

## Botox® for chronic anal fissure: is it useful? A clinical experience with mid-term follow-up

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**Abstract.** *Background:* Sphincterotomy has been the most commonly used treatment for chronic anal fissures. Although effective it is associated with incontinence (0-20%). Intrasphincteric Botulinum Toxin A injection seems to be a reliable option. The aim of this clinical report is to verify the effectiveness of this treatment in relieving symptoms and healing fissures without relapse. *Methods:* The study design was an open label non-comparative prospective trial to evaluate the efficacy of botulinum toxin injection in anal sphincters. In the period 2003-2005 sixty patients were enrolled in our Unit of Coloproctology. After inoculation hygiene measures (sitz baths, Vaseline oil and water intake) were recommended. After the first 4 weeks without improvement we administered a second injection (30 U.I). After failure of the second administration the patient was addressed to surgery. Mean follow-up was 24 months; patients were re-evaluated at the 6<sup>th</sup>, 12<sup>th</sup> and 24<sup>th</sup> month. *Results:* In 29 pts the fissure was healed (48.33%) after the first injection; 31 patients (51.6%) were re-treated; 20 pts presented a complete healing of the fissure in a period ranging between 4-5 weeks from the second injection and 11 patients were introduced to surgery. In 3 cases we observed haemorrhoidal thrombosis. Gas incontinence was reported in two patients and solved spontaneously. *Conclusions:* Our clinical experience suggests that botulinum toxin therapy can be considered effective and safe. It can be proposed to the patient as first line therapy before surgery. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** Anal fissure, botulinum toxin, follow-up, conservative therapy

### Background

Anal fissure, the most common disease in proctology, is a tear of the anoderma causing pain and bleeding during and after defecation. It is usually located in the posterior midline and unusual locations could be the expression of other diseases such as inflammatory bowel disease, venereal infections, tuberculosis, trauma, chemotherapy or at least malignancies. The onset of the injury is often due to hard stool or severe diarrhoea but the acute presentation can be simply solved by using stool softeners and accurate local hygiene (1) or by applying anaesthetic ointment (2). In many cases this is not true and the lesion becomes a chronic one. The cause of the lack of healing

seems to be related to a high anal resting pressure that impairs anodermal blood flow, causing an ischemic lesion at the end. Internal Sphincterotomy, open or closed, has been the most commonly used treatment since the first results of Eisenhammer in the 1950s (3) but they lead to a risk of incontinence varying from 0 to 35% (4, 5). Since the middle of the 1990's new therapies have been introduced to the armamentarium of the colo-proctologists, aimed at reducing anal resting pressure. They include toxin botulinum injection, nitroglycerine (GTN) and nifedipine and diltiazem ointments. Many papers have been published about these conservative therapies. Their aim is to demonstrate the superiority of one over the others. Many of them seem well conducted and are sustained by using

anal manometry, quality-of-life questionnaire and so on. After reading all the papers, a practitioner remains dumbfounded and has some difficulty to choose which could be the best one for the patient in proposing an alternative therapy to surgery. The demonstrated efficacy of botulinum toxin (6-8) in acting as a blocker to acetylcholine release thus decreasing muscle tone, although disputed in some papers (9), has urged us to begin this prospective study by assessing its efficacy in the short and mid-term follow-up. We are attempting to understand if there is a real space for this therapy in our clinical practice.

## Methods

The study design was an open label non-comparative prospective trial to evaluate the efficacy of botulinum toxin injection in anal sphincters in order to heal chronic fissure. In the period 2003-2005, sixty patients were enrolled in the study because they were affected by an anal fissure lasting for more than 30 days and previously unsuccessfully treated with other therapies. They were 23 females and 37 males with a mean age of 48.2 (29-82). A summary of data at recruitment is reported in table 1. During the first visit we recorded symptoms and performed an ano-rectal exploration. Pain was evaluated by administering to patients a visual analogue scale (VAS) 0-10 explaining that 0 is no pain and 10 corresponds to unbearable pain. The VAS score reduction was considered significant if  $\geq 3$  points. Exclusion criteria were association with haemorrhoids at III-IV Parks degree, pregnancy, fistula and large skin tags. End-points of the study were primarily the regression of pain in the first four weeks after inoculation, secondarily the complete healing of the fissure, thirdly absence of relapse in the next two years. After clearly explaining the treatment to the patients and their acceptance of it, we inoculated 30 U.I. of BOTOX (Allergan Pharmaceuticals, Ireland), which appears to be the most effective dosage (10), divided at both edges of the fissure in an outpatient regimen. We diluted the toxin (100 U.I.), stored it at  $-5^{\circ}\text{C}$ , with 5 ml of saline solution and then charged a 2.5ml syringe with 1.5 ml of solution. The toxin was preferably injected in the groove between the internal and external

**Table 1.** Summary of data at recruitment

Patients number	60
Mean Age	48.02 (29-82)
Sex M/F	37/23
Mean Post-defecatory pain (VAS scores)	5.7 (2-8)
Bleeding	29 (49%)
Pruritus	9 (15%)

sphincter in order to obtain the effect over the two muscles that seem to be better (11). Daily cleaning with sitz-bath and two large spoonfuls of Vaseline® oil in the evening for two weeks were prescribed as associated hygiene measures. Patients were re-evaluated at 7 days only with an interview asking about symptoms and administration of the VAS scale, then at 21 days they were submitted to a new interview and to anal inspection. If the tear was reduced in dimension, cleaned and symptoms disappeared or reduced, no more treatment was administered. On the contrary if the wound did not show objective signs of healing or the patients reported persistence of symptoms, one more administration of BOTOX (30 U.I.) was performed. The date of definitive healing was recorded. Treatment failure after the second injection led the patient to surgery consisting of lateral closed internal sphincterotomy. Complications and side effects were recorded. Mean follow-up was 24 months: in this period patients were clinically followed by inspection and re-evaluated at the 6<sup>th</sup>, 12<sup>th</sup> and 24<sup>th</sup> months for symptoms recurrence and/or fissure relapse. Data regarding the efficacy of BOTOX in reducing pain were analyzed with the Student "t" test and data about healing of the fissure were analysed with chi-square test. Data regarding healing or non-healing of the fissure after the first injection and at the end of treatment were also compared.

## Results

### *Recruitment data and immediate results*

The pain at presentation according to the VAS scale was between 4 and 8 except for one 72 year old male who provided a VAS of 2. Twenty-nine pts out of 60 (48.33%) presented associated bleeding; 9 pts (15%) referred to suffering from pruritus too. The VAS score at

7 days from inoculation went down by almost 4 points in almost all patients except from 4 of them in whom it remained the same or 2 points less ( $p$  Value : 0,000068). Bleeding persisted in 23 (38.3%) out of 29 patients. The reported side effects concerned two patients who referred to gas incontinence that was spontaneously solved in 4 and 15 days. In 3 cases (5%) we observed haemorrhoidal thrombosis that required associated therapy with defibrotide that solved the crisis in 7-10 days. They were probably related to the fortuitous injection of some drops of the toxin in the haemorrhoidal veins.

#### *Healing after first injection*

Twenty-one pts presented a complete healing of the fissure (35%) in the period ranging between the 3<sup>rd</sup> and no later than the 4<sup>th</sup> week from treatment; 5 pts (8.33%) out of 60 arrived to the control visit with complete regression of symptoms and with a cleaned wound and clear signs of healing that occurred after 40-50 days from treatment. The 3 patients who suffered from thrombosis presented healing after a period of 50-60 days.

#### *Second treatment and definitive results*

Thirteen pts (21.6%) presented persistence of pain but reduced (VAS 2-3) with bleeding and 10 more pts (16.6%) presented persistent bleeding at control but without pain; 7 patients (11.6%) presented important pain measured as 5-7 at VAS scale. Finally, one more pt was symptomless but evidenced a lack of improvement of the tear tissues. These thirty-one patients (51.6%) were re-treated with a further administration of BOTOX at the dose of 30 U.I: 20 pts presented a complete healing of the fissure in a period ranging between 4- 5 weeks from the second injection and 11 patients were sent for surgery because of a persistent pain (VAS scale ranged between 4 and 7) with or without bleeding. We observed a total healing rate of 48.33% after the first inoculation with a 33.33% increase of healing rate after the second treatment. In total BOTOX therapy was successfully for 49 pts out of 60 ( $p$  Value: 0.000005) with a failure rate of 18.33% (Table 2). Comparison of data regarding healing or non-healing of the fissure after the first in-

**Table 2.** Summary of data after treatment

	1 <sup>st</sup> Injection	2 <sup>nd</sup> Injection
Mean Post-defecatory pain	1.1 (0-7)	0.06 (0-7)
Bleeding N°(%)	23 (38.3%)	1(1.6%)
Pruritus N°(%)	4 (6.66%)	0
Healing rate N°(%)	29 (48.33%)	20 (33.3%)
Side effects	2 (3.3%)	0
Complications	3 (5%)	0

jection and at the end of treatment did not show differences at any time.

#### *Follow-up*

Patients were interviewed and visited at 6 – 12 – 24 months from the first treatment. We observed four relapses (8.16%) during the first 6 months and these patients were sent for surgery. No more relapses were recorded during the first two years of follow-up.

#### **Discussion**

The onset of anal fissure is basically described as being due to a defecation disorder consisting of multiple episodes of diarrhoea or, more frequently, of a strain to leave passage to large, hard, dehydrated faecal bolus. Conservative hygiene measures (e.g. sitz bath, diet) and topical anaesthetic frequently heals the wound. The lack of healing leads to the persistence of the split caused by an unknown mechanism that is probably related to an associated condition of hypertonic internal sphincter. In some authors' opinion (12) high anal rest pressure is consequent to the fissure and not the cause of it. An evident reduction in local blood flow demonstrated by Doppler measurements is claimed as another cause of the non-healing process (13). What is evident is that anal fissure is associated with internal sphincter hypertone and, indeed, since its first description by Eisenhammer in 1950, surgical internal sphincterotomy has remained the procedure of choice (14-15). New concepts of therapy were addressed to perform a *pharmacological sphincterotomy*. One of the first therapies introduced was blocking acetylcholine release at the neuromuscular junction, obtained by injecting Botulinum Toxin type A in the muscular fibres of the sphincter (16,

17). It is thus described that injection of botulin toxin-A in the external or in the internal anal sphincter or in both, causes relaxation of the sphincters, stimulates local microcirculation and the healing process (18). Alternatively nitric oxide donors such as glyceryl trinitrate/ nitroglycerin (GTN) and isosorbide dinitrate (19, 20, 21), could be able to heal the fissure just like calcium channel antagonists (diltiazem and nifedipine ointments) (22, 23). However, in the end, we do not have a clear definitive answer. Not even a review published on Cochrane Database System is capable of establishing whether one treatment is better than another (24). Moreover, every day practitioners have to deal with outpatients who are increasingly capable of discussing any diseases and related therapies with their doctor thanks to the extensive coverage on the Internet. Recently the American Gastroenterological Society and some groups of surgeons, including The Association of Coloproctology of Great Britain and Ireland, recommended trying a GTN treatment and Botulinum Toxin administration to patients with chronic anal fissure before undergoing surgery (15, 25, 26, 27, 28 and 29). In view of all this, we decided to perform a personal experience using the administration of Botulinum Toxin to outpatients referred to our colo-proctology office. The aim of this clinical trial was, in the end, only to report all the aspects of a daily use of BOTOX in order to give all clinicians the answer to the question "what happens if I use botulinum toxin with my patients?" The results of our experience are favourable as evidenced by the data. We obtained the healing of 52 patients out of 60 treated with one or two injections. In our experience, despite an accurate stratification of patients and strictly homogenous treatment, we cannot recognize factors or conditions that determine the non-healing of the fissure in 8 persons out of 60. Moreover, the study excluded those fissures lasting for more than 6 months often associated with large skin tags because of the presence of sclerotic tissue or fissures associated with III-IV Parks' degree haemorrhoids that bulk anal mucosa choking it. Another topic to discuss is the healing time: one group of patients responded well to the toxin and healing was observed in the first month (35%), on the contrary another group of patients showed the closure of the tear after a second injection thus after 2-3 months (33.3%). Analyzing the charts and the interviews with them, the only explanation of

this difference seems to be linked to a lack of observation of hygiene rules (diet, baths etc.) and with the use of bike/motorbike but we cannot demonstrate it statistically. Some authors report a certain incidence of relapse during the first year, up to the figure of 55% (27) but in our two year follow-up we observed only 4 relapses in the first 6 months and we sent them for surgery. No more relapses were observed in the following two years, maybe due to an aggressive dietary control and to the particular attention paid to evacuation. Patients were terrified of suffering fissure again! It seems obvious that a relapse might be expected in the first year after treatment. The major side effects of the BOTOX injection are described as gas incontinence and, occasionally, faeces incontinence but they are reversible when the toxin effect ends so the anal continence is completely regained without reliquates (30, 31, 32, and 33).

Finally we believe that before performing an operation, a pharmacological sphincterotomy, whether it be NTG or a BOTOX injection, must be attempted. With this in mind we can definitively avoid surgery for 48 patients out of 60. And this is no small achievement.

## Conclusions

Injection of botulinum toxin in the anal sphincter is a simple, safe and repeatable non-surgical therapy for chronic anal fissure that is administered in an outpatient regimen. Data coming from our clinical experience suggests that patients can be submitted to this therapy before introducing them to surgery. Complicated anal fissure with haemorrhoids and large skin tags are better treated directly with surgery.

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