



# Combination of Botulinum Toxin and Topical Diltiazem Versus Lateral Sphincterotomy in Treatment of Chronic Anal Fissure

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## ABSTRACT

**Introduction:** Chronic anal fissure (CAF) is a common anorectal condition with treatment modalities being introduced to avoid the complications of surgical intervention.

**Aims & Objectives:** To compare LIS versus combination of botulinum toxin injection and topical diltiazem in terms of frequency of healing in patients with chronic anal fissure. The outcome was measured frequency of healing of CAF within four weeks after treatment. Study design was randomized controlled trial (RCT)

**Place and duration of study:** The place was Surgical Department, Chaudhry Mohammad Akram Lahore. And duration of study is 6 months (1<sup>st</sup> Jan 2022 to 31<sup>st</sup> June 2022)

**Material & Methods:** Total 100 patients were enrolled and randomly allocated into two groups A& B (50 in each group). In Group A patients LIS (open technique) was performed. While in group B, patients were administered, 20 U of botulinum toxin A diluted in 2 ml normal saline was injected via 27 G insulin needle into the internal sphincter around the fissure area. Furthermore, diltiazem paste was applied twice daily up to two weeks. All patients were assessed for healing of the fissure weekly up to four weeks. Data was analyzed using SPSS version-24, P-value<0.05 was taken as significant

**Results:** Out of 100 patients, 82 (82%) patients showed complete healing within four weeks of treatment. The healing within four weeks was 94% in group A and 70% in group B (p value 0.002).

**Conclusion:** The frequency of healing of CAF by LIS is significantly higher than the combination of botulinum toxin plus topical diltiazem. The results can be applied after satisfactory confirmation from the larger RCTs.

**Keywords:** Botulinum toxin, chronic anal fissure CAF, Chemical sphincterotomy Diltiazem ointment, Lateral internal sphincterotomy (LIS)

## INTRODUCTION

Anal fissure is a linear tear in the anal canal affecting all age groups. Etiology is idiopathic, passage of hard stool leads to micro trauma of the anal mucosa which can lead to fissure formation. The continuous vibratory trauma can also lead to formation of fissure. The tone of internal sphincter is increased which leads to mucosal ischemia<sup>1</sup>. Every time patients passes stool, the pain and bleeding per rectum are evident. Acute anal fissure responds to medical treatment very well and thus conservative approach is the best option. Chronic anal fissure (CAF) is nasty condition for which surgical and medical both treatment modalities are used<sup>1</sup>. Initially sphincterotomy was done via posterior midline technique at the site of the fissure, but with poor healing. Hence, currently sphincterotomies are done in the right or left lateral quadrants with incision being given just to the

internal anal sphincter by sparing the external sphincter<sup>2,3,4,5</sup>.

Current treatment modality for anal fissure is Lateral internal sphincterotomy, done under spinal anesthesia with the aim to release the hypertrophied internal sphincter, which increases the blood supply thereby allowing the fissure to heal in a quick process. LIS can be performed via two techniques, open or a closed manner. A small sized blade is inserted into the intersphincteric plane between the external and internal sphincter with rotation of the blade sideways to cut the internal sphincter. Care being taken to spare the anal mucosa, to prevent fistula formation in the postoperative course.

The topical application of glyceryl trinitrate has been used as non-surgical remedy to decrease the tone of sphincter. The side effects like dizziness, headaches etc. are irritating to some patients. Topical application of diltiazem is another promising drug which can provide healing without any significant side effects<sup>1,6</sup>. Other local applications like emulgel have also been used<sup>11</sup>.

Acute or chronic anal fissures can be treated chemically by directly injecting Botulinum toxin (eg, onabotulinumtoxinA) at the site of fissure at the internal sphincter. Botox has a short-term effect of 3 months because of nerve regeneration, which is enough time to allow fissures to heal with resolution of the active symptoms. The chemical sphincterotomy by the botulinum toxin injection has been used as good alternative to LIS<sup>7</sup>. Gandomkar, H., et al. (2015) compared LIS with combination of botulinum toxin and topical diltiazem and found that frequency of healing was 65% versus 95% for botulinum-diltiazem versus LIS groups respectively (p value <0.001)<sup>8</sup>.

Some studies prefer the use of botulinum toxin as standard treatment to avoid the risks associated with surgical sphincterotomy<sup>9</sup>. The data regarding various treatment modalities is conflicting due to various side effects<sup>10</sup>. The present study was designed to compare combination of botulinum-diltiazem with internal sphincterotomy in terms of frequency of healing among cases of CAF. In Pakistan, there is no recent data available regarding this aspect as all studies compared LIS with single drug. The results produced would help choose a better modality in terms of frequency of healing in anal fissure. This was led to reduced morbidity associated with this nasty condition.

## MATERIAL AND METHODS

The study was conducted at the Department of Surgery, Chaudhry Mohammad Akram Hospital, Lahore after receiving Institutional IRB Clearance on 20<sup>th</sup> Dec 2021, Duration of this study was 6 months (1<sup>st</sup> Jan 2022 to 31<sup>st</sup> June 2022). The study design was randomized controlled trial.

Sample size of 100 cases (50 in each group) was calculated. Sequentially numbered opaque envelopes generated through randomly numbered table were used to randomise the study subjects into two groups. The expected healing in LIS group A was taken as 94%, and botulinum-diltiazem group B as 65%<sup>8</sup>. The power of test was 90% and level of significance was kept 5%. Consecutive Non-probability sampling technique was used, Patients with CAF as per operational definitions with age range of 18 to 55 years of both gender male and female included in this study. Exclusion criteria were history of chronic medical conditions like diabetes mellitus, chronic liver or kidney failure as diagnosed on history and investigations, previous history of any treatment for anal fissure in last one month and history of anorectal surgery.

## Operative Technique and Procedure:

In Group A Lateral internal sphincterotomy (open technique) was performed under spinal anaesthesia in the intersphincteric plane with the internal sphincter being brought up into the incision, given a cut under direct vision so as to let the cut ends fall back. After the procedure the gap was directly palpated which indicated a defect of the anal mucosa by cutting the internal sphincter.

## Injection Botulinum Toxin:

Group B patients received 20 U of botulinum toxin A diluted in 2 ml normal saline injected via 27 G insulin needle into the internal sphincter around the fissure area. Furthermore, diltiazem paste was applied twice daily up to two weeks. All patients were assessed for healing of the fissure weekly up to four weeks.

**Statistical Analysis:** Data was analyzed using SPSS version 24. The quantitative variables like age, body mass index (BMI) and duration of disease were expressed as mean  $\pm$  SD. The quantitative data like gender, location of fissure and healing expressed as frequency and proportions. Both groups were compared amongst each other in terms of healing by Chi square test. Effect modifiers like age, BMI, gender, duration of disease and location of fissure were controlled by stratification. Post stratification Chi square test was applied. P value  $\leq$  0.05 is considered as statistically significant.

## RESULTS

Total of 100 patients were studied for a period of eight months. The mean age was 31.64  $\pm$  8.41 years which was stratified, and groups are given below in bar graph. The mean duration of CAF was 9.20  $\pm$  3.56 months. The mean BMI was 26.61  $\pm$  3.478 kg/m<sup>2</sup>. Out of 100 patients, 82 (82%) patients showed complete healing within four weeks of treatment. The 84% of patients has posterior anal fissure in rest of the patients' fissure was located anteriorly.

The quantitative variables measured were age, BMI and duration of disease with no difference between groups as p values were 0.524, 0.24 and 0.14 respectively. Gender and location of fissure also showed no difference with p-values 0.812 and 0.275 respectively.

After four weeks 94% in group A showed healing and 70% in group B (p value 0.002). The data was stratified according to age, gender, BMI, duration of disease and location of fissure. The results showed that the frequency of healing was more in group A as compared to group B for following stratification groups; age <30 years (p value 0.008), male gender (<0.0001), BMI >25 kg/m<sup>2</sup> (p value 0.004),

duration of CAF <9 months (p value 0.048), duration of CAF >9 months (p value 0.019), anterior location of fissure (p value 0.013), posterior location of fissure (p value 0.018).

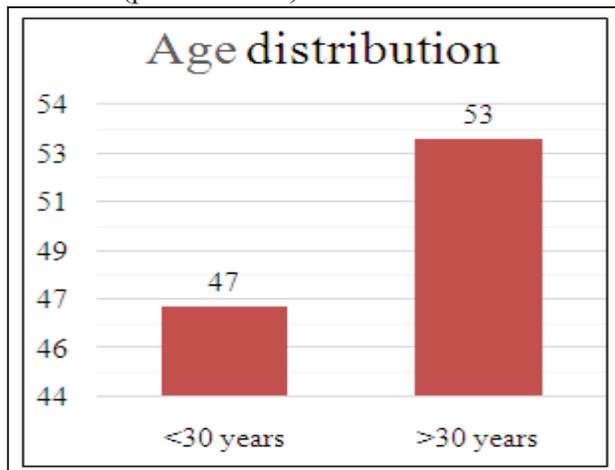


Fig-1: Age Stratification in two groups

Variable	Group	N	Mean	SD	P-Value
Age	A	50	32.18	8.775	0.524
	B	50	31.10	8.084	
BMI	A	50	26.20	3.499	0.240
	B	50	27.02	3.443	
Duration	A	50	8.68	3.650	0.145
	B	50	9.72	3.429	

Table-1: Baseline Characteristics of Both Groups

Treatment Groups	Group	Healing			P-Value	
		Yes	No	Total		
Group	A	Count	47	3	50	0.002
		% Within Group	94.0 %	6.0 %	100.0 %	
		% Within Healing	73.4 %	8.3 %	50.0 %	
	B	Count	35	15	50	
		% Within Group	70.0 %	30.0 %	100.0 %	
		% Within Healing	42.7 %	83.3 %	50.0 %	
Total	Count	64	82	146		
	% Within Group	64.0 %	82.0 %	146.0 %		
	% Within Healing	100.0 %	100.0 %	100.0 %		

Table-2: Healing among group A & B.

Healing is compared in group A and B on basis of age group. Table iii showing percentage of healing by LIS in Group A and group B includes use of botulinum toxin + diltiazem ointment. In group A

percentage of healing is 73% as compared to group B e.g., is 42.7%. Healing in group A is highly significant with P value of 0.002%.

Treatment Groups	Group	Healing			P-Value	
		Yes	No	Total		
Group	A	Count	23	1	24	0.008
		% Within Group	95.8 %	4.2 %	100.0 %	
		% Within Healing	60.5 %	11.1 %	51.1 %	
	B	Count	15	8	23	
		% Within Group	65.2 %	34.8 %	100.0 %	
		% Within Healing	39.5 %	88.9 %	48.9 %	
Total	Count	38	9	47		
	% Within Group	80.9 %	19.1 %	100.0 %		
	% Within Healing	100.0 %	100.0 %	100.0 %		

Table-3: Healing amongst groups for age <30 years.

Total 47 patients were included in this this age group (<30yrs) with significant p – value of 0.008 showing healing. It's found that in group A of < 30yrs age 23 patients (95.8%) with CAF healed with LIS. Only 1 patient could not heal (4.2%). Whereas in group B (Botulinum toxin + diltiazem) 15 patients (65%) were healed and 8 patients were not healed (19%). Total percentage of healing in both groups was 80.9% with significant P-value 0.008.

Treatment Groups	Group	Healing			P-Value	
		Yes	No	Total		
Group	A	Count	24	2	26	0.077
		% Within Group	92.3 %	7.7 %	100.0 %	
		% Within Healing	54.5 %	22.2 %	49.1 %	
	B	Count	20	7	27	
		% Within Group	74.1 %	25.9 %	100.0 %	
		% Within Healing	45.5 %	77.8 %	50.9 %	
Total	Count	44	9	53		
	% Within Group	83.0 %	17.0 %	100.0 %		
	% Within Healing	100.0 %	100.0 %	100.0 %		

Table-4: Healing amongst groups for age >30 years.

Total 53 patients were taken in this group with P-value 0.07. 24 (92.3%) patients were included in group A and only 2 (7.7%) patients could not heal. While in group B 20 (74%) CAF patients was healed and 7(25.9%) patients could not heal.

### DISCUSSION

Anal fissure is the linear tear in the epithelium of anal canal which can have both acute and chronic forms. The acute form can be managed with medical treatment effectively, but chronic form is refractory to most of the medical remedies. Its incidence is around 1 in 350 adults. Both male and female

patients are equally affected but young adults are more prone to it<sup>13,14</sup>. The location is mostly posterior. The physical examination shows that there is spasm of internal anal sphincter which is further increased in intensity when the stool passes and adds a new insult to fissure area. This positive feedback mechanism must be broken to achieve the satisfactory healing. The common cause of CAF is constipation but diarrhea and other events leading to local trauma can be causative. Most of the patients present with local pain which is cutting in nature. The itching and bleeding are also common. All the symptoms are started at the time of defecation<sup>10, 15</sup>.

All the treatment protocols are focused to reduce the anal tone. The medical treatment is started and local application of vasodilators like glyceryl trinitrate is used commonly<sup>10,16</sup>. The local application of calcium channel blockers like diltiazem, nifedipine are also effective<sup>1, 8</sup>. The botulinum injection into sphincter can break the tone also. The Botox is very safe, effective but associated with relapse<sup>5</sup>. The surgical option is reserved for the cases in which medical therapy is ineffective. Lateral internal sphincterotomy is the most common surgical procedure with excellent results<sup>13,14,15</sup>. LIS is associated with minor complications but at large the results are excellent. Early return to activities, healing, pain and psychological benefits are worthy<sup>17</sup>.

Giral, A., et al. (2004) compared LIS and botulinum injection for the treatment of CAF. The healing was higher in LIS group, but the results were not statistically significant (70% versus 82% for botulinum and LIS groups respectively,  $p > 0.05$ )<sup>19</sup>. The diltiazem was not assessed in combination in this study. Another study in 2005, compared the same modalities and found that LIS is more effective than botulinum injection which gives 60% healing rate ( $p < 0.05$ ). This study recommended the use of botulinum injection as first line of therapy for the treatment due to day care procedure. Moreover, the risk of incontinence was also reduced in injection group<sup>20</sup>. A meta-analysis by Shao, W. J., et al. (2009) concluded after assessing four studies encompassing 279 patients who underwent LIS had higher healing rate compared to BOTOX injection but with a minor side effect of anal incontinence<sup>21</sup>.

A study in 2010 by Nasr, M., et al. compared Botox and LIS in 80 patients who had failed medical treatment for CAF. The results went in favor of LIS then the Botox group ( $p = 0.0086$  and 95% CI = 7.38-45.69%)<sup>22</sup>. The healing rate noted by Valizadeh, N., et al. was 88% with LIS and 44% with Botox. This study had small sample size of 50 patients and the healing was assessed after two

months 'time<sup>23</sup>. The rate of incontinence associated with LIS is the main drawback and is shown in many studies. The choice of therapy for CAF should be individualized<sup>3,4,17</sup>.

Gandomkar, H., et al. (2015) had the same study parameters and groups as in the present study. Randomized control trial was conducted on 99 patients being randomly assigned to two treatment groups, one had LIS and another had combined BOTOX with diltiazem. The primary outcome was healing of the fissure. The results showed that LIS showed 94% and Botox plus diltiazem showed 65% healing at the end of treatment for six weeks ( $p$  value  $< 0.001$ )<sup>8</sup>. As compared, healing in my study was noted within four weeks. The healing was 94% in group A and 70% in group B ( $p$  value 0.002). As compared to above study the current research lacked the frequency of incontinence in outcome variables. Age, gender, BMI, duration of disease and location of fissure were the factors studied in our research which showed that the frequency of healing was more in group A as compared to group B for following stratification groups; age  $< 30$  years ( $p$  value 0.008), BMI  $> 25$  kg/m<sup>2</sup> ( $p$  value 0.004).

## CONCLUSION

The frequency of healing of chronic anal fissure by LIS is significantly higher than the combination of botulinum toxin plus topical diltiazem. The results can be applied after confirmation of larger RCTs.

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