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## Treatment Of Chronic Anal Fissure; Lateral Internal Sphincterotomy Versus Local Injection Of High Dose Botulinum Toxin. A Randomized Clinical Trial.

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### ABSTRACT

Chronic anal fissure (CAF) develops after failure of medical treatment of acute anal fissure mostly due to spasm of internal anal sphincter (IAS), the principals of treatment of (CAF) aim at (IAS) relaxation, lateral internal sphincterotomy (LIS) is the most popular surgical solution, botulinum toxin (BOTOX) injection is a less invasive procedure that achieve chemical sphincterotomy. In this study we are evaluating the outcome of each procedure. Two groups of patients with CAF each 48 patients the (BOTOX) group received 80 IU botulinum toxin injection in the IAS at 1,5,7, and 11 O'clock positions the (LIS) group underwent (LIS) under general anesthesia. Demographic, preoperative and postoperative outcome data was collected and properly analyzed. Demographic and postoperative data shows non-significant differences between both groups, postoperative pain is significantly less in (BOTOX) group, healing rate was significantly better in (LIS) group, being 37 (77.1%) in (BOTOX) group and 44 (91.7%) in (LIS) group, recurrence rate was significantly higher in (BOTOX) group (5 out of healed 37 cases) (13.5%) in (BOTOX) group, and (1 out of healed 44 cases) (2.3%) in (LIS) group. In the early postoperative time, Incontinence was significantly higher in (BOTOX) group, 8 cases, (16.6%) all of them improved over time, in (LIS) group 5cases (10.4%) developed incontinence, 2 of them (4.2%) were permanently incontinent to flatus. (BOTOX) injection is safer than (LIS) in treatment of CAF but with less efficacy, its dose need to be adjusted, (LIS) is more efficient but anal sphincter tone need to be assessed before the operation

**Keywords:** botulinum toxins, sphincterotomy, anal fissure, sphincterotomy

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## INTRODUCTION

Chronic anal fissure (CAF) is defined as vertical crack or ulcer in the anoderm with skin tag (sentinel pile) at its distal end and hypertrophied anal papilla at its proximal end with induration of the edges<sup>(1-2)</sup>, CAF usually presents with anal pain, fresh anal bleeding and constipation<sup>(3, 4, 5)</sup>. CAF is located posteriorly (90%), or anteriorly (more in female with vaginal delivery)<sup>(6)</sup>, if CAF is found in lateral position, specific disease i.e. Crohn's disease should be put in consideration<sup>(7)</sup>. Anal fissure is considered chronic if conservative treatment of acute anal fissure failed with persistence of symptoms for 8 to 12 weeks<sup>(8)</sup>. Chronicity of anal fissure is mostly attributed to decreased blood supply of the anoderm due to spasm of the internal anal sphincter<sup>(7)</sup>. Definitive treatment of CAF is mostly surgical and internal sphincterotomy (IS) is considered the standard management of CAF<sup>(9, 10, 11)</sup>, other measures include laxatives, stool softeners, pain killers and local anesthetics<sup>(12)</sup>. Calcium channel blocker (diltiazem)<sup>(13)</sup> and Glyceryl trinitrate (GTN) were extensively used as smooth muscle relaxants with good results when used with the other conservative measures<sup>(14)</sup>, botulinum toxin (BOTOX) injection have been used for chemical sphincterotomy with good outcome<sup>(15)</sup>. The outcome of the deemed treatment is complete healing of the fissure, and anal continence, with (IS) healing rate ranges between 80 and 100%, failure of treatment ranges between zero and 8%, and incontinence ranges between zero and 20%. Different studies on (BOTOX) injection revealed healing rate ranging between 25% and 96%, failure of treatment in 8 to 78%, and incontinence in zero to 19%.<sup>(1)</sup> In the current study we are trying to find which of (BOTOX) injection or (IS) is more efficient and safer for treatment of (CAF) regarding healing rate, recurrence rate and incontinence as a disabling complication.

## PATIENTS AND METHODS

This randomized comparative clinical trial was carried out over 2 year in the period between June 2017 and May 2019 on total number of 96 patients suffering chronic anal fissure, the participants were randomly allocated into two groups each 48 patients; group (1) the botulinum ( Botox) group, they were subjected to 80 IU (BOTOX) injection as an intervention for chemical sphincterotomy, and group (2) the surgical lateral internal sphincterotomy (LIS) group, underwent fissurectomy (LIS) as a surgical intervention for treatment of chronic anal fissure.

The study was approved by the institutional review board (IRB) and the local ethical committee of our university hospital, it was registered in clinical trials with the identifier number, NCT04166175.

The condition of the current study is chronic anal fissure defined as the presence of anterior or posterior vertical anal crack with skin tag at its lower end and hypertrophied anal papilla at its upper end with induration around its edges in patients complaining of anal pain, constipation, and/or fresh anal bleeding for at least two months.

Randomization was achieved using computer generated cards. , study sample size was calculated by the statistical unit of IRB in our institute.

### Inclusion criteria;

- patients suffering chronic anal fissure aged above 16 years old

### Exclusion criteria;

- those with previous anal surgery,
- complicated anal fissure,
- Patients unfit for surgery,
- Patients with specific disease as Crohn's disease, ulcerative colitis and anorectal malignancy,
- Malignancy,
- Anal fistula or abscess
- those with systemic disease requiring treatment with calcium channel blockers and /or nitrates
- Hypersensitivity to botulinum toxins

Patients of both groups were subjected to thorough history taking, obstetric history in female patients, clinical examination, digital rectal examination and anorectal manometry for diagnosis of chronic anal fissure and exclusion of any other anal condition and incontinence, patient signed an informed written consent, and routine preoperative investigations were performed as usual.

**Interventions;**

- 1- Botulinum toxin (BOTOX) injection; was performed under general anesthesia in the lithotomy position, where 80 IU of (BOTOX) was injected in four positions each 20 IU namely in 5, 7, 11, and 1 O'clock positions in the internal sphincter not deeper than the midpoint of the anal canal.
- 2- Lateral internal sphincterotomy; was performed under general anesthesia where the lower part of the internal sphincter was cut by electrocautery after opening the skin of the intersphincteric groove, on the left lateral site and not extending beyond the proximal end of the fissure, the chronic fissure complex was also removed. The wound was left open at the end of the procedure after sufficient hemostasis.

After the procedure patients were advised for stool bulking agents, stool softener, and sitz baths.

Follow up was carried out in the outpatient clinic by the attending surgeon (not a study participant) after 1 week then 1, 2, 3, 6, 9 and 12 months post-procedure.

The primary outcome of the current study is complete healing of the chronic anal fissure defined as complete epithelialization of the fissure crack detected on clinical examination, recurrence in the follow up time defined as development of fissure after complete healing. And development of incontinence, incontinence is described by patient's questionnaire as in terms of Vaizey score <sup>(16)</sup>, as shown in table 1.

**Table 1, Vaizey score**

Incontinence	Never	Rarely	Sometimes	Weekly	Daily
Solid stool	0	1	2	3	4
Soft stool	0	1	2	3	4
Flatus	0	1	2	3	4
Alteration in lifestyle	0	1	2	3	4
				No	Yes
Need to wear a pad or plug				0	2
Taking constipating medicines				0	2
Lack of ability to defer defecation for 15 minutes				0	4

*Daily, 1 or more episodes a day; Weekly, 1 or more episodes a week but <1 a day; Sometimes, >1 episode in the past four weeks but <1 a week; Rarely, 1 episode in the past four weeks; Never, no episodes in the past four weeks. minimum score = 0 = perfect continence, maximum score = 24 = totally incontinent.*

The secondary outcome is postoperative or post-injection pain measured by visual analogue scale (VAS) and the rate of complete healing (defined as complete epithelialization of the fissure or fissurectomy wound) each month.

Demographic data, presentation data, follow up data including primary and secondary outcome all collected and analyzed properly using t test, chi square test, and Z test in SPSS program 22 version.

**RESULTS**

As presented in table 2 the demographic data shows non-significant differences between both groups; the mean age of (BOTOX) group patients 33.46±10.18 years and 32.29±9.88 years in (LIS) group patients, in (BOTOX) group there were 32 (66.7%) males and 16 (33.3%) females, while in (LIS) group there were 26 (54.2%) males and 22 (45.8%) females, mean duration of the disease was 6.3 ±3.27 months in

(BOTOX) group and 5.5±2.3 months in (LIS) group there was history of vaginal delivery in 11 (22.9%) patients of (BOTOX) group and 10 (20.8%) patients in (LIS) group, the commonest presenting symptom was pain, followed by constipation, bleeding and pruritus in both groups with the same order, posterior fissure is more common in both groups.

**Table (2): demographic and preoperative criteria.**

		(BOTOX) group	(LIS) group	P-value
Age		33.46±10.18	32.29±9.88	0.29
Gender	Male	32 (66.7%)	26 (54.2%)	0.21
	Female	16 (33.3%)	22 (45.8%)	0.21
Duration		6.3 ±3.27 months	5.5±2.3 months	0.08
History of vaginal delivery		11 (22.9%)	10 (20.8%)	0.8
Presentation	Pain	48 (100%)	48 (100%)	
	Bleeding	26 (54.1%)	28 (58.3%)	0.68
	Constipation	39 (81.25%)	38 (79.2%)	0.79
	Pruritus	16 (33.3)	14 (29.1%)	0.66
Site	Posterior	34 (70.9%)	36 (75%)	0.65
	Anterior	14 (29.1%)	12 (25%)	0.65

*P < 0.05 = significant difference.*

The early follow up of patients, as presented in table 3; bleeding occurred in 2 patients of (LIS) group it stopped spontaneously, ecchymosis complicated 1 case in (BOTOX) group that disappeared after 2 weeks. VAS shows greater pain measurement in (LIS) than (BOTOX) group being 1.4 ± 0.94 in (BOTOX) group and 2.85 ± 1.33 in (LIS) group with significant difference after 1 week.

Incontinence to flatus occurred in 8 (16.6%) cases 4 of them were also incontinent to soft stool, the condition improved with time and all patient were fully continent after 5 to 6 months,

In the (LIS) group incontinence to flatus complicated 5 (10.4%) patients which improved by time but 2 (4.2%) patients continue to suffer incontinence even after 6 months, the mean Vaizey score measurement as presented in table 3 shows significant difference between both groups regarding development of incontinence in the early months of follow up.

Healing rate after 1 month was in favor of (BOTOX) group without significant difference but it turned to be better in (LIS) group after 2 months with significant difference in both groups.

Delayed healing (after 2 months) occurred in 11 cases of (BOTOX) group and 4 cases of (LIS) group with significant difference.

Recurrence after complete healing shows significant difference between both groups as it occurred in 5 cases out of healed 37 cases in (BOTOX) group in 1 case out of healed 44 cases in (LIS) group, the follow up data presented in table 3.

**Table (3): follow up data.**

		(BOTOX) group	(LIS) group	P-value
Bleeding		0	2	0.76
Ecchymosis		1	0	0.17
Pain score (VAS) after 1 week		1.4 ± 0.94	2.85 ± 1.33	< 0.001
Incontinence rate	1 <sup>st</sup> months	8 (16.6%)	5 (10.4%)	0.37
	After 6 months	0	2 (4.2%)	0.15
Vaizey incontinence score)	After 1 week	0.65±1.56	0.19±0.61	0.03
	After 1 month	0.54±1.3	0.15±0.46	0.025
	After 6 months	0	0.06 ± 0.31	0.09
Healing per month	1 <sup>st</sup> month	17	18	0.42

	2 <sup>nd</sup> months	37 (77.1%)	44 (91.7%)	0.024
Delayed healing		11 (22.9)	4 (8.3%)	0.024
Recurrence		5/37 (13.5%)	1/44 (2.3%)	0.027

*P < 0.05 = significant difference.*

### DISCUSSION

Pathogenesis of CAF depends mainly on increased tone of the internal anal sphincter, Opazo et al<sup>(17)</sup> in his study stated that patients with CAF have higher internal sphincter tone together with reduced sphincter relaxation, based on that theory treatment of CAF runs in two lines the first is symptomatic measures to alleviate patient complain, the second is relaxation of the internal anal sphincter to promote vascularity of anoderm and improve healing power.

In acute fissure the condition can be treated by pain killers, laxatives, stool softeners and local topical agents as nitrates (GTN) and calcium channel blockers (deltiazem). Deltiazem is preferred than nitrates as it causes less headache.

In CAF, and together with conservative measures, (LIS) and (BOTOX) injection were used as invasive maneuvers to control the increased tone of IAS, posterior sphincterotomy was first introduced in 1951 by Eisenhammer<sup>(18)</sup> later, Notaras in 1969 described (LIS), since that time (LIS) had become the gold standard surgical treatment of CAF after failure of conservative measures<sup>(19)</sup>, (LIS) has complications which is not uncommon, as postoperative bleeding, urine retention, delayed healing, fissure recurrence and incontinence.

(BOTOX) injection was introduced for chemical sphincterotomy with the advantages of less invasiveness and temporary action, the dose of injection varies between 20 IU and 80 IU, but in some studies for control of cardiac achalasia, the whole vial (100) IU was injected in the cardiac sphincter without complications. The incidence of incontinence with (LIS) varies among studies, Garg et al reported in systematic review an overall incidence of incontinence about 14%, Valizadeh<sup>(6)</sup> reported 20% incontinence incidence after 3 months follow up which reduced to 4% after 1 year, with (BOTOX) he reported (12%) after 2 months, this was reduced to zero on the 3<sup>rd</sup> month follow up, in our study we recorded incontinence rate 16.6% in (BOTOX) group which improved to zero after 6 months follow up and 14.2% with (LIS), some patients improved but 4.2% got permanent incontinence, if accurate preoperative assessment of the anal sphincter was carried out we could adjust the bulk of the internal anal sphincter muscle to be cut, the higher rate of early incontinence among (BOTOX) group may be due to high dose or higher level of injection.

The healing rate in our study was in favor of (LIS) (91.7%) more than that in (BOTOX) group (77.1%) the results of healings varies among the studies but (LIS) had a better healing rate, and (BOTOX) injection had to be re injected for delayed or failure of healing in many studies, it was noticed that patient with longer history of the disease had a higher incidence of delayed or failed healing<sup>(21)</sup>.

The rate of recurrence in our study is higher in the (BOTOX) group (13.5%) than (LIS) group (2.3%) the botulinum toxin temporary action may explain these findings.

There were no significant differences between groups regarding bleeding, hematoma or ecchymosis, but post-operative pain was significantly higher in the (LIS) group, this was recorded also by Chen et al<sup>(21)</sup>.

### CONCLUSION

(BOTOX) injection is safer than (LIS) in treatment of CAF but with less efficacy, its dose need to be adjusted, (LIS) is more efficient but anal sphincter tone need to be assessed before the operation.

N=96

- Exclusion criteria;**
- those with previous anal surgery,
  - complicated anal fissure,
  - Patients unfit for surgery,
  - Patients with specific disease as Crohn’s disease and ulcerative colitis,
  - Malignancy,
  - Anal fistula or abscess
  - those with systemic disease requiring treatment with calcium channel blockers and /or nitrates
  - Hypersensitivity to botulinum toxins

- Inclusion criteria;**
- patients suffering chronic anal fissure aged above 16 years old

Botox group n=48

Allocation

LIS group n=48

Injection of 80 IU botulinum toxin in the internal anal sphincter

Intervention

Lateral internal sphincterotomy

Bleeding	0
Ecchymosis	1
Pain score (VAS) after 1 week	1.4 ± 0.94
Incontinence rate :	
After 1 month	8 (16,6%)
After 6 months	0
Healing rate:	37 (77.1%)
Delayed healing	11 (22.9%)
Recurrence	5/37 (13.5%)

Outcome

Bleeding	2
Ecchymosis	0
Pain score (VAS) after 1 week	2.85 ± 1.33
Incontinence rate :	
After 1 month	5 (10.4%)
After 6 months	2 (4.2%)
Healing rate:	44 (91.7%)
Delayed healing	4 (8.3%)
Recurrence	1/44 (2.3%)

**Conclusion;**

BOTOX injection is safer than LIS in treatment of CAF but with less efficacy, its dose need to be adjusted, LIS is more efficient but anal sphincter tone need to be assessed before the operation.

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