

# Toxin Botulinum In The Treatment Of Anal Pain Due To Anal Fissure: Is The Definitive Solution?

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## Citation

A Arroyo, F Perez-Vicente, E Miranda, A Sánchez, J Navarro, P Serrano, F Candela, R Calpena. *Toxin Botulinum In The Treatment Of Anal Pain Due To Anal Fissure: Is The Definitive Solution?*. The Internet Journal of Surgery. 2005 Volume 8 Number 1.

## Abstract

**Background and aims:** Anal pain due to fissure is a common and painful proctologic disorder in healthy population. The pathogenesis is understood but persistent hypertonia of the internal anal sphincter seems to play an important role. The aim of this prospective trial was to evaluate the effectiveness and morbidity of chemical sphincterotomy with botulinum toxin that produce relaxation of anal sphincter and disappearance of pain.

**Methods:** We treated 200 consecutive patients with chronic anal pain with 25U botulinum toxin injected into the internal sphincter. Clinical results were recorded at the time of admission and at one-week, two-month, six-month and annually visits.

**Results:** No major complications were found; initial incontinence (5%) spontaneously reversed at the six-month. There was a tendency of progressive recurrence over time, with an overall recurrence in the exploration after one year of 52%. However, 80% of the global serie heal or dissapear or improve previous pain; and did not complementary medical or surgical treatment. We found a group of patients with clinical factors (length of the disease longer than 12 months and presence of a sentinel pile) associated with a higher recurrence.

**Conclusions:** We recommend the use of botulinum toxin for the treatment of anal pain due to anal fissure because improve anal pain in 80% of patients. In patients with symptomatic recurrence associated to risk clinical parameters surgical treatment should be considered in the view of the high probability of recurrence in the long-term follow-up.

## INTRODUCTION

Anal fissure is a common and painful proctologic disorder in healthy population, whose pathogenesis is incompletely understood (Xynos et al. 1993). Most fissures respond to conservative management such as fiber-rich diet and sitz baths; however, some persist for several weeks and become chronic. The pathogenesis of chronic anal fissure is not completely understood but persistent hypertonia of the internal anal sphincter, associated with increases in resting anal pressure, seems to play an important role (Mc Namara et al., 1990; Xynos, 1993).

For this reason, medical and surgical therapies that reduce internal sphincter pressure have been described to treat anal fissure. Surgical sphincterotomy has been widely accepted as the treatment of choice for chronic anal fissures, resulting in healing of >90% of patients (Nelson RL, 1999; Arroyo,

2004). However, the high rates of incontinence (0-66%) reported in surgical sphincterotomy has led to the study and implementation of other alternative medical treatments (Lund and Scholefield 1996; Brisinda et al., 1999; Knight et al., 2001; Pitt et al., 2001; Rodhe, 2003; Arroyo et al., 2005) mainly botulinum toxin (BT) that produce reversible reduction in sphincter pressure, thereby disappearing pain and allowing the anal fissure to heal.

The aim of this prospective controlled trial was to analyze the clinical findings (effectiveness and morbidity) with long-term follow-up of chemical sphincterotomy with BT in the treatment of anal pain due to chronic anal fissure.

## MATERIAL AND METHODS

Between January 1998 and December 2002, 200 consecutive patients with chronic anal fissure were enrolled in this study.

Before definitive definition as chronic anal fissure and ensuing inclusion in the study, all patients diagnosed as having chronic anal fissure based on their medical history and physical exploration were treated for a minimum of six weeks with conservative medical treatment (high residue diet, analgesics, and warm sitz baths). Chronic anal fissure was defined as the presence of a fibrous induration or exposed internal sphincter fibres with anal pain.

The exclusion criteria were: associated anal pathologies (stenosis, abscess, fistula and haemorrhoids), patients with associated conditions (inflammatory bowel disease, acquired immunodeficiency syndrome, tuberculosis, sexually transmitted disease and immunosuppressed), anti-coagulative therapy and pregnancy.

All the phases of the study (first visit, injection toxin botulinum and postoperative revision) were rendered in ambulatory setting in the Coloproctology Unit-Surgery Department of Elche University Hospital. The study received ethics approval and each patient signed an informed consent before study participation.

The 100-U vial of lyophilized botulinum toxin type A (BOTOX, Allergan, Inc., Irvine, CA) are stored at a temperature of  $-20^{\circ}\text{C}$  and diluted in saline to 0.1ml/2,5U the day of injection. With a 25g needle, a total of 25U are injected in the internal sphincter (8-U dose into each side of the sphincter and 9-U into the anterior verge).

Preoperative laboratory test and enema preparation were not required. The patients were discharged home with instructions regarding high residue diet, laxatives, analgesics, and warm sitz baths.

Information regarding sex, age, symptoms, bowel habits, examination findings, early and late complications, pain before and after treatment, fissure healing and recurrence was collected at the time of admission and at one-week, two-month, six-month and one-year follow-up visits. We used a lineal analogical scale for pain from 0 to 10 (0= no pain; 10= unbearable pain). The continence score was determinate with Cleveland Clinic Scoring System (Jorge et al., 1993). Healing was defined as complete re-epithelization of fissure and absence of pain.

## RESULTS

The characteristics of the population studied were as follow: average age of presentation: 45 years (range: 20-83), 90 women vs. 110 men, duration of symptoms: 20 months

(range: 1-70). The number of patients with symptoms of presentation and anal exploration were: mean age (years):  $45\pm 15$ ; gender (men/women): 90/110; duration of symptoms (months):  $20\pm 18$ ; site of fissure (posterior midline/anterior midline): 160/40; skin tag: 160; bleeding: 140; constipation: 139; pruritus: 120; anal pain (0-10:lineal analogical scale): slight (1-3): 20/Moderate (4-6): 100/Inexplorable ( $>7$ ): 80.

The early complications found were: eight patients with ecchymosis at the point of injection and two patients with hemorrhoid thrombosis. There were no anal abscesses, perianal fistula or urinary retention.

With regard to incontinence, in the two-month revision there were 6 patients with occasional incontinence to gases, and 4 patients with daily incontinence diaria to gases and liquid faeces. However, at the 6-month revision, no patient reported any incontinence. Of all the preoperative variables analyzed, only an age of  $>50$  years was associated with incontinence. All the incontinent patients were older than 50 years.

The results after treatment with BT are shown in Table 1. The number of patients with persistence or recurrence of the fissure at the revisions was as follow: 24 patients at 2 months, 30 more patients at 6 months, 42 new patients at 1 year; with an overall recurrence of 48% (96 patients). However, of these 96 patients with persistent anal fissure in the exploration at 1 year 29 patients refered dissapearence of pain and 27 patients clinical improvement. Then, 80% (160 patients) of the global serie heal or dissapear or improve previous pain; and did not complementary medical or surgical treatment. In the follow-up, only 3 patients recurred symptoms and were realized surgery.

**Figure 1**

Table 1: Results after treatment with botulinum toxin in the first year follow-up.

	Recurrence fissure n patients	Similar Pain n patients	Disappeare pain n patients	Improve pain n patients
two-month	24	8	10	6
six-month	30	10	8	12
one-year	42	22	11	9
Overall	96	40	29	27

We can see the progressive rate of recurrence over time. However, in a high number of patients with recurrence fissure in the exploration, improve or dissapear previous treatment pain.

Fissures were significantly less likely to heal in patients in whom the condition had been present for over twelve months and who had a sentinel pile. No relationship was found between the other pre-operative variables analyzed and healing.

### **DISCUSSION**

Botulin toxin is one of the most lethal biologic toxins; it exerts its effects on the peripheral nerve endings at the neuromuscular junction, resulting in a flaccid paralysis due to selective multiphasic blockade of acetylcholine. Transmission of neuromuscular impulses resumes after the growth of new axon terminals, and clinical weakening of muscle is seen for 3 to 4 months. BT has been used to weaken striated muscle in the treatment of disorders such as blepharospasm and spasmodic torticollis; it may also weaken smooth muscle in the gastrointestinal tract. It has also been used to weaken the external anal sphincter and puborectalis muscle in constipated patients with Parkinson's disease or anismus. Recently, it has reported the use of locally injected BT for the treatment of anal fissure (Jost and Schimrigk 1993; Gui et al., 1994). The advantage of using BT injections in internal anal sphincter is that the ensuing reduction in anal pressure for 3-4 months should allow the fissure to heal eliminating the need for surgery (Jonas and Scholefield 2001; Madoff and Fleshman JW).

Many studies have been published about BT in the treatment of pain due to anal fissure, but a number of questions about BT regarding the correct dose, site and number of injections, the role played by re-injection, adverse effects (temporary incontinence), and long-term relapse rates remain unanswered. The best results in terms of healing in the short term (>80%) have been obtained using 20-25U of BT with rescue doses in persistently fissure, injected directly into the internal sphincter, dividing the dose between various injection points, and it is more effective to inject into the anterior face than into the posterior face (Maria G et al., 1998; Minguez et al., 1999; Maria G et al. 2000).

Most studies reports short and heterogeneous follow-up. If we analyze the studies with longer follow-up times, it is possible to see a trend to progressive recurrence over time with lower healing rates than those initially reported. Minguez (Minguez et al., 2002) present the longest-term follow-up (42 months) with a relapse of anal fissure in 41.5% of patients. Our study also shows this tendency, since there is a progressive rate of recurrence. This is not surprising, since it could be related to the temporary

reversible effect of the toxin. But certain, a high percentage of these patients with recurrence referred improvement or disappearance of previous pain and did not required complementary medical or surgical treatment.

Some studies describe clinical factors related to recurrence (Pitt J et al., 2001; Minguez et al., 2002; Arroyo et al., 2005); in our study we can also find some clinical parameters related to a higher rate of recurrence indicating that the fissure has become chronic (longer duration of disease over 12 months and presence of a sentinel pile), and therefore reversible sphincterotomy with BT does not appear to be sufficient to achieve healing. For these reason, we think that patients with symptomatic recurrence associated to these clinical parameters surgical treatment should be considered in the view of the high probability of recurrence in the long-term follow-up. However, in patients with symptomatic recurrence not associated to risk clinical parameters, re-injection with higher doses of BT must be valorated. BT has been described as an alternative therapy with very good results in patients with recurrence (Jost and Schimrigk, 1999). Brindisa (Brindisa et al., 2002) reported a healing rate of 96% with reinjection of 50 units of BT in patients with recurrence of fissure. However, it is difficult to ascertain before starting treatment which patients should be administered this higher dose of BT, since the higher and more effective doses may stimulate production of antibodies and lead to an increase in the rate of complications and recurrence (Nelson RL, 1999; Madalinski, 2003).

Concerning the morbidity of BT (Klein, 2001), the bibliography points out its safety on the grounds of the infrequent complications that arise (incontinence to faeces, postinjection haemorrhoidal thrombosis, anal haematoma and epididymitis) and their banal and reversible nature.

In conclusion, we recommend the use of BT for the treatment of anal pain due to chronic anal fissure because improve anal pain in 80% of patients, it is less expensive and easier to perform than surgical treatment, does not anesthesia, and avoids the greater risk of incontinence found in the surgical sphincterotomy.

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