

COMPARING THE EFFICACY OF BOTULINUM TOXIN INJECTION AND LATERAL INTERNAL SPHINCTEROTOMY FOR CHRONIC ANAL FISSURE

Muhammad Imran Khan, Hameed Khan, Atta Ullah Khan, Hizb Ullah Jan, Tahir Saeed

ABSTRACT

Objective: The objective of this study is to: “compare the effectiveness of Botulinum toxin injection with lateral internal sphincterotomy for the treatment of chronic anal fissure in terms of healing”.

Material and Methods: Informed written consent was taken from patients and ethical approval was taken from the Institutional Research and Ethical Board (IREB). All patients fulfilling inclusion criteria were included in the study. Patients in group ‘A’ were treated with 0.5 ml (20 units) of Botulinum toxin injection in the internal anal sphincters under direct vision and digital examination at 3 or 9 o'clock position at lithotomy position under strict aseptic measures. Patients were sent home after one hour with stool softeners. Patients in group ‘B’ underwent lateral internal sphincterotomy under general anesthesia. In both groups, patients were followed after 2 months. At follow up, patients were examined for healing (yes or no) to determine intervention effectiveness.

Results: A total of 396 patients of chronic anal fissure were included in the study, which were divided into two equal groups. Efficacy was significant in both the procedure with p-value=0.045.

Conclusion: Botulinum toxin injection is more effective than lateral internal sphincterotomy in the management of chronic anal fissure.

Key Words: Botulinum toxin, lateral internal sphincterotomy, chronic anal fissure, healing

INTRODUCTION

Chronic anal fissure is one of the most common proctologic problems. It usually presents as painful defecation and per rectal bleeding. It is common in both sexes¹. The exact etiology of anal fissure is unknown, however traumatic or ischemic damage to mucosa due to passage of hard fecal matter is thought to be the cause. Other rare causes include prior anal surgery and prolonged occupational sitting. HIV and malignancy are also other uncommon causes of fissures present at unusual sites^{2,4}.

Hyper tonicity and hypertrophy of internal anal sphincters are the most common pathologies associated with it, which not only produces symptoms but are also the cause of persistence of the disease⁵. Over time; many methods of treatment have been designed, both medical and surgical. Medical treatment options include nitroglycerine, diltiazem and nifedepin^{6,7}. Surgical methods are considered to have low recurrence rate and symptomatic improvement, but there exists a risk of faecal incontinence (8– 35%) with it. Recently, injection of Botulinum toxin is introduced which is claimed to decrease sphincter tone and pressure and

is associated with good outcome in term of pain relief, complications and recurrence^{8,9}. Lateral sphincterotomy is also one of the best treatments for chronic anal fissure but there is high rate of faecal incontinence as compare to Botulinum toxin¹⁰. In one study both the treatment options were compared and it was observed that overall healing rate was 82% in patients treated with lateral sphincterotomy and 70 % in patients treated with Botulinum toxin group¹¹.

The rationale is, that there is no common agreement on single method for treatment of chronic anal fissure and if we find the efficacy of Botulinum toxin injection, either equally or more effective than lateral sphincterotomy, then, In the light of results we will further modify the treatment options of chronic anal fissure and we will advise to consultant surgeons that the Botulinum toxin injection is the first line treatment option, because it is good, safe, cost effective, non-invasive and need no hospital stay as compared to the lateral sphincterotomy which is an invasive procedure and needs anesthesia as well as hospital stay.

OBJECTIVE

The objective of this study is to: “compare the effectiveness of Botulinum toxin injection with lateral internal sphincterotomy for the treatment of chronic anal fissure in term of healing”.

HYPOTHESIS

Botulinum toxin injection is more effective than lateral internal sphincterotomy in the treatment of chronic anal fissure.

1 Department of Surgery, Khyber Teaching Hospital, Peshawar, Pakistan.

Address for correspondence:

Dr. Hameed Khan

Registrar Surgical D unit, Khyber Teaching Hospital, Peshawar.

E-mail: hameedwazir1976@gmail.com

DATA COLLECTION PROCEDURE

After taking permission from hospital ethical committee, this randomized control trial study was conducted in surgical unit "D" of Khyber Teaching Hospital Peshawar from 01/01/2013 to 31/12/2014. Patients were admitted in Surgical "D" Unit from outpatient department, Khyber Teaching Hospital, Peshawar, and diagnostic criteria was the presence of longitudinal break in the mucosa of distal anal canal for more than six weeks. Patients were randomly allocated in two groups, group A and B by Lottery method. Patients in group 'A' were receive treatment with 0.5 ml (20 units) Botulinum toxin injection in the internal anal sphincters under direct vision and digital examination at 3 or 9 o'clock position at lithotomy position under strict aseptic measures by single expert surgeon having at least five years' experience. Patients were sent home after one hour with stool softeners.

Patients in group 'B' underwent lateral internal sphincterotomy under general anesthesia by single expert surgeon also having at least five years' experience. The procedure was performed at lithotomy position under strict aseptic measures. Patients were discharged on 1st post operation day on oral antibiotics, analgesics, stool softeners and were advised sitz bath. In both groups, patients were followed for 2 months. At follow up, patients were examined for healing (yes or no) to determine intervention effectiveness. Data was collected on a specially designed Proforma. Patient's demographic data, history and examination findings were recorded.

Table 1: Comparison of wound healing rate

	Group A	Group B	P=0.045
yes	166(83.8%)	150(75.8%)	
no	32(16.2%)	48(24.2%)	

Known cases of intestinal tuberculosis (will be detected by history and previous medical record), inflammatory bowel diseases(detected by Colonoscopy and biopsy) and anorectal carcinoma(by proctoscopy and biopsy), Pregnant women due to risk of complications, anticoagulant therapy due to risk of bleeding were exclude as they act as confounders. Strictly exclusion criteria were followed to control confounding variables and bias in the study result.

RESULTS

A total of 396 patients of chronic anal fissure were followed, which were divided into two equal groups. Patients in group A were managed by Botulinum toxin injection and group B patients underwent lateral internal sphincterotomy.

Gender wise distribution shows that 119(60.1%) were male and 79(39.9%) were female in group A with male to female ratio was 1.15:1 while group B contains 101(51%) male and 97(49%) female patients with male to female ratio of 1.01:1. Overall Male to female ratio was 1.25:1. Sex distribution among the groups was insignificant with p-value=0.069

Average age was 45.11 years+ 13.26SD in group A and contains 31(15.7%) patients having less than 30 years, 76(38.4%) patients 31-45 years, 58(29.3%) patients 46-60 years and 33(16.7%) patients' were more than 60 years of age. While group B patients have average age of 45.74 years +14.28SD and have 34(17.2%) patients in less than 30 years, 67(33.8%) in 31-45 years, 57(28.8%) in 46-60 years range and 49(20.2%) patients have age more than 60 years. The overall average age of the patients was 45.42 years +13.76SD. The age distribution among the group was also insignificant with p-value= 0.707.

Efficacy wise distribution in terms of healing at two months of follow up shows that treatment in Group

Table 2: Age Wise Distribution of Efficacy

		Efficacy			p-value
		Yes	No	Total	
Age (in years)	<= 30.00	54	11	65	0.046
		83.1%	16.9%	100.0%	
	31.00 - 45.00	123	20	143	
		86.0%	14.0%	100.0%	
	46.00 - 60.00	86	29	115	
		74.8%	25.2%	100.0%	
	61.00+	53	20	73	
	72.6%	27.4%	100.0%		
Total		316	80	396	
		79.8%	20.2%	100.0%	

Table 3: Gender Wise Distribution of Efficacy

		Efficacy		Total	p-value
		Yes	No		
Gender	Male	167	53	220	0.031
		75.9%	24.1%	100.0%	
	Female	149	27	176	
		84.7%	15.3%	100.0%	
Total		316	80	396	
		79.8%	20.2%	100.0%	

A was effective in 166(83.8%) patients and not effective in 32(16.2%) patients, while in group B it was effective in 150(75.8%) patients and not effective in 48(24.2%) patients which shows that efficacy was significant in both the procedure with p-value=0.045. table 1

Age wise distribution of procedure-efficacy shows that efficacy was greater in younger age group and decreases with the increase of age. The efficacy was significant with p-value=0.046. (Table 2). When efficacy was stratified among the gender it showed also significance with p-value=0.031. (Table 3).

DISCUSSION

Lateral internal sphincterotomy (LIS) is the most common treatment for chronic anal fissure (CAF)¹¹. It is considered the gold standard treatment as it can be effective in more than 90 percent of cases¹². The fundamental drawback of this surgery is its potential to cause gas, mucus or occasionally stool incontinence which may be permanent in 8 to 30 percent of patients¹³⁻¹⁸.

Other reported complications include abscess, fistula and anal deformity. Intrasphincteric injection of Botulinum toxin (BT) is a reliable and effective new option in the treatment of uncomplicated CAF. This method has been described initially by Jost and Schmrigrk¹⁹, and was found to be an effective treatment in comparison with placebo²⁰. Furthermore, BT was more effective than topical nitrate, which constitutes another therapeutic option²¹, and no permanent damage to the continence mechanism was detected in patients treated with BT²⁰⁻²².

Any prolonged increases in sphincter pressure may cause ischemic damage by decreasing blood flow to the sphincter muscle and overlying epithelium²³. As a consequence, therapies that reduce internal anal sphincter (IAS) pressure have been used for fissure healing. Many chronic fissures do not heal with aggressive local measures and are considered for lateral sphincterotomy. Although surgery is effective, fissure healing and relapse rates are quite variable. After lateral sphincterotomy the healing rates range from 78 to >90 percent²⁴ percent²⁵, and the recurrence rates range between 1.3 and 13.1 percent^{12,17,26}.

These variations could be due to the type of surgical technique (open vs. closed sphincterotomy) or the length of the sphincterotomy incision. Fissure healing rate is relatively low (83.3 percent) after LIS procedure in this study, which may be related to a more conservative approach in sphincterotomy in order to prevent anal incontinence. Neither significant incontinence nor relapse was observed during follow-up period.

Botulinum toxin injection into anal sphincter is another therapeutic approach which has been used to treat chronic anal fissure and avoid the risk of permanent injury to the anal sphincter^{19,20,27}. Although chemical denervations with Botulinum toxin have been mostly used for weakening of striated muscles, it has also been found to weaken smooth muscle in the gastrointestinal tract^{28,29}.

The toxin acts rapidly and prevents the release of acetylcholine by presynaptic nerve terminals. Paralysis occurs within a few hours, and the transmission of neuromuscular impulses resumes after the growth of new axon terminals^{28,30}. On the third day after the injection, the external anal sphincter (EAS) tone was obviously reduced¹⁹.

Chemical denervation produced by the toxin is not permanent and the clinical efficacy lasts for 2-3 months. In anal fissure, however, the duration of action of the toxin roughly corresponds to the time required to reduce the resting pressure of the anal sphincter and allows enough time for healing. In our study we noticed significant drop in the MRP for the first 2 weeks after treatment in both groups (P< 0.001), however 2 months later the reduced MRP was still statistically significant (P< 0.01) only in the LIS group. This significant drop in the resting pressure was not correlated with significant incontinence in our patients. These results are similar to that reported by Ram et.al, 2005³¹.

In the present study the healing rate of 61.5% in the BT group is similar to that in previous studies^{19,20,22,27}. We observed significant decrease in both IAS and external anal sphincter (EAS) but interestingly, Gui et al.²⁷ and Maria et al.²⁰ did not observe any effect of BT on EAS after injection to IAS.

They concluded that toxin injected to the IAS had not spread into EAS²¹. This suggestion may not be valid as spread of the toxin through the EAS is very possible due to the small thickness of IAS and the proximity of EAS to the IAS. It is also well known that a diffusion gradient allows a spread to a distance of 30–45 mm from the injection point, even crossing the bone and fascia³². The other reason of this controversy may also be related to the volume of the toxin that might have diffused beyond the target muscle and might have weakened the adjacent muscles. The change in resting pressure was not mentioned by Jost and Schimrigk in their initial studies where they injected BT into the EAS^{19,22}.

In this study, we did not try to inject BT specifically into the IAS or EAS. We also observed that if the toxin was applied on both sides of the fissure it spread into the EAS and IAS, and we believe it is easier to inject the toxin in this manner. In conclusion, the target muscle for injection of BT seems to be irrelevant.

After therapy with BT, higher recurrence rates are expected, because the sphincter tone is only temporarily reduced. However, we and others have shown that relapse rates after BT injection was very low^{20-22,27}. Recently in posteriorly localized fissures, significant reduction in maximum squeeze pressure and short duration of symptoms (<12 months) were suggested as predictive factors for a favorable outcome in botulinum toxin treatment in CAF³³. All of our patients were selected from those suffering from posterior anal fissure for an average duration of eleven months, and those who were treated with BT injection showed significant reduction of MSP (-26.1%). These positive predictive factors could be related with the good outcome of our patients treated with BT.

Theoretically BT injection can produce anal incontinence. BT produces a significant and global reduction in mean resting pressure of the anal canal, but also induces a significant increase in manometric asymmetry of the anal canal²⁸. However, incontinence has been a negligible complication of BT treatment. EAS is an important component of continence. Toxin injection produces sufficient weakness of this muscle, but does not completely block voluntary control which is enough for incontinence prevention³⁴.

The therapeutic success rate of BT seems to be related with injection site and toxin dose. We injected the BT on each site of the fissure, mainly to the posterior of the anal sphincter. However it was suggested that anterior injection of BT could better reduce the resting pressure of the anal sphincter (88 percent vs. 60 percent) which could be due to the fibrotic base of the fissure or ischemic degeneration of the myenteric plexus of posterior sphincter³⁵. In addition the dose of BT is important. We used 20 units in this study. However, it was suggested that higher doses (up to 50 units) provide a higher success rate (up to 96 percent), without a significant rise in complications or side effects³⁶.

In a recent randomized, prospective study comparing BT with LIS for CAF, it has been suggested that the healing effect of BT appears slowly and wanes with longer follow-up, whereas LIS provides a faster, more stable and permanent effect³⁷. The success rate of the BT group fell to 75.4 percent, whereas it remained stable in the LIS group (94 percent) at 12 months. In conclusion, the authors suggested that BT injection is inferior to LIS in the treatment of CAF. However they reported 16 percent rate of anal incontinence of varying degrees after surgery, compared with Zero prevalence in the BT group ($p < 0.001$) within the same follow-up period. If anal incontinence is considered as a failure of LIS, the advantage of this treatment will disappear³⁸.

CONCLUSION

In conclusion, BT injection is effective in the treatment of CAF. It is relatively less invasive than surgery and the complication rate seems negligible. However BT injection treatment may provide temporary remissions. Larger scale, randomized controlled studies with long term follow up are needed before making firm conclusions about the advantages of this treatment modality over the conventional methods.

REFERENCES

1. Ahmed S, Ahmed S, Pervaiz N, Naseem R. Closed lateral internal anal sphincterotomy for anal fissure with von-greaves (cataract) knife. *J Surg Pak* 2008;28:220-3.
2. Nzimbala MJ, Bruyninx L, Pans A. Chronic anal fissure: common aetiopathogenesis, with special attention to sexual abuse. *ActaChirBelg* 2009;109:720-6.
3. Ali SA, Shah FA. Prolonged sitting occupation: etiological factor of anal fissure. *J Surg Pak* 2007;12:80-1.
4. Abramowitz L, Benabderrahmane D, Baron G. Systematic evaluation and description of anal pathology in HIV-infected patients during the HAART era. *Colorectal Dis* 2009;52:1130-6.
5. Farid M, El-Nakeeb A, Youssef M. Idiopathic hypertensive anal canal: a place of internal sphincterotomy. *J Gastroenterol Surg* 2009;47:112-4.
6. Sajid MS, Hunte S, Hippolyte S, Kiri VA, Maringe C, Baig MK. Comparison of surgical versus chemical sphincterotomy using botulinum toxin for the treatment of chronic anal fissure: a meta-analysis. *Colorectal Dis* 2008;10:547-52.
7. Hashmat A, Ishfaq T. Anal fissure. *Professional Med J* 2008;5:420-4.
8. Shaukat A, Zafar F, Aslam M, Choudhri AA. Chronic anal fissure; role of chemical sphincterotomy. *Professional Med J* 2006;3:354-7.
9. Abd Elhady HM, Othman IH, Hablus MA. Long-term prospective randomised clinical and manometric comparison between surgical and chemical sphinc-

- terotomy for treatment of chronic analfissure. *S Afr J Surg* 2009;47:112-4.
10. Arroyo A, Pérez F, Serrano P, Candela F, Lacueva J, Calpena R. Surgical versus chemical (botulinum toxin) sphincterotomy for chronic anal fissure: long-term results of a prospective randomized clinical and manometric study. *Am J Surg* 2005;189:429-34.
 11. Giral A, Memisoglu K, Gultekin Y, Imeryuz N, Kalayc C, Ullusoy NB, Tozum N. Surgical versus chemical (botulinum toxin) sphincterotomy for chronic anal fissure: non randomized controlled trial. *BMC Gastroenterol.* 2004;4:7.
 12. Jonas M, Scholefield JH.: Anal Fissure. *Gastroenterol Clin North Am.* 2001;30:167-81.
 13. Oh C, Divino CM, Steinhagen RM. Anal fissure: 20-year experience. *Dis Colon Rectum.* 1995;38:378-382.
 14. Abcarian H, Lakshmanan S, Read DR, Roccaforte P. The role of internal sphincter in chronic anal fissure. *Dis Colon Rectum.* 1982;25:525-8.
 15. Pernikoff BJ, Eisenstat TE, Rubin RJ, Oliver GC, Salvati EP. Reappraisal of partial lateral internal sphincterotomy. *Dis Colon Rectum.* 1994;37:1291-5.
 16. Lund JN, Scholefield JH. Aetiology and treatment of anal fissure. *Br J Surg.* 1996;83:1335-44.
 17. Garcia-Aguilar J, Belmonte Montes C, Perez JJ, Jensen L, Madoff RD, Wong WD. Incontinence after lateral internal sphincterotomy: anatomical and functional evaluation. *Dis Colon Rectum.* 1998;41:423-7.
 18. Hsu TC, MacKeigan JM.: Surgical treatment of chronic anal fissure: a retrospective study of 1753 cases. *Dis Colon Rectum.* 1984;27:475-8.
 19. Madoff RD, Fleshman JW. AGA technical review on the diagnosis and care of patients with anal fissure. *Gastroenterol.* 2003;124:235-45.
 20. Jost WH, Schimrigk K.: Use of botulinum toxin in anal fissure. *Dis Colon Rectum.* 1993;36:974.
 21. Maria G, Cassetta E, Gui D, Brisinda G, Bentivoglio AR, Albanese A.: A comparison of botulinum toxin and saline for the treatment of chronic anal fissure. *N Engl J Med.* 1998;338:217-20.
 22. Brisinda G, Maria G, Bentivoglio AR, Cassetta E, Gui Albanese A.: A comparison of injections of botulinum toxin and topical nitroglycerin ointment for the treatment of chronic anal fissure. *N Engl J Med.* 1999;341:65-9.
 23. Jost WH.: One hundred cases of anal fissure treated with botulinum toxin. Early and long term results. *Dis Colon Rectum.* 1997;40:1029-1032.
 24. Schouten WR, Briel JW, Auwerda JJ.: Relationship between anal pressure and anodermal blood flow. The vascular pathogenesis of anal fissures. *Dis Colon Rectum.* 1994; 37:664-669.
 25. Hananel N, Gordon PH.: Lateral internal sphincterotomy for fissure-in-ano-revisited. *Dis Colon Rectum.* 1997; 40:597-602.
 26. Marby M, Alexander-Williams J, Buchmann P, Arabi Y, Kappas A, Minervini S, Gatehouse D, Keighley MR.: A randomized controlled trial to compare anal dilatation with lateral subcutaneous sphincterotomy for anal fissure. *Dis Colon Rectum.* 1979;22:308-311.
 27. Abcarian H. Surgical correction of chronic anal fissures: results of lateral internal sphincterotomy vs. fissurectomy-midline sphincterotomy. *Dis Colon Rectum.* 1980;23:31-6.
 28. Gui D, Cassetta E, Asastasio G, Bentivoglio AR, Maria G, Albanese A. A comparison of botulinum toxin and saline for the treatment of chronic anal fissure. *Lancet.* 1994;344:1127-8.
 29. Jankovic ,Brin MF. Therapeutic uses of botulinum toxin. *N Engl J Med.* 1991;324:1186-94.
 30. Pasricha PJ, Rai R, Ravich WJ, Hendrix TR, Kalloo AN. Botulinum toxin for achalasia: long-term outcome and predictors of response. *Gastroenterol.* 1996;110:1410-5.
 31. Hallett M. One man's poison-clinical applications of botulinum toxin. *N Engl J Med.* 1999;341:118-20.
 32. Ram E, Alper D, Stein GY, Bramnik Z, Dreznik Z. Internal Anal Sphincter Function Following Lateral Internal Sphincterotomy for Anal Fissure: A Long-term Manometric Study. *Annals Surg.* 2005;242:208-11.
 33. Shaari, ChM. Sanders I. Assessment of the biological activity of botulinum toxin. In: Jankovic J, Hallett M, editor. *In Therapy with botulinum toxin.* New York: Dekker; 1994. p.159-70.
 34. Minguez M, Herreros B, Espi A, Garcia-Granero E, Sanchiz V, Mora F, et al. Long-term follow-up (42 months) of chronic anal fissure after healing with botulinum toxin. *Gastroenterol.* 2002;123:112-7
 35. Chen R, Karp BI, Goldstein SR, Bara-Jimenez W, Yaseen Z, Hallett M. Effect of muscle activity immediately after botulinum toxin injection for writer's cramp. *Mov Disord.* 1999; 14:307-312.
 36. Maria G, Brisinda G, Bentivoglio AR, Cassetta E, Gui D, Albanese A. Influence of botulinum toxin site of injections on healing rate in patients with chronic anal fissure. *Am J Surg.* 2000;179:46-50
 37. Brisinda G, Maria G, Sganga G, Bentivoglio AR, Albanese A, Castagneto M. Effectiveness of higher doses of botulinum toxin to induce healing in patients with chronic anal fissures. *Surg.* 2002;131:179-84.
 38. Menteş BB, İrkörücü O, Akın M, Leventoğlu S, Tatlıcioğlu E. Comparison of Botulinum toxin injection and lateral internal sphincterotomy for the treatment of chronic anal fissure. *Dis Colon Rectum.* 2003;46:232-7.
 39. Brisinda G, Maria. Botulinum Toxin in the Treatment of Chronic Anal Fissure (letter). *Dis Colon Rectum.* 2003; 46:1144-1147.