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EFFICACY OF BOTULINUM TOXIN TYPE A IN THE TREATMENT OF CHRONIC ANAL FISSURE

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Abstract

Lateral partial internal sphicterotomy has been the goal standard for the treatment of chronic anal fissure. The main drawback of this approach remains its effect on the anal continence. Intrasphincteric of botulinum toxin seems to be a reliable and safe option resulting in temporary paralysis of the internal sphincter spasm and so promoting the chronic fissure to heal. The aim of this prospective control randomized study was to compare the effectiveness and the outcome of botulinum toxin injection with the lateral internal sphicterotomy in the treatment of the chronic anal fissure.

Ninety male patients who have been presented with chronic uncomplicated anal fissure, were randomized to either lateral internal sphincterotomy or intrasphincteric injection of botulnium toxin. Postoperative complications and pain, healing rate of the fissure, anal incontinence and recurrence of the fissure after treatment during six months follow up period were studied and assessed.

The healing rate was 95.5% in the surgical group with recurrence noted in only one patient and one patient had a partial permanent incontinence while in the botulnium toxin group the healing rate was 84.4%. Two patients had transient incontinence which improved spontaneously over six months period. Five patients had recurrence within the same follow period.

Lateral internal sphicterotomy and botulinum toxin injection both seems to be effective treatment of the chronic anal fissure. Although surgical approach is still the most common and gold standard treatment for the chronic anal fissure, It shows a higher incidence of incontinence and greater morbidity and pain than botulinum toxin injection. We conclude that the use of botulinum toxin to treat chronic anal fissure is safe, simple and effective approach especially in patients older than 50 years or those with risk of anal incontinence despite the higher rate of recurrence which can be minimized by the second session of botulinum toxin injection.

Introduction

Anal fissure is a tear in the mucosal lining of the anus usually in the midline posteriorly below the dentate line. The tear typically extends into the internal anal sphincter. The fissure is described as acute if it has been present for less than six weeks or chronic if present more than six weeks which is characterized by the presence of distal sentential pile or skin tag distally at the anal verge and proximally by hypertrophied anal papillae[1].

Once a fissure develops, the internal anal sphincter typically goes into spasm, causing further separation of the tear and such impairing healing and causing more pain. Exposure to feces also slow healing. Patients with anal fissure characteristically present with a tearing anal pain on or after defecation and often accompanied by bright blood on toilet papers[2].

The pathogenesis of chronic anal fissure is not completely understood. For many years, it was thought that passage of hard large stool during a period of constipation tore the anoderm causing the fissure. Several studies have found that the blood supply to the anoderm at the posterior midline is significantly lower than the other side of the anal canal. This may explain the propensity for a fissure to occur in the midline posteriorly. In addition the persistent hypertonia of the internal anal sphincter

may also impair blood flow to the sphincter and overlying epithelium leading to ischemic damage. Fissures are thus predominantly located in the posterior midline but 25%of women and 8%of men have anterior fissure. Multiple or other locations around the anal canal should raise the suspensions of the inflammatory bowel disease, TB, leukemia, syphilis or infection with HIV[2,3].

About 80% of acute anal fissures heal by a conservative measures and medical treatment and only 20% become chronic. Increased anal pressure, both resting and during straining have been observed with chronic anal fissure and considered as a major pathological factor. Infection or lymphatic obstruction secondary to persistent inflammation and mainly the ischemia secondary to hypertonia may be responsible for poor healing and development chronic anal fissure[4].

The current surgical treatment of the chronic anal fissure is lateral partial internal sphincterotomy and not anal dilatation. This surgical approach can be effective for more than 90% of cases but need general or local anesthesia. The main drawback of this operation is its potential risk to cause gas, mucous or occasionally stool incontinence which is permanent in 8-30% of patients and this surgical approach may also associated with abases formation and anal deformities[5].

During the recent years new treatment modality of inducing medical or chemical sphincterotomy such as the local application of topical nitric oxide cream or ointment, calcium channel blockers and more recently the injection of botulinum toxin type A (BTX-A) have been tried and used to achieve fissure healing[6].

Botulinum toxin is neurotoxin produced by bacterium; Clostridium botulinum. It temporarily paralyzed muscles for up to three months and can be injected into internal anal sphincter muscles in a clinician office without anesthesia or sedation. This method has been described initially by Jost and Schmrigk and found to be effective treatment in comparison with placebo. Furthermore, botulinum toxin was more effective than topical nitrate which constitute another therapeutic option. The dose is extremely low and has virtually no risk of causing botulism poisoning. Mild anal incontinence (gas or stool leakage) noted in about 7% of the patients. The toxin is injected directly into internal anal sphincter and in effect, it performs a chemical sphincterotomy. This effect last about three months period and allow anal fissure to heal and symptoms to resolve In cases were toxin injection provide initial relief of symptoms but there is a recurrence after three months period, these patients may benefit from a second trail of toxin injection or from a surgical sphincterotomy[6,7].

The aim of this study was to compare the therapeutic effects of botulinum toxin and lateral internal sphincterotomy in selected patients with chronic anal fissure.

Patients and methods

Ninety consecutive adult patients with chronic anal fissure were included in this prospective randomized control study. Patients were assigned to either surgical sphincterotomy (group I, n=45) or chemical sphincterotomy with botulinum toxin type A 40 IU (group II, n=45). The study was conducted as a day case procedure. Patients included were all males and diagnosed clinically as chronic anal fissure based on history and physical examination. Previous perianal operations, other anal pathology such as piles or fistula, inflammatory bowel disease, bleeding disorders and suspicion of malignancy were excluded from this study.

Treatment options were decided according to the patient's choice after a detailed explanation and advantage and disadvantage of each option. All patients underwent a preoperative evaluation which includes preoperative routine investigation and the clinical inspection of the fissure. The diagnosis of chronic anal fissure was based only on the history of defecatory, postdefecatory or nocturnal pain, bleeding

or both and on evidence of posterior midline circumscribed ulcer with a large sentinel skin tag and exposure of the white horizontal fiber of the internal sphincter and indurations at the edges of the fissure. Most middle age and elderly patients preferred botulinum toxin rather than surgery. Patients who allocated to botulinum toxin therapy, the chemical sphincterotomy was carried out using 100 IU vial of type A botulinum toxin (Botox, Allergan) which was stored at temperature of 20C^{o} and diluted in one ml of normal saline, the dilution was carried out immediately after injection. The injection done at outpatient clinic using 27 gauge needle with insulin syringe one ml without anesthesia and 0.5 ml of diluted toxin(20 IU) injected into internal sphincter by feeling the sphincter on each side of anal fissure.

In the surgical group, lateral internal sphincterotomy technique was performed under general or sometime local anesthesia in the lithotomy position by open technique through a circumferential incision placed laterally to the skin outside the anal verge at 3 o'clock position. The anoderm and intersphincteric groove were dissected and then the internal sphincter was divided under direct vision below the dentate line by using a monopolar electrocautery. The wound was then either left open or closed with single interrupted catgut 3/0 suture. Postoperatively in both groups patients were put on high fibers diet, frequent sitz bath, laxative and analgesic on need. Patients after discharge, patients were followed up for the degree of pain, bleeding, constipation, healing and incontinence after one week, three weeks, two months and after six months for persistence, recurrence and incontinence.

The primary goal of this study was complete healing of the chronic anal fissure by usage of botulinum toxin. The treatment was considered successful if the fissure healed two months after the treatment. Complications were described as incontinence for flatus and feces, abscess formation and perianal fistula and thrombosed external hemorrhoid.

Continence status was evaluated by asking the patients about their ability to control flatus, liquid stool and well form stool. The patients who failed to heal or improve after botulinum toxin injection were preferred a second session of injection of a same dose (40 IU). No patient was lost on the follow up period of six months duration.

Figure 1: Botulinum toxin type 100 units vial

Results

Ninety male patients were included in this study, 45 patients received botulinum toxin injection into the internal sphincter and the other group underwent open lateral partial internal sphincterotomy. Patients age ranged between 16-78 years (mean age 41.2).

The two groups were similar regarding the age, sex and duration of symptoms. Posterior midline location was the most common site of the fissure. The clinical presentation was similar in both groups, and pain with minor bleeding was the most common presentation.

Table I: Clinical characteristic of both groups.

LIS Group (45)	BTX A Group (45)	Base line characters
42.3	40.2	Age
6	4.5	Duration of symptom in month
44	42	Pain
8	7.5	Pain severity (VAS)*
33	28	Bleeding
37	40	Constipation
5	3	Anal itching

VAS*-visual analogue score.

The severity of pain and duration were similar in both groups and it was assessed by using the visual analogue score. Constipation was also a common symptoms in most of the patients in both groups. Bleeding was present in 28 patients in botulinum toxin group and in 33 patients in LIS group.

After two months periods, single injection in the botulinum group resulted in complete healing in 32 patients (71%), while in the sphincterotomy group complete healing after two months was noted 43 patients (95.5%). Of the 13 failure patients in the botulinum group, 8 patients were treated with a second injection of BTX which resulted in healing of six patient with an overall healing rate of 84.4%[38] patients out of 45 patients in BTX group. Five patients refused the second injection of BTX and they were subjected then to the lateral internal sphincterotomy. After six months followed period, two patient in the lateral internal sphincterotomy group developed recurrence of symptoms and so the healing rate in this group fall to 88.8% while in the BTX group recurrence was observed in one patient only after six month resulting in overall healing rate 82.2%. The two patients who failed to heal after second injection of BTX was offered to lateral internal sphincterotomy. No fissure relapse was observed after six month in the two treated groups.

No complications or side effects were observed during injection of botulinum toxin or immediately after it. Three patients only in BTX group reported mild incontinence mainly for flatus and this incontinence was transient and lasting for one week and disappeared spontaneously. On the other hand sphincterotomy was associated with a significantly higher incontinence rate (7 patients) which last about four to the eight weeks to improve. Perianal hematoma or abscess formation were not observed in botulinium toxin group while observed in three patients in the surgical group. Time required to return to daily physical activity was significantly less in botulinium toxin group patients.

Table II: Complications and outcome of treatment

Complications	Group I (BTX) 45	Group II (LIS) 45

healing after 2 months	71 (%)	95.5(%)
Incontinence with 1 week	2	7
Incontinence with 2-6 week	0	1
Hematoma	0	2
Peri anal abscess	0	1
Recurrence	5	1
Overall healing after 6 months	82.2%	88.8%

Discussion

Chronic anal fissure is a common and distressing problem which occurs with equal frequency in men and women. The majority occur in the posterior midline below the dentate line extending up to the anal verge[7,8]. The painful ulcer is believed to ischemic origin with hyper tonicity and spasm of the internal sphincter are main factors contributing to the pathology[9]. The onset is attributed to the passage of hard stool which result in a tear over the posterior aspect of anal verge with characteristic symptoms of pain during defection and streaking of stool with blood. Fear and avoidance of motion leads to vicious cycle of constipation and more recurrent anal injury[10]. The incidence of anal fissure is around the 35%adults[11] and most often occur in adult aged 15 to 40. Anal fissure was first described by Recamier in 1829 was recommended stretching the anal sphincter to treat this condition. Acute anal fissure is treated usually by conservative method with fiber supplement; stool softener and generous intake of water along with sitz path and local anesthetic ointment, these measures usually bring about complete healing in most cases[12].

However, chronic anal fissure (more than six weeks duration) does not usually respond to the conservative treatment[13]. Since the internal sphincter spasm is the main factor in the pathogenesis of chronic anal fissure, therefore the treatment of this condition is aimed to reduce the internal sphincter hypertonia and spasm. Lateral internal sphincterotomy is the most frequently performed surgical procedure for the treatment of chronic anal fissure which results in healing rate of about 90-95%[14]. It works by reducing the sphincter hypertonia which is the main etiological factor in the development of the chronic fissure. Reduction of anal pressure by sphinctro-tomy improve anodermal blood flow at the posterior midline, resulting in fissure healing. So the basic requirement for a successful treatment is decrease of sphincter tone relief of pain and restoration of normal rectoanal coordination[15].

The optimal therapy must be safe and successful about healing and continence. Although lateral partial internal sphincterotomy is regarded as a goal slandered in the treatment of anal fissure but the surgery carries a potential risk of subsequent fecal and flatus incontinence that is reported in up to 40% of cases, that is why some surgeons prefer initial conservative treatment and if it is not effective or failed surgical sphincterotomy may be required then[16].

Advances in the understanding of the physiology of the internal anal sphincter have resulted in more conservative treatment option instead of surgery. Topical glyceryl trinitrate, diltiazim and botulinum toxin A are the most common

pharmacological treatment option[16,17]. Chemical sphincterotomy using botulinum toxin A has recently become one of the most popular first line treatment option. It offers reducing internal anal sphincter pressure with the risk of incontinence[18].

Increase in the resting anal pressure is documented in a patients with chronic anal fissure which usually exceed 30 mmHg or may be more when compared with the healthy control and associated with a decrease in a posterior anal blood flow[18]. As a result of this, therapy that reduce lateral internal sphincter have been used for the fissure treatment.

After lateral sphincterotomy, the healing rate range from more than 90 to the 78 %[19]. And the recurrence rate range between 1.3 and 13.1%. These variations could be due to the type of surgical technique (open vs. closed sphincterotomy) or the length of the sphincterotomy incision. In our study, fissure healing rate is high (90%) after lateral internal sphicterotomy with relatively high rate of incontinence although this incontinence was temporary in most of the patients and neither significant incontinence nor relapse was observed after six months after surgical treatment.

Although chemical denervation with botulinum toxin has been mostly used for weakening of striated muscles, it has also been found to weaken smooth muscle in gastrointestinal tract. The toxin acts rapidly and prevent the release of acetylcholine by presynaptic nerve terminals. Chemical denervation produced by the toxin is not permanent and the clinical efficacy last only for 2-3 months[20,21]. The duration of the action of the toxin roughly correspond to time required to reduce the resting pressure of the anal sphincter and allows enough time for the healing of chronic anal fissure. In the present study the healing rate of about 80%in the botulinum toxin group is similar to that found in the previous studies[12,13,22].

In this study, botulinum toxin was injected to the internal sphincter rather than external sphincter or inter sphincter space on both sides of the fissure. The maneuver of injection was easy and effective. Although previous similar study concluded that the target muscle and site of injection seems to be irrelevant. So the healing rate in this study was higher in the surgical group and it was significant ($p>0.05$). Regarding the incontinence, it was higher in the surgical group and it was noted in 7 patients after LIS and only 2 patients in botulinum toxin group. The long term incontinence occurred in 2 patients from the surgical group which last up to one year and it was treated and improved conservatively while in the chemical group none of the patients had long term incontinence. Recurrence occurs in 11 person of chemical group (5 patients) while only 2 patients 44% in the surgical group develop recurrence over the period of follow up. All of unhealed fissure and recurrent fissure after second injection in botulinum toxin group were subsequently treated with lateral internal sphincterotomy and all of them ultimately had complete healing of the fissure. Significant pain score reduction after LIS comparing to the botulinium toxin injection has been reported[23]. In this study symptomatic improvement after the treatment was demonstrated in both groups, however significant reduction of postoperative pain was noted in the patients treated with sphincterotomy.

Table III: The results of internationally published studies using botulinum toxin for chronic anal fissure treament

Authors	Year	No. of Patients	Unit/injection Into	Complete response
Gui et al	1994	10	15B/IAS	90
Jost &Shimrigk	1994	12	5B/EAS	83
Jost et al	1995	54	5B/EAS	78
Maria et al	1998	15	20B/IAS	73
Minguez etal	1999	23	10B/IAS	83
		27	15B/IAS	78

		19	21B/IAS	90
Brisinda et al	1999	25	20B/IAS	96
		25	NITROGLYCERN	60
Fernandez et al	1999	76	40B/IAS	67
Lysy et al	2001	15	20B/IAS+ NITROGLYCERN	73
		15	20B/IAS	60
Madalinski et al	2001	14	25-50B/EAS	54
Brisinda et al	2002	75	20B(+20)/IAS	89
		75	30B(+50)/IAS	96
Trcinski et al	2002	13	100D/IAS	85
Colak et al	2002	3	30B/IAS	71
		28	Lidocain	21
Wollina et al	2002	5	20-25B/EAS	40
Lindesy eta	2003	40	20B/IAS	43
Giral etal	2004	10	30B/IAS	70
		11	Sphinctrotomy	82
Arroyo et al	2005	100	25B/IAS	47
Massoud et al	2005	25	20B/IAS	64
		25	SPHICTROTOMY	100
Floyd et al	2006	32	30-100B/IAS	94
			30-100B/IAS+Nifidipin	94
Radwan et al	2007	38	10-20B/IAS	89

IAS-Internal anal sphincter, EAS: External anal Sphincter, B: Botox.

Conclusion

The standard surgical internal sphincterotomy has a higher healing rate and a lower recurrence rate than intra sphincteric injection of botulinum toxin in the treatment of uncomplicated chronic anal fissure. Injection of botulinum toxin however is effective alternative modality in the treatment of chronic anal fissure. Its relatively less invasive than surgical approach and the complications are negligible, but it has a higher recurrence rate than lateral internal sphincterotomy. The risk of anal incontinence is higher in the surgical group especially in elderly patients.

This study recommend surgical internal lateral sphincterotomy as the first therapeutic modality in patients with clinical factor of recurrence. On the other hand botulinum toxin injection is preferred option in the middle aged and elderly patients or those with the risk factor for anal incontinence, despite the relatively higher rate of recurrence since it avoid the greater risk of incontinence. The recurrence rate in the botulinum toxin treatment can be reduced by a second trail of injection.

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