Original Article

Randomized Clinical Trial Comparing Botulinum Toxin Injection with Nitroglycerine Ointment for Treatment of Chronic Anal Fissure

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Abstract

Background and Objectives: Although surgery is the gold standard treatment for anal fissure, the main concern remains its side effects and complications in terms of permanent incontinence. In recent years, treatment of chronic anal fissure has shifted from surgical to medical. This study compares the efficacy and safety of two non-surgical treatments- botulinum toxin (BTX) injection with nitroglycerine (NTG) ointment for the treatment of chronic anal fissure.

Methods: One hundred and twelve adults were assigned randomly to receive treatment with either type A botulinum toxin (15 units) injected into internal anal sphincter or 0.2% nitroglycerine ointment applied thrice daily for 8 weeks.

Results: After 2 months, the fissures were healed in 50 (89.3%) of 56 patients in botulinum toxin group and in 39 (69.6%) of 56 patients in nitroglycerine group (P= 0.01). Seventeen (23%) patients in nitroglycerine group complained of headache while none of the patients in botulinum toxin group had any forms of adverse effects. The recurrence rate of nitroglycerine group was higher than botulinum toxin group at 3 months (4.3% in BTX vs 16.7% in NTG, P = 0.057) and at 6 months (8.5% in BTX vs 36.1% in NTG, P = 0.002).

Conclusion: Although treatment with either topical nitroglycerine or botulinum toxin is effective as an alternative to surgery for patients with chronic anal fissure, botulinum toxin is the more effective option.

Key words: Chronic anal fissure; Botulinum toxin; Nitroglycerine.

Introduction

An anal fissure, first recognized as a clinical entity in 1934,[1] is one of the most common benign anorectal conditions. An anal fissure is a longitudinal split in the anoderm of the distal anal canal.[2] Most fissures occur in the posterior midline at 6 o'clock position. In 1-10% of total cases and 10-20% of female cases, anal fissures are located in the anterior midline.[3] Multiple or lateral fissures may have other causes, such as crohn's disease, ulcerative colitis, tuberculosis, or infection with HIV or syphilis.[3,4] Acute fissures are usually defined as those healed spontaneously within 6 weeks. Conversely, chronic anal fissures (CAF) persist much longer and tend not to heal without intervention.

As fissures are most commonly seen in the posterior midline, inadequate blood flow to this region due to hypertonia of internal anal sphincter (IAS), has been hypothesized to play a role in its development.[5] The principle aim of treatment is to decrease internal sphincter tone and hence, increase the blood flow with subsequent tissue healing. 'Gold standard' for treatment of anal fissure has been lateral internal sphincterotomy (LIS), as described by Eisenhammer since 1951.[6-8] LIS has healing rates in excess of 95%; however, it carries the risk of fecal incontinence in up to 30% of

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patients.[9] This led to the search for nonsurgical therapies for anal fissure. Due to high anal incontinence rate, medical sphincterotomy is being chosen as first line therapy now.

Two such medical approaches- injection of botulinum toxin (BTX) and application of nitroglycerine (NTG) ointment- have been used to treat CAF avoiding the risk of permanent injury to IAS. The aim of this clinical trial was to compare the clinical results of BTX injections with those of application of 0.2% NTG ointment for the treatment of CAF.

Materials and Methods

Between March 2013 and May 2014, consecutive patients with symptomatic anal fissure were scheduled for treatment. The diagnosis of CAF was based on the following clinical criteria: evidence of a posterior circumscribed ulcer with a sentinel tag, induration at the edges and exposure of horizontal fibres of the IAS, and symptoms (post-defecatory pain and bleeding or both) lasting for more than 6 weeks.

Exclusion criteria were age less than 18 years; acute anal fissure; anal fissure associated with different pathologies (such as inflammatory bowel disease, HIV infection, hemorrhoids, anal fistula, anal abscess, anal or perianal cancer); location of anal fissure other than 6 o'clock; previous surgery to the anal canal; known hypersensitivity to component of the formulations of type A BTX; pregnant or breast-feeding women and refusal of consent.

The study protocol was performed in accordance with the principle of the declaration of Helsinki and was approved by the institutional ethical review board.

Study design

Permuted block design of randomization was utilized with allocation ratio of 1:1 and a block size of 4 was created using www.randomization.com. A sequentially generated number with the treatment group was written in sealed envelope. All patients were assigned a patient identity number and allocated to receive either 0.2% NTG or type A BTX injection for the treatment of CAF, depending upon the treatment specified in sealed envelope.

The primary endpoint of the study was clinical evidence of complete healing at 8 weeks. The treatment was considered successful if the fissure healed. Secondary endpoints were measurement of post defecatory pain on Visual analogue scale (VAS**)** at each visits at 1, 4 and 8 weeks; side effects in terms of incontinence in duration (days) and Cleveland Clinic incontinence score and headache; and recurrence measured at 3 and 6 months of treatment.

Treatment

Patients after confirmation of the diagnosis by physical examination, and giving informed understood consent regarding the procedure were assigned randomly to either type A BTX injection or topical 0.2% NTG treatment depending upon the treatment specified in sealed envelope.

Botulinum toxin group

Each patient received 30 units of type A BTX (Botogenie: India, Biomed company). The

formulation was administered as two injections of equal volume, one on each side of the anterior midline of the internal anal sphincter approximately 1-2 mm below the anal mucosa at 3 and 9 o'clock positions. Procedures were performed under all aseptic precautions. Neither sedation nor local anaesthesia was used during the procedure.

Nitroglycerine group

The 0.2% NTG ointment (Nitrogesic, India, Troikaa company) was applied by fingertip to the anus and anal canal, three times daily for 8 weeks. Patients were provided with a dose regulator, which allowed about 1 gram of ointment to be dispensed in each application.

Supportive treatment

Patients were advised about local hygiene, plenty of water intake and high fibre diet. They were advised for syrup lactulose 3 tsf per orally at night and sitz bath thrice daily for 8 weeks or till the ulcer healed.

Clinical care, follow-up and outcome measures

All patients were followed up at 1st week, 4th week, 2 months, 3 months and 6 months. At each monthly visit, patients were asked whether they want to continue their participation in the study. If they did not, they were offered LIS.

Recurrence was assessed at 3rd and 6th month from the start of the treatment.

Statistical analysis

Data entered in Microsoft EXCEL and analyzed by SPSS 10. Frequency tables were generated for descriptive analysis. For inferential statistics, Chi-square or Fisher exact, student t-test, Wilcoxon Sign rank and Mann-Whitney U tests were carried out to find the significant difference between the two groups at the level of significance (p-value less than 0.05). A sample size was estimated on assumption of healing rates for BTX injection and NTG ointment as 92% and 70% respectively, based on published data by Brisinda et al in 2007.[12] A total of 98 patients were sufficient to detect a difference of 22% between the two groups with 80% power and P value <0.05. However, considering the 15% lost to follow up, a total 112 patients (56 in each group) were considered for the study.

Results and discussion

One hundred and sixty consecutive outpatients were assessed for eligibility; of these, 36 did not meet the inclusion criteria and 12 refused to participate. One hundred and twelve patients were randomized: 56 to receive BTX injection and 56 to receive NTG ointment (*Fig. 1*). The groups were similar with regard to age, sex, duration of symptoms and post defecatory pain on VAS at baseline (*Table 1*). There were no complications during the injection of BTX.

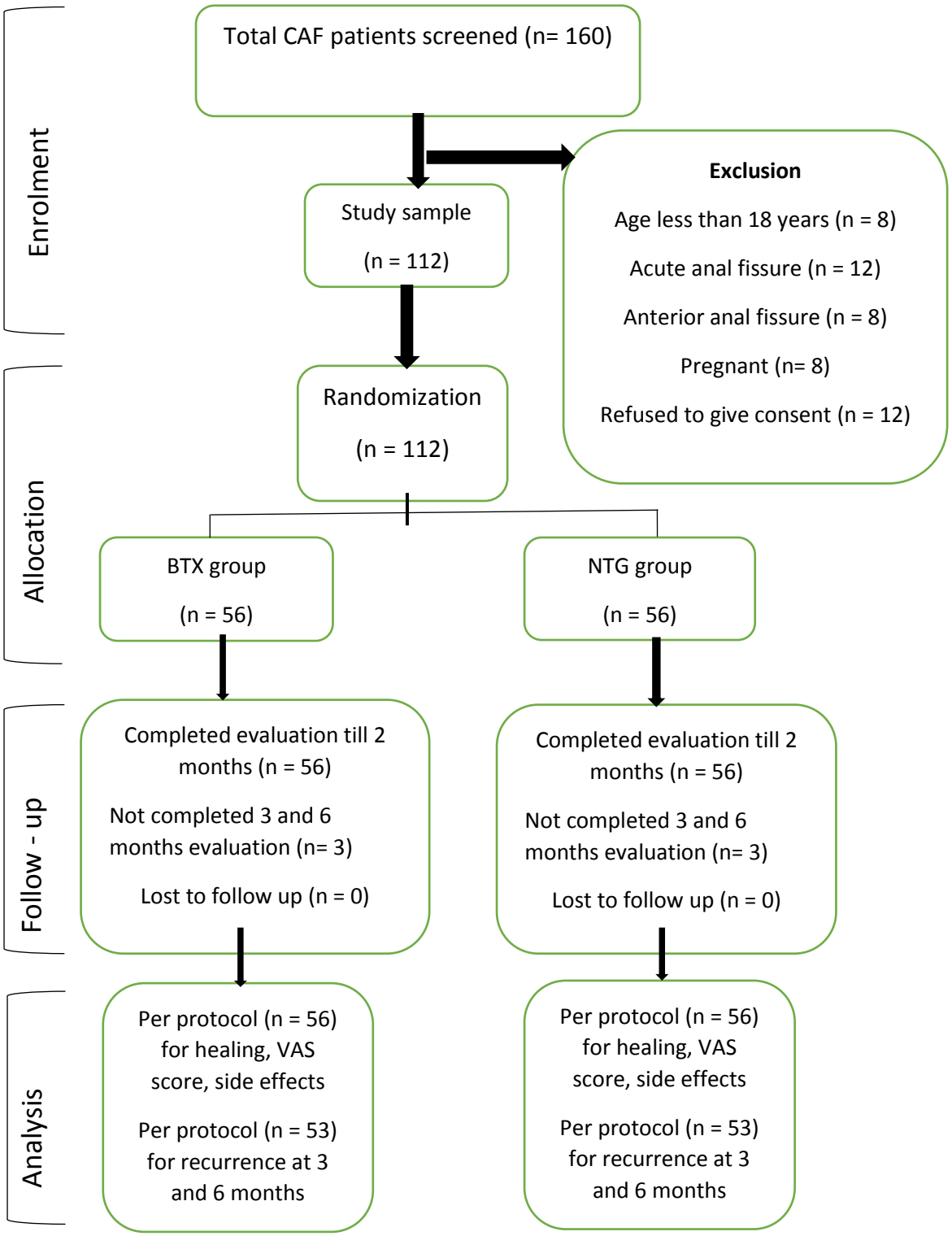

Figure 1: Trial Consort flowchart

Table 1: Baseline characteristics of 112 patients with CAF

Data		Group		Total (n= 112)	CHI SQUARE* / t TEST** / mann whitney U***	p - value
		BTX group (n= 56)	NTG group (n= 56)			
Age (years) mean ± SD (median)		30.9 ± 10.8 (28)	31.5 ± 11.6 (29.5)	31.23± 11.19 (28)	-0.286**	0.775
Gender n (%)	Female	41 (73.2%)	35 (62.5%)	76 (67.9%)	1.474*	0.225
	Male	15 (26.8%)	21 (37.5%)	36 (32.1%)		
Duration of illness (months) Mean ± SD (median)		20.7 ± 33.7 (7.5)	16.4 ± 30.9 (6)	18.54 ± 32.29 (6.5)	0.715**	0.476
Symptoms n (%)	Bleeding P/R	47 (83.9%)	42 (75%)	89 (79.5%)	1.368*	0.242
	Itching	10 (17.9%)	12 (21.4%)	22 (19.6%)	0.226*	0.634
	Discharge	6 (10.7%)	6 (10.7%)	12 (10.7%)	0.000*	1.000
Pain in VAS mean ± SD (median)		7.4 ± 1.6 (8)	7.1 ± 1.4 (7)	7.2 ± 1.5 (7)	1353***	0.196

Treatment outcome analysis

There was a significant reduction of pain in VAS score at subsequent follow ups in both the groups. More reduction was observed in the first follow up in both the groups. However, patients in BTX group had experienced significant reduction of pain than NTG group (p value < 0.05 at each follow ups) (*Fig. 2*).

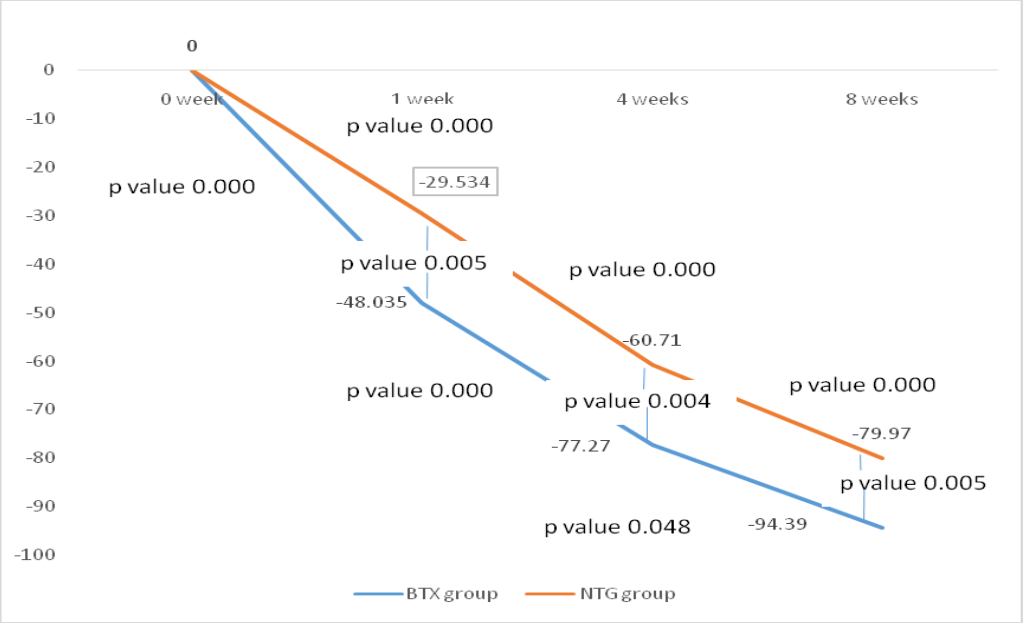

Figure 2: Figure showing mean percentage reduction of pain at subsequent follow ups

At two months, the fissure was healed in 89 (79.5%) patients, of which 50 (89.3%) patients were in BTX group and 39 (69.6%) in NTG group. Significant number of patients had healed anal fissure at 2 months in BTX group (p-value 0.01). The healing rate of BTX group was 96% in a study done by Brisinda et al in 1999,[14] 87% by Mentes et al in 2003[17] and 56% by Nasr et al in 2010.[18] For NTG group, it was 59% in a study done by Lund et al in 1997[4] and 60% by Brisinda et al in 1999.[14]

At 8 weeks, 1 patient in each group (2.1% in BTX group and 2.4% in NTG group) had persistence of bleeding per rectum; 2 (20%) patients in BTX group and none in NTG group had persistence of itching; and 1 (16.7%) patients in each groups had persistent discharge.

Till 2 months of follow up, no adverse effect was observed in BTX group. Seventeen (30.3%) patients complained of headache in some time of their application in NTG group, most (13 patients) at first week of evaluation. The various studies reported varied rates of headache. It was 19% in the study by Lund et al in 1996,[4] 56.4% in the study done by Lund et al in 1999,[7] 20% in the study by Brisinda et al in 1999.[14]

Since 6 patients (3 in each BTX and NTG groups) had not completed 3rd month of treatment, recurrence could not be evaluated in them. By the end of 3 months, 2 (4.26%) patients in BTX group and 6 (16.67%) patients in NTG group had recurrence, with no significant difference between the two groups (p value= 0.057).

At 6 months, total recurrence of anal fissure was observed in 4 (8.5%) patients in BTX group and 13 (36.1%) patients in NTG group. Significant difference of recurrence rate was observed at 6 months (p-value= 0.002).

Various studies have been done comparing the recurrence rate of BTX and NTG ointment. Brisinda et al in 1999 found no recurrences in each groups during the follow up for 15.4 months in BTX group and 16.1 months in NTG group.[14] Fruehauf et al in 2006 reported no recurrence in both the groups when followed for 24 months.[19] De Nardi et al in 2006 reported the recurrence of 20% in both the groups when followed for 30 months.[15]

This heterogeneous recurrence rates amongst various studies is due the difference in doses of Botulinum toxin, site of injection and lack of well-designed multicentric double blinded randomized trial.

Conclusion

In view of recent trends of medical therapy in chronic anal fissure, BTX injection and NTG ointment can be an effective form of therapy alternative to LIS.

BTX injection had the advantage of being more efficacious than NTG ointment in view of more healing rate, lesser recurrence rate and safety.

This study had a few limitations like short term follow up and being an assessor blinded study only.

Recommendation

BTX injection may be considered as first line of treatment for CAF for patients who refuse surgery, who have had previous sphincter surgery, or who are at a particular risk of incontinence with sphincterotomy. It is a minimal invasive therapeutic option with high healing rate, more pain relief, few adverse effects and lesser recurrence.

However, further large scale, high quality, multicentric trials based on commonly accepted end points with a long term follow up are required for the valid estimation.

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