Original Article

The Efficacy of Botulinum Toxin Injection Site in Chronic Anal Fissure Healing

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Abstract

Background: Chronic anal fissure is a common disease of the anoderm. Botulinum toxin injection has recently been recommended. However, the injection sites are still debatable. **Aims:** This study aimed to assess the site-dependent efficacy of Botulinum toxin injection for chronic anal fissure healing. **Methods:** Randomized clinical trial was performed, 80 patients were enrolled in two semi groups according to the site of botulinum toxin injection. Lateral sites of internal sphincter muscle were used in group 1, anterior and posterior regions were used in group 2 in lithotomy position. In this prospective study, the effect of injection site preference on the early complications (pain, infection, hematoma, incontinence) and late results (clinical fissure healing) of chronic anal fissure treatment were assessed. **Results:** There was no statistical significant difference between the number of patients who achieved complete healing at the end of the 12th week. Postoperative pain scores were significantly lower in group 2 at the end of 1st week and they stayed lower at the end of the 2nd week. Thrombosed haemorrhoids were encountered significantly lower in group 2. **Conclusions:** Even though there was no statistical difference in the long term healing rate between groups 1 and 2, choosing 6 and 12 o'clock alignments of internal sphincter muscle for botox injection is more advantageous than 3 and 9 o'clock alignments in terms of better postoperative pain and lower complication rate in the early period.

Keywords: *Anal fissure, botulinum injection, complication, endoanal ultrasound, healing*

Introduction

The anal fissure is defined as a linear split or tear in the skin of the distal anal canal, extending below the dentate line to the anal verge.[1-5] It can occur at any age, including infants, but mostly affects young and middle-aged adults and lifelong incidence rate is 11.0%.[3,5-7] Besides, both men and women are exposed equally. Fissure persisting over 6 weeks is called chronic anal fissure. The exact cause of primary anal fissure remains unknown, the precipitating factors are thought to be trauma caused by constipation, diarrhoea, internal sphincter hypertonia, trauma during vaginal delivery or sexual abuse.[3-5] An anal fissure may lead to complications such as hypertrophic anal papilla, sentinel skin tag or mucosal defect exposing the internal sphincter muscle.

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The treatment options for chronic anal fissure are challenging. American Society of Colon and Rectal Surgeons (ASCRS) recommends non-operative treatment for initial management; which includes topical nitrate treatment (ASCRS Grade 1A) and topical calcium channel blockers (reported to have fewer adverse side effects than topical nitrates) (ASCRS Grade 1B).[8] To manage patients' refractory to topical medications, ASCRS recommends administering botulinum toxin injections into the internal anal sphincter (ASCRS Grade 1C). In the last 2 decades, botulinum toxin injection has been getting more popular as an alternative

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treatment. A low rate of side effects and a better treatment rate made it as a first-line treatment option. Other than ASCRS, American College of Gastroenterology (ACG) and Association of Coloproctology of Great Britain and Ireland (ACPGBI) suggest administering botulinum toxin (20-25 units in 2 divided doses injected on either side of fissure into internal anal sphincter) (ACPGBI Grade A, Level I) for the treatment of chronic anal fissures in cases which initial treatment failed because of none responsive to conservative management nor topical medications.[2,9]

Lateral internal sphincterotomy (LIS) is also recommended as surgical treatment of choice in patients requiring surgery by ACG (Strong), ASCRS (Grade 1A) and ACPGBI (Grade A, Level 1). LIS involves the partial transection of the internal anal sphincter.[10] despite a high fissure healing rate, the surgery has been thought to carry a 45% risk of incontinence to flatus and 22% risk of permanent faecal incontinence.[11] Moreover, by the randomized control trial lead by Gandomkar H *et al*., it put forth for consideration that combined botulinum injection with topical application of diltiazem could be as effective as partial lateral internal sphincterotomy in patients who have chronic anal fissure. In these subgroups, no significant statistical difference was observed in the incontinence score between treatments.[12] To this day, there is no consensus about the ideal location of injection nor does the dosage of the drug to be injected. With the help of developing technology and improved imaging methods, this project aims to investigate the effects of different botulinum injection sites on short-term complications and healing.

Methods

A randomized prospective analysis for chronic anal fissure healing was performed with 80 patients. They were grouped into 1 and 2 of 40 each. Fissurectomy and botulinum toxin injection were done for all of them at Acibadem Fulya Hospital from 2014-2018. Fissures were localized posteriorly or anteriorly in all patients. Patients who had anal surgery or inflammatory bowel disease in their history were excluded from the study. All patients underwent cauterization after debridement of the fissure bed. Intravenous sedation (propofol 3 mg/kg + fentanyl 1, 5 microgram/kg) and analgesic (1 gram Paracetamol) were used during procedure in lithotomy position. Total 50 U (25 + 25 for each site) botulinum was injected into the internal sphincter muscle using endoanal ultrasound imaging guidance [Figure 1]. We chose 3 and 9 o'clock alignments in group 1, 6 and 12 o'clock alignments in group 2. Follow-up was at the 1st, 2nd and the 12th week. The primary outcome of the study is postoperative pain. Postoperative pain was assessed by Visual Analogue Scale (VAS). VAS is a horizontal scale that contains two ends which one is "no pain" (0 mm) and the other is "worst imaginable pain" (100 mm). Secondary outcomes are infection, haemorrhage, incontinence, thrombosis incidences and fissure recovery for long term healing rate evaluation. All patients were informed about procedures and written consent was taken before the operation. Clinical consideration was done for patients until the asymptomatic stage. If symptoms were revealed, patients were referred to further treatment. The definition of healing was symptomatic relief which the patient does not require any further intervention.

Endoanal ultrasonograph has a 5-15 MHz cylindric probe 19 mm in diameter. Its length is 6 cm that has the capability of demonstrating of the anal canal with 360° view. It gives the structural bodies of sphincter muscles and it also guides to inject botulinum into the internal sphincteric muscle properly.

All demographic data and results were compared statistically by using student's *t*-test, Chi-square and Whitney-Mann-U tests with the help of a statistical program, SPSS (version 21.0 for Windows, SPSS Inc., Chicago, IL, USA). A *P* value of less than 0.05 was considered statistically significant.

Results

Mean age was 34 ± 2.8 in group 1, 31 ± 3.5 in group 2. Men to female ratio was 1.3:1 and gender distribution was similar in each group [Table 1]. As the primary outcomes of the study, no difference in both the long-term healing rates and mean VAS score between groups was seen. However, postoperative VAS scores showed that significantly lower pain was perceived in group 2 than group 1 at the end of the 1st week (4.6 ± 0.5 vs. 2.2 ± 0.2, $P = 0.01$) and this

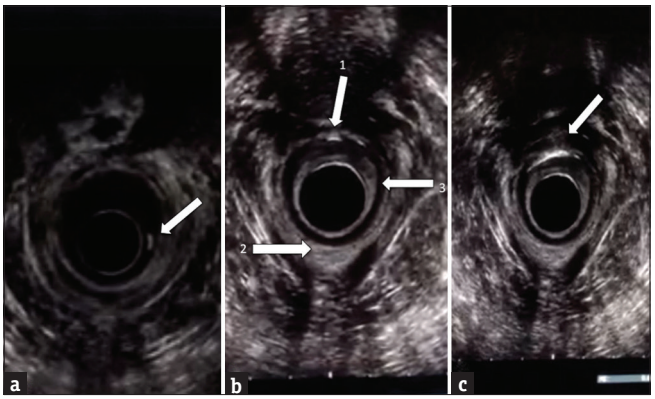

Figure 1: Ultrasonic view during botulinum injection. (a) Arrow shows the tip of the needle at 3 o'clock alignment, (b) Arrow 1 shows the tip of the needle at 12 o'clock alignment, Arrow 2 shows external sphincter and Arrow 3 shows internal sphincter muscle, (c) Hyperechogenic appearance of internal sphincter muscle during the injection

Table 1: Patients' demographic data

		Group 1	Group 2	*P*
Patient Number		40	40	
Mean Age		34±2.8	31±3.5	not significant
Gender	Female	18	16	not significant
	Male	22	24	not significant

Table 2: Results

		Group 1	Group 2	*P*
Mean VAS Score during defecation	1st week	4.6±0.5	2.2±0.2	**0.01**
	2nd week	1.8±0.2	1.6±0.2	**0.08**
Number of patients with complete mucosal healing at 12th week		33 (82%)	31 (78%)	0.1
Mean VAS at 12th week		0.4	0.3	0.1
Number of patients needed repeated botox injection		1	1	
Number of patients needed sphincterotomy after botox injection		0	0	

Table 3: Complications

	Group 1	Group 2	*P*
Hematoma	0	0	
Infection	0	0	
Incontinence	0	0	
Thrombosed Haemorrhoids	5	1	0.01

continued also at the end of the 2nd week (1.8 ± 0.2 vs. 1.6 ± 0.2, $P = 0.08$). No infection, incontinence or hematoma was seen. On the other hand, 5 patients in group 1 encountered thrombosed haemorrhoids, while only 1 patient encountered this in group 2 ($P = 0.01$). At the end of the 12th week, the mucosa healing rate was 33/40 (82%) patients in group 1 and 31/40 (78%) patients in group 2 [Tables 2 and 3]. Additional botox injection was repeated in one patient in both groups, but no sphincterotomy was needed.

Discussion

This randomised study failed to show a statistically significant difference in long term healing rates for botulinum toxin injection sites. However, it showed that 6 and 12 o'clock alignments offer better postoperative pain scores and as a result better satisfaction with the operation.

Botulinum injection has become prominent in the treatment of fissure in recent years with its low side effect and high therapeutic ability. Randomized controlled trials with nitrates and calcium channel blockers have suggested that botulinum treatment is a better option with lower-level side effects as well as better efficacy as an alternative to the foreground.[1,13-16] However, application methods for botulinum are still debatable.

While research for optimal dose and ideal injection site in botox therapy has continued, Bobkiewicz *et al*. suggested that the dose of botulinum toxin did not have any effect on recovery success or complications in their meta-analysis.[17] Pilkington *et al*. compared the unilateral and bilateral botulinum toxin injections, but there was no significant difference between the groups in terms of pain and fissure healing.[18] However, Lin *et al*. reported that low dose botulinum injections are advantageous than high dose, similar healing effect and low side effects.[19] Our study showed that choosing 6 and 12 o'clock alignments for 50 U botulinum injection into the internal sphincteric muscle was more advantageous than lateral sites.

The combination of fissurectomy-botulinum injection, which was first described by Engel in 2002, has been shown to be favourable in other studies in the following years, but it may result in about 7% of gas incontinence.[20-24] In general, complications in our study were lower than the rates reported in the literature, especially incontinence was not seen in any of our patients. We think using ultrasound during procedure is advantageous. It provides us radiological confirmation of injection administered into the internal sphincter muscle. Thus, it is ensured that the botulinum is not injected into the submucosal area or external sphincter muscle, so more efficient paralysis in the internal sphincter muscle may be provided and an undesirable paralysis in the external muscle may be prevented. As there are not enough comparative studies using ultrasound in the literature, additional studies are needed for a certain opinion.

All fissures were localised anteriorly or posteriorly in our patients, so it may be the reason of better postoperative results of group 2. Because botulinum injection into the fissure base seems to be effective by not only relieving spasm at the base of the fissure but also increasing microcirculation causing better wound healing pain reduction.[25,26] Less pain scores may be due to the lower incidence rate of thrombosed haemorrhoids in group 2 and it may probably be the result of limited dissemination of botulinum in the fibrotic fissure bed. Of course, we need further prospective studies which include manometric examinations, but our study can conclude that choosing 6 and 12 o'clock alignments is more advantageous with less thrombosis and less pain in the early period.

Conclusion

Anterior and posterior botulinum injections can directly offer better postoperative pain scores and less complications. Therefore, we concluded that ultrasound-guided botulinum injection (50 units) into

the anterior and posterior region of the internal sphincter muscle is a more reliable, effective and advantageous method of chronic anal fissure treatment than the lateral regions.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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