BOTULINUM TOXIN FOR TREATMENT OF CHRONIC ANAL FISSURE

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ABSTRACT

Background

Chronic anal fissure is a common disease that affects both sexes especially young adults. It causes pain and bleeding after defecation.

Objectives

The objective of the study was to determine whether injection of botulinum toxin into the internal anal sphincter to treat chronic anal fissures is safe and effective.

patients and Methods

A prospective study was conducted from April 1, 2018, to March 31, 2023, over a five-year period in a private surgical clinic in Sulaymaniyah, Iraq. Data were collected from 63 patients about presenting symptoms, physical examination, procedure and follow-up. A dose of 50 U of botulinum toxin were injected into either side of the fissure at three and nine o'clock. Re-epithelization of the anal fissure and total absence of pain defined complete healing of the fissure. A previously healed fissure that relapsed, had recurring symptoms, and was clinically detectable upon physical examination was referred to as a recurrence.

Results

At 2-months follow-up complete healing of the fissure was present in 46/63 patients (73.01%) after receiving one dose of botulinum toxin injection. At 12-months follow-up, complete healing of the fissure was present in 52/63 patients (82.53%) after receiving two injections of botulinum toxin injection. The recurrence rate was 9/63 patients (12.28%), anal incontinence rate for flatus was 1/63 patients (1.58%) that was mild, temporary, lasted for 3 weeks and disappeared spontaneously.

Conclusion

A safe, and effective method for treating chronic anal fissure is injection of botulinum toxin into the internal anal sphincter

Keywords: Chronic anal fissure · Botulinum toxin .

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INTRODUCTION

An ulcer that runs from the anal verge to the dentate line in the distal portion of the anal canal is known as a chronic anal fissure (CAF). It usually affects young ages between 20 and 40 years. The lifetime incidence of anal fissures is estimated to be around 11%, with males and females equally at risk [1]. They are classified into primary anal fissure and secondary anal fissure. Primary (idiopathic, typical) anal fissures are most likely caused by local trauma in the form of vaginal delivery, internal sphincter hypertonia, hard stools, and persistent diarrhea. Secondary (atypical) anal fissures occur in patients with previous anal surgery, inflammatory bowel diseases, granule disease (such as tuberculosis, sarcoidosis), infection (such as HIV/AIDS, syphilis), or malignant diseases [2]. Anal fissures are classified as acute anal fissures with the pain persisting for less than 8 weeks and chronic anal fissures with the pain persisting for more than 8 weeks [3]. The presenting symptoms are pain and bleeding per rectum after defecation [4].

The conservative approach is the first line of treatment, which includes a high-fiber diet, increased water intake, sitz baths, laxatives, anti-inflammatory, analgesic, anesthetic, and healing ointments, as well as calcium channel blockers such as diltiazem hydrochloride 2% ointment [5,6]. Injections of botulinum toxin (BT) type A, which inhibits acetylcholine release and induces temporary paralysis of the internal sphincter muscle for about three months, are the second line of treatment. This allows the fissure to heal. It has also a direct analgesic effect causing pain relief before the healing of the fissure occurs [7]. A systematic review showed a BT overall healing rate of 67.5% 8. After the second session of BT injections, other assessments of the literature indicated that healing rates range from 60 to 95 percent [5, 8, 9]. Although gaseous or fecal anal incontinence rates as high as 10–30% have been observed, lateral internal sphincterotomy (LIS), the third line of treatment, has a success rate of up to 96% and a recurrence rate of 2.3–3% [10,11].

The objective of the study was to determine whether injection of botulinum toxin into the internal anal sphincter to treat chronic anal fissures is safe and effective.

METHODS

A prospective study was conducted from April 1, 2018, to March 31, 2023, over five years in a private surgical clinic in Sulaymaniyah, Iraq. During that period 79 patients were seen, 16 patients (22.53%) lost to follow-up during the follow-up period of 12 months and were excluded and the study was continued with the remaining 63 patients.

Inclusion criteria included patients with CAF, with symptoms of anal pain during and following defecation that was persistent for more than 2 months, bleeding per rectum and chronic anal ulcer which was sometimes accompanied by a sentinel skin tag located at the distal pole of the fissure, all these symptoms and signs together or combination of some. Patients with secondary anal fissures associated with chronic inflammatory bowel disease, tuberculosis, sexually transmitted diseases, immunosuppression, HIV infection, anorectal or perianal cancer, also patients with associated pathologies like 4th degree hemorrhoids, anal fistula, and patients with a history of anorectal surgeries were excluded. Pregnancy, breastfeeding, known sensitivity to botulinum toxin and patients lost to follow-up were all excluded. All patients received a full explanation of the proposed procedure and gave informed consent.

Patient's characteristics were recorded including age and sex. History was taken from the patients and the following data were recorded: chief complaint (anal pain during or after defecation, bleeding per rectum and itching) and its duration, bowel motions whether normal bowel motions, constipation, or diarrhea. Physical examination was performed and the following findings were recorded, the presence of circumscribed fissure, indurated edges, fissure site (posterior, anterior or both) and sentinel pile. Digital rectal examination and proctoscopy were not performed on our patients because of the pain induced by the procedure. Anal continence status was evaluated by asking the patients about their ability to control flatus and feces.

The procedure of BT injection was done in a private surgical clinic by a single surgeon (the author). The procedure was done with the patient lying on the left lateral position. Ten minutes before the treatment, local anesthetic cream called EMLA (lidocaine 2.5% and prilocaine 2.5%) was applied to the anal verge. The area was prepped (with povidone-iodine 10% solution) and draped. BT type A, 100 Units/Vial (Botox®; Allergan, Irvine, California, USA) was used. Each vial was prepared by adding 2 ml of normal saline. We used a high dose of BT, 50 units (1ml) BT in 1 ml insulin syringe, 27G gauge needle and 1.25 mm (0.5 inches) length. The internal anal sphincter was identified by

digital palpation, BT was injected into the internal anal sphincter, 25 U into each side of the fissure, at 3 and 9 o`clock and the depth of injection was below the level of the dentate line. The patients were sent home 30 minutes after the procedure. Instructions were given to all of the patients to take a high fiber diet, generous intake of water, frequent sitz baths, and analgesic tablets (paracetamol tablet 1000 mg) on need for 2 weeks.

The patients were followed up by telephone interview 2 weeks after treatment with BT injection and then by clinic visits, 2 months, 4 months, 6 months and 12 months after treatment with BT injection and thereafter as clinically indicated. To encourage the patient to complete the follow-up period, they were reminded about their clinic visit appointment 1 week before by a telephone call. During follow-up by telephone interview or clinic visits, we asked about time for pain relief, anal incontinence for flatus or feces, allergic reactions, skin irritation, bleeding, perianal swelling and pain and asked to visit the clinic if these problems arise. Re-epithelization of the anal fissure and total absence of pain defined complete healing of the fissure [(12)]. An unhealed fissure was defined as little or no improvement in symptoms of anal pain and bleeding after the initial BT injection. A previously healed fissure that relapsed, had recurring symptoms, and was clinically detectable upon physical examination was referred to as a recurrence, it mostly occurs between 6-12 months [(12,13)].

If the fissure was healed, the patients were asked to visit the clinic at 4 months, 6 months and 12 months for follow-up and evaluation. On the other hand, if the fissure was not healed or recurred after the 1st dose, a second dose of BT injection was given. If the fissure was not healed after the 2nd dose of BT injection or refused the 2nd dose of BT injection, the patient was treated with LIS.

The reference list was formulated with Mendeley`s Reference Management Software. Approval from the Ethical Committee of Sulaimani University Medical College has been obtained for conducting this research. Statistical data analysis was done by SPSS 24 (Statistical Package for the Social Sciences, Version 24), under Microsoft Windows 10 operating system.

RESULTS

Basic patient characteristics and clinical features are shown in Table 1.

At 2 2-week follow-up by telephone interview, we found that all of our patients had pain relief at 2-week follow-up. The interview also revealed that one patient (1/63, 1.58%), had mild anal incontinence for flatus, he was reassured that it is usually temporary and self-limiting. There was no incontinence for feces. Their bowel habits were controlled with our dietary advice given to the patients.

At 2-month follow-up, figure 1, we found that 73.01% of the patients had complete healing of the fissures and 26.99% of the patients showed unhealed fissures, of which 17.64% were treated with a second dose of BT and 9.52% refused the 2nd dose of BT and treated with lateral internal sphincterotomy. At 4-month follow-up, figure 1, we found that that 73.01% with healed fissures continued to show healed fissures and there were no recurrences. That 17.64% of the patients that received the 2nd dose of BT, 14.28% of them showed healed fissures and 3.17% of them showed unhealed fissures and treated with LIS. At 6-month follow-up, figure 1, 9.52% of the patients developed recurrence and were treated with 2nd dose of BT. At 12 months follow-up, in figure 1, all of the patients continued to have healed fissures except 4.76% of them that developed recurrence and were treated with LIS.

At 12-month follow-up, 63.49% of the patients had healed fissures after receiving one dose of BT injection. Another 9.52% of the patients had healed fissures at 12-month follow-up after receiving the 2nd dose of BT injection at 6-month follow-up. Another 9.52% of the patients had healed fissures at 12-months follow-up after receiving the 2nd dose of BT injection at 2-month follow-up. Making the overall healing rate after BT injection 82.53%. We also found that among those patients with healed fissures, the majority of them, 63.49%, had healed fissures after one dose of BT injection and the remaining minority, 19.04% (9.52% + 9.52%), had healed fissures after two doses of BT injection.

Recurrence developed in 9.52% of the patients at 6-month follow-up and in 4.76% of the patients developed at 12-month follow-up. Both make the total recurrence rate in this study 14.23%.

Among those 63 patients treated with BT injection, 1 patient (1.58%) had incontinence for flatus after receiving the 1st BT injection, it was mild, temporary and disappeared spontaneously after 3 weeks. There was no incontinence for feces. We found no allergic

reaction, skin irritation, bleeding, perianal hematoma, or perianal infection following BT injection.

Table 1. Basic Patient Characteristics and Clinical Features.

	Frequency	%
Age (Years)		
Range 20-46 years		
Mean age 35.43 ± 11.212 years		
20-39 years	42	66.7
40-59 year	19	30.2
60 years and >	2	3.2
Sex		
Male	21	33.3
Female	42	66.7
Symptoms		
Anal pain during and after defecation	63	100
Fresh bleeding per rectum during and after defecation	44	69.8
Anal itching	12	19.04
Constipation	49	77.77
Diarrhea	2	3.17
Normal bowel motion	13	20.60
Duration of symptoms		
Ranged 2-24 months		
Mean 5.48 ± 3.963 months		
Location of the fissure		
Anterior midline	12	19
Posterior midline	44	69.8
Both anterior and posterior midline	6	9.5
Sentinel pile	34	38.1

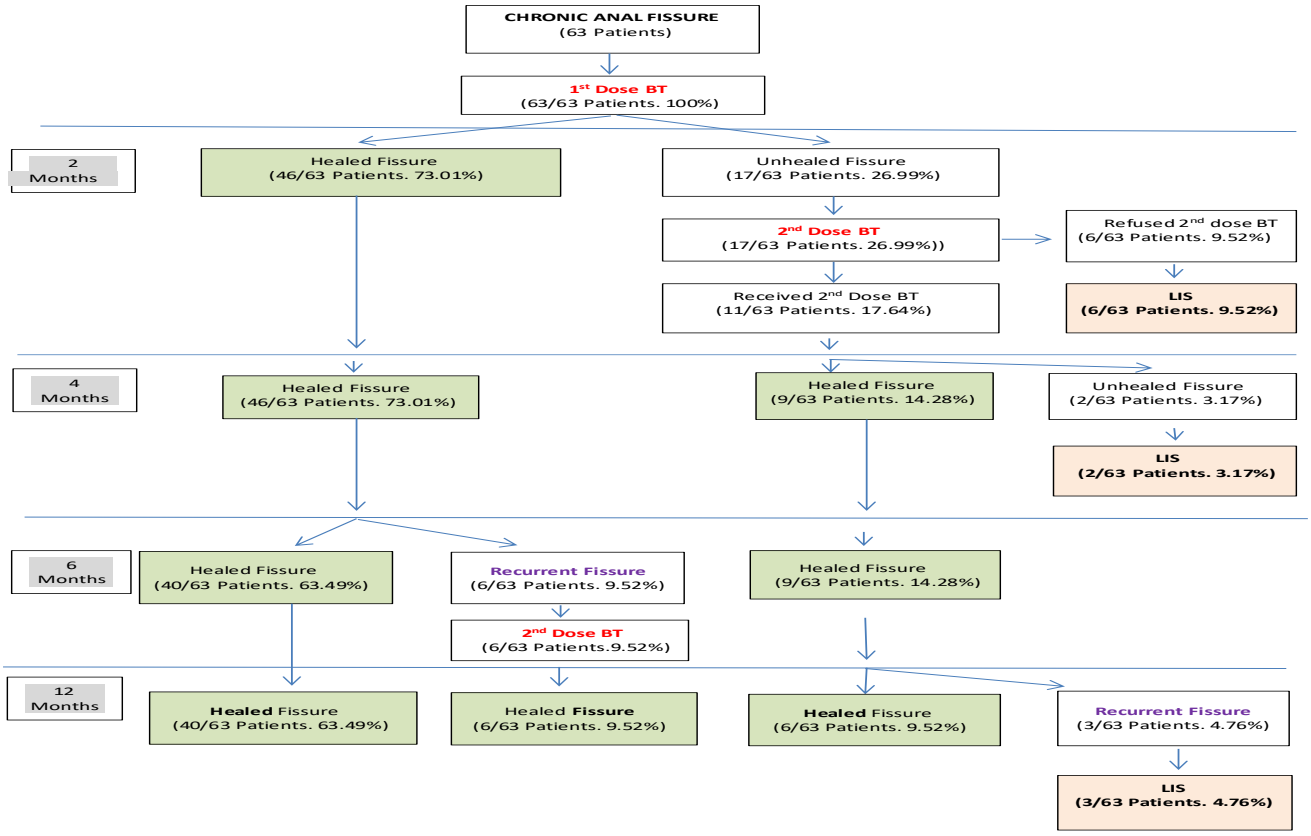

Figure 1. Treatment of Chronic Anal Fissure with Botulinum Toxin.

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CONFLICT OF INTEREST

There is no conflict of interest to be disclosed

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DISCUSSION

The most potent toxins known to man are the Clostridium botulinum neurotoxins (BoNTs), which are produced by C. botulinum and are classified into seven serotypes (A–G) that share structural similarities but differ antigenically, among which BoNT/A and BoNT/B are approved by the FDA for clinical and esthetic indications [14-16]. Clinical use of BT type A was pioneered by the ophthalmologist Alan Scott, who first reported its use therapeutically in a series of patients with strabismus [17]. Applications now include cosmetic, gastroenterology (including anal fissure), otolaryngologic, genitourinary, neurologic, and dermatologic conditions [18].

The majority of our patients (66.7%) were young (aged 20-39 years) and were females (66.70%). All of our 63 patients complained of anal pain during and after defecation. The majority of them (69.8%), had fresh bleeding per rectum during and after defecation. This is going with Pilkington et al 19, who found that the majority of their patients (86.66%) had bleeding per rectum. However, it is unlike Brisinda et al 20, who found that less than half of their patients (32.40%), had bleeding per rectum. In addition, most of our patients, (77.77%) had constipation, (20.60%) had normal bowel motion and (3.17%) had diarrhea. This is unlike the results of Brisinda et al 20, who found that the majority of their patients, (49.5%) had normal bowel motion, (45.8%) had constipation, and (4.7%) had diarrhea. In the majority of our patients (69.8%), the fissures were located in the posterior midline, in (19%) the fissures were located in the anterior midline and in (9.5%) the fissures were located in both anterior and posterior midline. This is going with Barbeirio et al 21, who found that in the majority of their patients (77.2%) the fissures were located in the posterior midline, in (20.5%) were located in the anterior midline, and in (2.3%) were located in the anterior and posterior midline.

Regarding the optimal dosage of botulinum toxin, there is no consensus [12]. However, this dose is within the range of 20-50 U reported by most studies [13, 22]. Numerous studies reported that the dose of toxin directly correlates with the results [19,20,23,24]. Brisinda et al 20 described 3 dosing groups: low (15–25 UI), medium (30 UI), and high (50–100 UI), they found that the optimal dose was found to be 50 IU of the American toxin 2, also found that with the higher dosage a statistically significant increase in healing rate without complications can be obtained [2].

The follow-up periods in the literature varied significantly, ranging from two months to 71 months [20, 24].

However, generally, the patients were followed up for at least 8 weeks to evaluate the effects of treatment [25].Studies showed that follow-ups were done through interviews conducted by telephone, postal questionnaire, clinic visits or by combinations of the above methods [3,19,20].

All our patients had pain relief within the 1st 2 weeks following the injection. This is in agreement with Maurice et al [26] who found that all their patients had pain relief 2 weeks after treatment. It is also going with Jost 27, who found that within the 1st week, 95% of their patients were pain-free. This is explained by the fact that before the fissure heals, BT has a direct analgesic action that causes pain relief [7].

Out of those 63 patients treated with BT injection, a healing rate of 63.49% was achieved with one dose of BT injection, however after the 2nd dose of BT injection the total healing rate of 82.53% was achieved at 12-month follow-up. We attribute this high healing rate of our study to the high dose of BT injection we were using (total 50 U) and to the 2nd dose of BT we used after the failure of the 1st dose of BT injection. Various studies have various healing rates, which can be explained by variations in patient selection criteria, various injection techniques and the use of different dosages and injection sites [24]. A systematic review revealed that the overall healing rate for BT was 67.5% [8]. Reviews of the literature revealed that during the second BT injection session, healing rates range from 60 to 95 percent, with recurrence rates of 12 percent at six months [5, 8, 9]. Other studies showed that there is a correlation between the higher doses of BT injected and the higher healing rate [23,28]. Another study found that

higher dosages (at least up to 50 U) and a second dose of BT injection are associated with a higher success rate, with a healing rate of 93.5% and no increase in complications or side effects [21].

Recurrence occurred in (9/63 patients, 9.52%) of our patients (6 patients at 6 months follow up and 3 patients at 12 months follow up), making the total recurrence rate in the current study 14.28%. This is going with Roble 3, who found that recurrence was observed in 14.81% of their patients. Generally, recurrence rates vary between 10 and 55% [27]. We also found that the recurrences occurred in our patients at 6-month and 12-month follow-ups, this is similar to Brisinda et al 20, who found that recurrence occurred mainly between 6 and 12 months and subsequent relapses are not anticipated. In agreement with Ravindran's findings fewer than half (37.5%) of their recurrences progressed to sphincterotomy and only one-third of our recurrent fissures were treated with LIS [23].

Incontinence for flatus occurred in one patient (1.58%) which was mild, temporary, lasted for 3 weeks and disappeared spontaneously. There was no incontinence for feces. This is going with Cakir et al 4, who found that there was no serious incontinence problem, except for only 1 patient (1.63%) who had temporary intestinal gas incontinence and no fecal incontinence. This is going with Mahgoob & Kamal 29, who discovered that 2 patients (6%) reported having gas incontinence, which resolved on its own in 2 weeks. However, it is unlike Brisinda et al 20, who found that incontinence was not observed in any of their patients. Also, it is unlike Jost 27, who found that there was no serious incontinence problem, only temporary fecal incontinence in 7 patients (7%) patients.

We did not find allergic reactions to BT injection, skin irritation, bleeding, perianal hematoma, or perianal infection following BT injection. This is similar to Barbieri 21 who found that the BT injections were well tolerated and there were no complications or side effects. However, Cakir et al 4, found that perianal abscess was observed in one (0.74%) of their patients.

CONCLUSION

A safe, and effective method for treating chronic anal fissures is injection of botulinum toxin into the internal anal sphincter

RECOMMENDATION

This study presents private surgical clinic data on the use of BT injection into the internal anal sphincter for the treatment of CAF, we recommend doing further studies on larger numbers of patients.

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