variables	50 ± 10 units of botulinum toxin A: N(%)	70 ± 10 units of botulinum toxin A: N(%)	100 units of botulinum toxin A: N(%)	Total number of patients
Type of incontinence				
• Gas	1(10.0)	5(50.0)	4(40.0)	10(8.6)
• Liquid	0	0	2(100)	2(1.72)
Duration of the incontinence				
• 7 days	0	3(25)	0	3(25)
• 30 days	1(8.3)	1(8.3)	6(50.0)	8(66.6)
• 90 days	0	0	1	1(8.3)

Table 6 Time until the pain completely disappear

Days	Patients: N(%)
• ≤ 7 days	17(14.2)
• 14 days	69(59.4)
• 21 days	27(23.2)
• 28 days	3(2.5)

tively. The rate of incontinence was also lower among the 70-unit group (82.1%) (► **Table 5** and ► **Table 6**).

Discussion

The treatment of anal fissures was chaotic until 1951, when Eisenhammer proposed the performance of partial lateral internal sphincterotomy (LIS), and it has since been considered the standard treatment for anal fissure.⁵ However, it has a noticeable risk of permanent fecal incontinence (1%), which may occur many years after the procedure, if the sphincter is exposed to further damage, such as during a complicated delivery or anal surgery.⁶

Since BTA injection was introduced as a potential treatment for anal fissures in 1993, several studies^{6–8} have been conducted to prove effectiveness, with variable rates of

healing and recurrence. Botulinum toxin A works by inhibiting the release of acetylcholine within the internal sphincter to cause chemical sphincterotomy, which helps to heal the anal fissure.⁷ On the other hand, fissurectomy alone has been advocated in children and adults in some area⁹ it enhances healing by removing the edges of the fibrotic fissure; nevertheless, it does not address the hypertonicity of the anal sphincter. There are various studies¹⁰ describing the effectiveness of the combination of fissurectomy and BTA to achieve an excellent healing rate of 79% after 1 year.

Our population was selected to be all female, as they are at a higher risk of developing incontinence¹¹ due to the facts that women are exposed to a unique set of risk factors during pregnancy and childbirth.

A total of 84 (72.4%) of our patients displayed posterior fissure, and 15 (12.9%) patients were had anterior fissures, which is consistent with the reports in the literature,¹²⁻¹⁴ in which 90% of all fissures occur posteriorly, and 10%, anteriorly, and less than 1% of the patients have both anterior and posterior fissures. However, in the present study, there was a higher number of patients (17) with both anterior and posterior fissures in comparison to the reports in the literature.

In comparison with the study by Barnes et al.,¹⁵ who used a similar technique, combining fissurectomy and Botox, the present study has a larger sample, and we were able to achieve an overall healing rate of 99.1% (115 patients) at 1 year without resorting to surgical sphincterotomy. There was only one recurrence in the first year follow-up period, a figure slightly more favorable than that reported by Barnes et al.¹⁵ It is noteworthy that these authors used in all patients 100 units injected into the base of the fissure, whereas we injected half of the amount at the fissure and the other half, in two doses administered at 3 o'clock and 9 o'clock, for we believe this relaxes the whole sphincter, which could be the reason behind our higher rate of success.

There is a considerable variation in the literature in regard to the most effective site for the BTA injection. Our technique is similar to what was reported by Sileri et al.,¹⁶ who used only 25 units, and reported a healing rate of 81.8%. In comparison to our data, injecting patients with a higher dose of BTA, such as 100 units, did not yield a superior result in terms of shortening the time until symptom resolution neither the onset when compare with 50 or 70 units where all happen > 7 days 87% versus 83.9% versus 85.7% for the groups who received 50,70, and 100 units of BTA respectively. However, it yielded superior results to the other groups (50 and 70 units) in terms of lack of recurrence in the 100-unit group, but with more incidence of liquid incontinence.

In the present study, we observed a rate of incontinence in the immediate postoperative period of 10.3%. This appears to be on the upper limit of the range reported (4% to 7%) in previous studies,^{14,17,18} and is likely due to the technique of injection in 3 areas. However, the incontinence was transient, and all patients reported normal continence by the 8th week of follow-up. According to our data, when we compare the 3 groups, there was superior result with the use of 70 units, with complete resolution of the symptoms in 7 to

14 days in 76.74% of the patients, compared with no more rate of incontinence at rate of 82.1%.

Though Bobkiewicz et al.,¹⁹ in tcosheir meta-analysis, claim the efficacy of the treatment is not dose-dependent, in our experience, we probably observed a higher success rate because all of our patients were female. Soltany et al.¹⁶ have also identified a superiority of the results among female patients. Our results compare favorably with those published in the literature: 94.83% of our sample achieved resolution of symptoms and complete healing of the fissure(s). Only one case of recurrence was observed after complete healing, and this particular patient revealed later non-compliance with the conservative therapy and bad eating habits. There were five cases of recurrence in a mean follow-up of eight weeks, and they were completely resolved with the use of diltiazem.

Conclusion

In conclusion, 70 units of BTA injection combined with fissurectomy is a suitable second-line treatment of choice for chronic idiopathic anal fissure which is not associated with other anal conditions. Because of the high rate of success and low rate of major morbidity, the procedure may be considered a straightforward, safe, and effective treatment for anal fissure.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms.

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Conflict of Interests

The authors have no conflict of interests to declare.

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