



Effectiveness of Botox in Treating Chronic Anal Fissure: A Clinical Experience with Mid-Term Follow Up

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ABSTRACT

Chronic anal fissure (CAF) is a common distressing problem with high recurrence rates. For many years, lateral internal sphincterotomy was the main treatment for CAF. Recently, intrasphincteric injection of botulinum toxin (BT) seems to be a good alternative option. The aim of this study was to evaluate the effectiveness and safety of BT type-A (botox) injection in the treatment of CAF. A total of 62 patients (45 males, 17 females; mean age of 41.3 years) with CAF who presented to surgical outpatient clinic at my hospital in the period between January 2014 and September 2015 were treated with BT injections of 20-30 units in the internal sphincter. They were followed up for one year to evaluate the effects of this treatment. The results of this study revealed that all patients had significant symptomatic relief with high rates of fissure healing reaching 74.2% (46 patients) after the first treatment session and 87.1% (54 patients) after the second session. During injections, no complications or side effects were reported. After injections, 19 patients experienced minor incontinence in the form of a fecal and gas soiling which solved spontaneously later. There were 3 relapses during 12 months of follow-up. I conclude that BT therapy can be considered effective, safe and without significant complication. It can be proposed to the patient as first line treatment before surgery.

Keywords: Chronic anal fissure, Botulinum toxin, Botox

INTRODUCTION

Anal fissure is a common painful health problem that causes high morbidity. It is a linear ulcer in the anal canal, usually single, and posterior midline in location. Multiple or atypical locations could be the expression of other diseases such as chronic inflammatory bowel disease, malignancies, venereal infections, trauma, or chemotherapy [1]. If the anal fissure does not heal after 4-12 weeks of treatment, it is termed chronic anal fissure (CAF) [2]. It affects both men and women especially young adults causing severe pain and bleeding during or after defecation [3]. The pathogenesis of chronic anal fissure is not completely understood. The onset of the disease is often due to the passage of hard stools with expansion of the anal mucosa out of its capability causing a tear of the anal lining. Usually, the acute anal fissure will heal spontaneously or by medical therapy using stool softeners and accurate local hygiene or by applying anaesthetic ointment [4]. In many cases, this is not true and the lesion becomes a chronic one, and will not heal. Spasm of the internal anal sphincter muscle is the main underlying cause for this, with consequent reduction in vascularity of the anal mucosa producing chronicity and non-healing of the ulcer since it is blocked of normal blood supply [5]. Surgical sphincterotomy, which is commonly arranged to provide pain relief and healing since the first results of Eisenhammer in the 1950s is highly effective, but they lead to a risk of incontinence varying from 0% to 24% [2]. Since the middle of the 1990's, new non-surgical therapies have been introduced for the treatment of CAF, aimed at reducing anal resting pressure and alleviating the distressing symptoms. These include botulinum toxin (BT) injection, nitroglycerine (GTN) and nifedipine and diltiazem ointments. Intrasphincteric injection of BT is a reliable and effective new method of therapy which has been introduced firstly by Jost and Schmrigk [6]. Chemical denervation with BT type-A as a blocker to acetylcholine release will result in symptomatic improvement and produce healing in the majority of patients. BT causes a transitory sphincter palsy with reduction in the anal pressure for 3 or more months, allowing fissure healing [7], and thus eliminates the need for surgery. Medical therapy is successful in the majority of patients with surgery confined for those who have no response to conservative treatment [7]. Two

productive types of serotype A of BT are obtainable for therapeutic use, the European type (Dysport; Speywood Biopharm Ltd, Wrexham, UK) and the American type (Botox; Allergan, Irvine, CA, USA) [8]. Botox appears to be more effective. The optimal dose of BT in patients with CAF is indistinct. Some reported that the injection of 20 units into each side of the internal sphincter may be optimal [9].

The aim of this prospective study is to assess the efficacy and safety in the short and mid-term follow-up of botox in the management of CAF.

PATIENTS AND METHODS

All patients with single posterior symptomatic CAF presenting to the general surgery outpatient department in my hospital during the period from January 2014 to September 2015 were enrolled in this study. They were 17 females and 45 males ranging in age from 20 to 65 years with a mean age of 41.3 years. The diagnosis was based on the following clinical criteria: severe anal pain after defecation &/or bleeding, lasting for more than 4 weeks, evidence of posterior typical circumscribed ulceration with a large sentinel tag of skin or hypertrophied anal papilla or indurations at the edges of the fissure and exposure of the horizontal fibers of the internal sphincter. Patients with acute fissure, or fissure associated with other diseases such as Crohn's disease, ulcerative colitis, haemorrhoids, fistula in ano, anal abscesses, as well as those with previous surgical interventions on the anal canal and pregnant or breast-feeding women were excluded from this study. After initial assessment and informed written consent, patients were fully informed about the effect and possible side effects of the procedures. The study protocol was approved by the ethics committee of Al-kindy College of Medicine and hospital. All patients were asked to choose between operative therapy (lateral internal sphincterotomy) and medical therapy (BT injection) for treatment of their CAF. A questionnaire of history and patient record including telephonic contact numbers was maintained. The clinical details were noted and no special investigations or anal manometry was undertaken. All injections were administered on outpatient department basis, 30 minutes after application of topical 2% lignocaine jelly. The patients were given an injection of BT type-A (Botox, Allergan, stored at -5°C to -20°C) using 25 G needle. The anal canal is gently dilated with a narrow blade bivalve speculum. A total dose of 20-30 units was diluted in 1 ml isotonic saline immediately before injection and then injected into each side of the fissure. Internal anal sphincter was felt with gloved finger while the patient in the left lateral position or knee elbow position. Half of this dose was injected on both sides of the fissure at 3/9'0 clock position. The patient was discharged immediately after the procedure. The patients were advised to continue high fiber diet and to drink at least 2 litres of liquids at least daily with topical use of 2% lignocaine jelly and local hygiene measures. The patients were followed up in the outpatient department initially after one week and then every two weeks until the 8th week to evaluate the effects of treatment. Thereafter every month for 6 months. Telephone follow-up was made every 2 months to complete 1-year follow-up. The patients' records were reviewed for the presence or absence of pain and bleeding on defecation, occurrence of side effects or any complications. Visual examination of the anus was done to assess healing of the fissure. If the fissure healed with a scar 8 weeks after the injection, then the treatment was considered successful. But if there was persistence of the fissure in the absence of symptoms, then it was considered to be symptomatic improvement. Clinical follow up for 12 months was achieved for those patients with healed fissures and disappeared symptoms. In the follow up period, patients were assessed by visual inspection of the fissure area and re-evaluated for symptoms at 6th and 12th months. On the contrary if the wound did not show objective signs of healing or the patients reported persistence of symptoms, then the decision was to retreat the patient. The retreated patients received the same units of BT in the same site as the first injection and were then followed up with the same protocol. Treatment failure after the second injection led the patient to surgery consisting of lateral closed internal sphincterotomy.

RESULTS

Forty-five males (72.58%) and seventeen females (27.42%) consecutive outpatients with chronic posterior anal fissure were enrolled in this study ranging in age from 20 to 65 years with a mean age of 41.3 years. Symptoms of moderate-severe pain during defecation ranged in duration from 1 to 6 months (average 3.6 months) was the main presenting symptoms in all patients. Habitual constipation and bright red bleeding were less common presenting symptoms, while anal itching and mucous discharge were much less common (Table 1). All patients in this study had a posterior anal fissure with a large sentinel tag of skin and exposure of fibers of the internal anal sphincter, so that the internal anal sphincter was easily palpated in all patients.

Table 1 Clinical data of patients included in the study

Age	20-65 year
Sex	Males 45 (72.58%)
	females 17 (27.42%)
Presentation	Pain 62 (100%)
	Constipation 36 (58%)
	Bleeding 34 (54.8%)
	Pruritus 8 (12.9%)

An average of 27 units (20-30 units) of BT type-A (botox) was injected in each patient. Majority had significant symptomatic improvement after BT starting as early as 3rd day after injection. Fifteen (24.2%) patients reported partial pain relief at the passage of the first motion compared with pre-treatment post-defecation pain. Twenty-three (37.1%) patients had complete relief of post-defecation pain by the 2nd week while six patients had less than 50% relief. There was progressive improvement in symptoms during follow up with 10 (16.1%) patients becoming free of pain at 4 weeks. Two months after the first session of injections, post-defecation pain had disappeared in 4 patients and was reduced in 2 patients (Table 2).

Table 2 Time of pain relief after 1st session of injection

Time of pain relief	No. of patients
After first motion	15 (24.2%)
After 2 weeks	23 (37.1%)
After 4 weeks	10 (16.1%)
After 8 weeks	6 (9.7%)
Total	54 (87.1%)

Post-defecation bleeding disappeared in most of the patients who had previously reported it. Bleeding persisted in 4 (11.7%) out of 34 patients. Complete healing was not registered in any patient after two weeks of BT injection while it was noted after 4 weeks in 34 patients (54.8%) (Table 3).

Table 3 Time of complete healing after 1st session of injection

Time of complete healing	No. of patients
After 2 weeks	0
After 4 weeks	34 (54.8%)
After 6 weeks	7 (11.3%)
After 8 weeks	5 (8%)
Total	46 (74.2%)

Seven patients (11.3%) arrived to the control visit with a cleaned wound and clear signs of healing that occurred after 6 weeks from treatment. At the 2-month evaluation, 5 patients (8%) showed complete healing while 16 patients (25.8%) showed still no healing (no evidence of improvement of the tear tissues with little or no symptomatic improvement) and those were re-treated with a second session of BT injection with the same previous dose (20-30 units). Two months after the second trial of BT injections, the anal inspection revealed completely healed fissures in 8 patients. The remaining 8 patients (12.9%) showed no signs of healing and were referred to surgery (lateral internal sphincterotomy). It was observed that healing rate was 74.2% (46 patients) after the first treatment session with a total healing rate of 87.1% (54 patients) after the second treatment (Table 4).

Table 4 Follow up results after two sessions of injection

Follow up results	After two sessions of injection
Complete healing	54 (87.1%)
No healing (treated with surgery)	8 (12.9%)
Relapse (treated with surgery)	3 (5.5%)
Hematoma	4 (6.4%)
Fecal incontinence	13 (30.6%)

The healed patients (54) were followed up for a total period of 12 months. It was also observed that 3 relapses (5.5%) during the first 6 months and these patients were sent for surgery. No more relapses were recorded during the period of follow-up. No complications or side effects were reported during injections. Hematoma after injection occurred in 4 patients (6.4%). Nineteen patients (30.6%) reported minor incontinence in the form of flatus incontinence and soiling of the underwear that lasted 2-16 days after treatment, but disappeared spontaneously. All patients remained continent during follow up period. No other complications have been noticed.

DISCUSSION

For many years, surgery was the first line of treatment of CAF. Traditional surgical techniques may be results in uncontrolled disruption of the sphincter with unacceptably high incidence of incontinence [10]. This important complication necessitates a search for another therapy for the management of anal fissure. BT was a good choice as an alternative therapy as it prevents the release of acetylcholine from presynaptic nerve terminals and causes denervation of the internal anal sphincter [11] and as a result, paralysis run within few hours and transitory weakness of the internal anal sphincter manifest for 3-4 months [12].

The complete healing rate accomplished for CAF in my study was 87.1% (54/62) which is similar to that reported in many other studies [13-16]. Nevertheless, other studies demonstrated a healing rate between 41% to 90.7% at 3 months, with recurrence rates of 20.6% to 54% at 6 months [15,17-21].

All patients of this study had posterior anal fissure and short symptom duration (mean 10 months). Recently, posteriorly localized fissures, and short duration of symptoms (<12 months) were suggested as predictive factors for a favourable outcome in BT treatment in CAF [22]. Furthermore, the injection site and toxin dose may affect the therapeutic success rate of BT. The dosage of BT reported ranged from 20 U to 100 U, with different procedures of injection application (directly under the fissure or in both sides of the fissure or circumferential injections). The method used in my study comprised two injections of 10 U to 15 U of BT injected on both sides of the fissure, with 12-month follow-up. Some studies reported that higher doses (up to 50 units) give a higher success rate reaching 96% with no comparable rise in complications or side effects [9]. However, there is no superiority of certain dosage or procedure than the others [2,23-25]. It was found that the variation of the total dose and the number of injection sites does not affect the healing rate.

When type-A BT is injected on both sides of the fissure (at 3 and 9 o'clock) not directly under the fissure, it induces a higher fall in resting pressure and improves the clinical outcome. Fibrosis of the internal anal sphincter, which is more distinguished at the location of the fissure than in another place in the smooth muscle, may reduce its compliance and restrict the diffusion of BT which could be due to the fibrotic base of the fissure or ischemic degeneration of the myenteric plexus of posterior sphincter [8]. However, initial using of BT at a specific dose may result in variable clinical responses caused by many factors, involving the dilution volume used, the number of applied injections, the presence or absence of certain antibodies, and the sensitivity of cholinergic cells to neurotoxin.

Maria, et al. study [8] of 57 patients injected with 15 or 20 units of BT revealed that the higher dose was more successful than the lower dose with consideration to long-term healing and was not linked with a significant rise of complications.

The present study showed no significant variation in healing with the dose of BT within the used range in our work (20-30 units). This may be explained by small range of the total dose used in this study and secondly to small sample size. Based upon these results, it can be said that higher doses are not needed, sufficient effect can be seen using lower doses. Moreover, higher doses will increase the costs and may give unwanted effects.

Some authors report a certain incidence of relapse during the first year, up to the figure of 55% [20], but in one year follow up, only 3 relapses in the first 6 months were observed and were sent for surgery. A 2nd injection of BT may be an essential therapeutic choice for patients with non-satisfactory response to a 1st injection, because it was efficient, well tolerated and with no complications. No more relapses were observed in the period of follow up, may be due to an aggressive dietary control and attention paid to evacuation. In general, the relapse rates after BT injection was very low as shown to me and others. In theory, BT injection can make anal incontinence [11]. However, incontinence has been a trivial complication of BT therapy.

Finally, it can be summarized that before performing an operation, a pharmacological sphincterotomy, with botox

injection, must be attempted. With this idea, surgery for 51 patients out of 62 was avoided which is remarkable achievement.

CONCLUSION

BT injection was efficient as substitution to surgery for patients with CAF. It was comparatively less invasive than surgery and the complication rate seems trivial. The key limitations of this study were the absence of a control group and lack of anorectal manometry examinations. Further studies including more patients with long-term follow-up are advisable to confirm the results.

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