

High-dose botulinum toxin in chronic anal fissure treatment: Short term results

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Abstract

Aim: Botulinum toxin (BT) injection into the internal anal sphincter is gaining popularity as a second line therapy for chronic anal fissures if medical therapy fails. There is no consensus on BT dosing to be used in chronic anal fissure (CAF) treatment. The aim of our study is to research the complication of high-dose BT in CAF treatment and its treatment effectiveness.

Material and Methods: The data of 19 patients who underwent BT injection for CAF treatment between the years of 2014 and 2018 were analyzed retrospectively. Demographic characteristics of the patients, complications observed due to BT injection, healing and recurrence cases were recorded.

Results: Nineteen patients who underwent 90 IU BT treatment followed for an average of 9.4 (min 3- max 46) months, It was observed that anal fissure was completely healed in 16 (84.2%) but no improvement was observed in 3 (15.8%). One of the recovered 16 patients was found to have recurrent anal fissure on the 5th month. In the patients who had BT, it was observed that 2 of the patients (%10.5) had abdominal pain in the first day requiring analgesic use, 2 of the patients (%10.5) had abdominal bloating (gas) which healed itself spontaneously within approximately one week, 2 (%10.5) of the patients had redness on the injection area on the first day and 3 (%15.8) of the patients had gas incontinence which healed itself spontaneously within approximately 2 weeks.

Conclusion: High-dose BT injection can be safely performed with low complication, high recovery rate and low recurrence rate. Prospective studies in larger series of patients are needed to obtain clearer results.

Keywords: Anal Fissure; Botulinum Toxin; High Dose.

INTRODUCTION

Anal fissure is one of the most frequent and painful anal diseases that causes high morbidity. It is a linear ulcer in the anal canal distal to the dentate line. It is classically located in the posterior midline (1). Anal fissures can be classified as acute or chronic, based on both chronology and morphology. Anal fissure is observed equally in both women and men. Although it can be seen in all age groups, it usually occurs in 3rd-4th decades of age (2).

Despite the improvements in medical and surgical treatments, chronic anal fissure (CAF) is a disease which is quite difficult to treat. The most significant deficiencies of the medical treatments are their short-term effects and high recurrence rates. As for surgical treatments, despite effective healing rates, due to complications such as fecal incontinence and infection, it is disadvantageous (3,4).

Hence, there have been attempts to develop alternative

ways to treat anal fissure, one of which is botulinum toxin (BT), which temporarily paralyzes the sphincter. The main indication for use of BT injection in our study was CAF that did not heal after 6 weeks of conservative treatment. There still has not been any consensus on dosing of BT treatment in the literature. The aim of our study is to examine the safety, effectiveness and complications of high-dose BT in chronic anal fissure treatment.

MATERIAL and METHODS

Nine-teen patients diagnosed CAF who did not benefit from conservative treatment between 2014 and 2018 in Ordu University Training and Research Hospital General Surgery Department were treated either outpatient or inpatient by giving 90 units of BT. Data of all the patients were examined retrospectively. It was observed that all the patients came to the initial control examination after the procedure, but rate of the patients coming to the

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later controls were low. Patients who did not come to the controls or whose data could not be accessed were called by phone. The patients who could come were re-examined. Patients' ages, genders, fissure localizations, complaints (pain, bleeding, itching, constipation), post-treatment early and late complications (bleeding, redness, abdominal pain, abdominal bloating, anal incontinence and recurrence) were examined.

Vials containing 100 units of BT (Vial containing Botox 100 IU lyophilized powder, Allergan Pharmaceuticals Ireland) were diluted with 1 ml serum physiologic (SF). The diluted vial content (0,9 ml) was taken into a 1 ml injector which was attached a tuberculin needle (26 G) to its tip. Thus, 90 units of BT were administered to the patient as diluted with 0,9 ml SF. The administration was performed in the operating room or in the policlinic, in lithotomy (knee-elbow position with sedation anesthesia or local anesthesia. BT injection was performed in 30+30+30 units into 3 different points (left and right of the anterior mid line and base of the fissure). Injections were made in the internal sphincter and intersphincteric ranges. The ethical committee approval of the study was taken from Ordu University Faculty of Medicine Clinical Researches Ethics Committee.

Statistics: While descriptive statistics for continuous variables were expressed as mean, minimum and maximum values, for categorical variables they were expressed as number and percentage. SPSS (IBM SPSS for Windows Ver.24) statistical package program was used in the calculations.

RESULTS

Four-teen (73.7%) of the patients were females and 5 (26.3%) of the patients were males. The mean age was 48.8 (min 27 – max 82) years. Anal fissure was located posteriorly in 18 (%94.7) of the cases and it was located anteriorly in only 1(%5.3) of the cases. Mean follow-up time of the patients was 9.4 (min 3 – max 46) months.

There were no anorectal intervention in 18 patients' medical history, but there was lateral internal sphincterotomy (LIS) in one of the patient's medical history. Symptoms of moderate/severe pain during defecation were the main presenting symptoms in all patients. Habitual constipation (n:13; 68.4%), bright red bleeding (n:5; 26.3%) and anal itching (n:2; 10.5%) were less common presenting symptoms.

Ninety units of BT type-A (Botox) was injected in each patient. The patients were either sent to their home or stayed in the hospital only one day. Majority had significant symptomatic improvement after BT starting as early as 3rd day after injection. On day 10 controls, it was possible to do rectal palpation without pain in all the patients and it was seen that anal sphincters were relaxed. At the end of the 3rd month, 84.2 % of the patients (16 patients) showed improvement. The remaining 3 patients (15.8%) showed no signs of healing and were suggested to surgery (LIS). In our study the mean follow-up period was 9.4 months

and 1 (6.2 %) of the 16 patients who recovered during this period had recurrent anal fissure in the fifth month. Surgery was suggested to the patient. No complications or side effects associated with BT were reported during injections (Table 1).

Table 1 The results of the study and demographic findings of the patients

| | | |
|--|--------------------------------|--------------------|
| Number of the patients | | 19 |
| Age | | 48.8 (27- 82) year |
| Gender | Female | 14 (%73.7) |
| | Male | 5 (%26.3) |
| The localization of the fissures | Posterior | 18 (%94.7) |
| | Anterior | 1 (%5.3) |
| Symptoms of the patients | Pain | 19 (100%) |
| | Constipation | 13 (68.4%) |
| | Bleeding | 5 (26.3%) |
| | Itching | 2 (10.5%) |
| Follow-up period | | 9.4(3-46) month |
| Recovery after botulinum toxin treatment | Yes | 16 (%84.2) |
| | No | 3 (%15.8) |
| Recurrence | | 1(6.2%) of 16 |
| The complications of BT | Abdominal Pain | 2 (10.5%) |
| | Abdominal Bloating | 2 (10.5%) |
| | Redness of Injection Area | 2 (10.5%) |
| | The transient gas incontinence | 3 (15.8%) |

In the patients who had Botox administration, it was observed that 2 (10.5%) of the patients had abdominal pain in the first day requiring analgesic use, 2(10.5%) of the patients had abdominal bloating (gas) which healed itself spontaneously within approximately one week, 2 (10.5%) of the patients had redness on the injection area on the first day and 3 (15.8%) of the patients had gas incontinence which healed itself spontaneously within approximately 2 weeks. No other complications have been noticed. All the complaints seen after BT were temporary.

DISCUSSION

Although anal fissure is a common disease, its etiology has not been fully elucidated. Local trauma is the most known etiologic factor in anal fissure formation. Constipation, gastroenteritis, suppository or rectal enema applications which cause local trauma and tools used in surgical interventions such as stapler and anal retractor can cause anoderm injury and fissure (5). However, current evidence shows that anal fissures are associated with increased tone and spasm of the internal anal sphincter (6-8). The sphincter spasm seems to cause relative local ischemia that precludes the healing of the fissure (9,10).

The most common complaints of anal fissure patients that cause them to apply to the hospital are pain that occurs during and after defecation. A small amount of bright-red new bleeding after defecation is one of the most common symptoms. Fear of defecation developing secondary to pain and increasing constipation as a result can cause symptoms to become more severe (11).

The diagnosis of anal fissure is based on the presence of intense pain, with possible bleeding, during or after defecation. Acute anal fissure usually heals spontaneously or with conservative treatment within weeks (12). A chronic fissure, on the other hand, is usually characterized by symptoms persisting for 8–12 weeks as well as chronic inflammatory features such as fibrosis, hypertrophied anal papillae (1).

Current therapies for chronic anal fissure aim at the reduction of the tonus of the internal anal sphincter and relief of pain. Medical treatments such as local anesthetic use, fibrous food intake are recommended to reduce pain; and to reduce sphincter spasm, surgical treatments such as anal dilation and sphincterotomy are used (13).

If medical treatment and diet does not help to heal fissure, surgical treatment comes to the table. While conservative treatment provides a significant healing in acute fissures, the main problem is chronic fissures. Although various surgical methods have been tried, LIS is still currently the most widely accepted surgical treatment option in the treatment of CAF with up to 90% efficiency (14,15). Although simple and effective, its principal drawback is the potential to cause disabling anal incontinence and postoperative infection seen in 17% and 2% of patients respectively (16).

Despite the high rates of recovery, post-surgery complications such as anal incontinence and infection have led clinicians to find other methods for CAF treatment (13). For this purpose, items to relax anal sphincter temporarily has come to the agenda. One of these is BT synthesized by *Clostridium botulinum* which is a Gram (+) anaerobic bacteria (17).

The effect of BT is that the release of acetylcholine at the presynaptic nerve endings with neuromuscular transmission blockade causes a chemical denervation of the sphincter muscles (10). BT is used for anal fissure treatment as it causes 3-4 months of temporary paralysis in the internal anal sphincter after injection. After the resulting paralysis and relaxation, the vascularity of the anoderm will increase and the fissure will heal (18,19). BT was first used in 1988 and has been the standard treatment since 1992 (20). Although it has been in use for a long time, there are different opinions about its place of application and dosing. Optimal dosing is unknown and varies from 10 to 100 U, with higher doses postulated to enhance healing (4,21).

In the literature, there are studies showing that as BT dosing increases, the rate of anal fissure healing increases without increasing complications but there are also studies showing that dosing does not have any effect on healing. Maria et al., revealed that the higher dose BT was more

successful than the lower dose with consideration to long-term healing and was not linked with a significant rise of complications (22). On the other hand, Marzooq could not find any connection between BT dose and anal fissure healing in his study (23). In the study performed by Hazar in 11 cases, 90.9% of the cases which 90 units of BT were given showed recovery and no complications were observed. During follow-up, recurrence was observed in 1 (9.1%) patient in 6th month (5). Despite the limited number of studies available in the literature showing that high-dose BT injection to anus is safe in the management of CAF, there is a need to elucidate this (5,22,24).

BT studies demonstrated a healing rate from 45% to 90.9% at 3 months with recurrence rates of 8% to 55% at 1 year (5, 25-27). In accordance with the literature, in our study, 84.2 % of the patients were healed with high dose BT at 3 months. In the mean follow-up period of 9.4 months, 6.25% of 16 patients who healed with high dose BT had recurrence. BT injection superior to placebo but it appears to be worse in terms of curative efficacy and recurrence when compared to surgical internal sphincterotomy, but the risk of gas incontinence after surgery is 9 times higher than that of botulinum injection (4,25). BT can also cause incontinence, but this is temporary and resolves quickly. BT causes a temporary lesion of the anal sphincter, and subsequently some patients may develop transient flatus (up to 18%) or fecal (5%) incontinence, that resolves quickly (21,28). In our study, it was observed that 2(10.5%) of the patients had abdominal bloating (gas) which healed itself spontaneously within approximately one week and 3 (15.8%) of the patients had gas incontinence which healed itself spontaneously within approximately 2 weeks.

Due to the rate of incontinence and the invasiveness of surgery, BT has gained recognition. Compared with surgery, the BT procedure is simpler, cheaper, minimally invasive and well tolerated, does not need anesthesia, is performed in an outpatient setting, and patients are discharged immediately, with a resting period after the procedure not necessary. BT may be the first-line therapy for chronic and medical refractory anal fissure (29).

CONCLUSION

High-dose BT could safely be administered to the patients with CAF and no serious side effects due to BT have been observed. Recovery and recurrence rates of the cases were acceptable and persistent anal incontinence, which is the most frightening complication of patients and clinicians, has never been seen. While larger and prospective series are needed to clearly demonstrate the efficacy of high-dose BT in CAF treatment, it can safely be administered prior to surgical treatment in cases failing to respond to medical treatment.

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