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Treatment of a chronic anal fissure with a botulin toxin A injection and fissurectomy

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ABSTRACT

Introduction: pharmacological treatment of a chronic anal fissure (CAF) achieves healing in half of cases and lateral internal sphincterotomy (LIS) is the definite treatment. The objective of this study was to assess the combination of fissurectomy and botulin toxin A (BTA) injection.

Methods: this was a retrospective study of 54 patients with anal sphincter hypertonia and CAF treated with an injection of BAT and fissurectomy, after an unsuccessful management with topical nitroglycerin (NGT) for eight weeks. Fissurectomy and an injection of BTA (33 or 50 units) in the internal anal sphincter was performed during the same session. The main outcome measure was the healing rate, with incontinence and the need of LIS as secondary outcomes.

Results: two patients were excluded from the study, one due to Crohn's disease and the other was lost to follow-up. Of the 52 patients included in the study, there were 36

females (70%) and 16 (30%) males, with a mean age of 49 years (range 22-75). Fissure healing was initially achieved in 49 patients (94.2%) and LIS was required in the remaining three patients (5.8%). After initial healing, 18 patients (34.7%) developed 23 recurrences at a mean time of 27 months (5-83 months). Of these patients, healing with conservative sphincter measures was obtained in eleven cases (NGT in eight and repeat fissurectomy and BAT in three); two patients are currently under treatment with NGT and five underwent LIS.

Conclusions: BTA injection associated with fissurectomy is a safe and effective procedure in patients with CAF, avoiding the need of LIS in a high percentage of patients.

Key words: Chronic anal fissure. Botulin toxin A. Fissurectomy.

INTRODUCTION

Anal fissure is a longitudinal tear that originates in the anal canal and is usually associated with a hypertonia of the internal anal sphincter. When the lesion persists for more than six or eight weeks, it is defined as a chronic anal fissure (CAF) (1). Lateral internal sphincterotomy (LIS) is the gold standard for the treatment of CAF, with a healing rate of 88-100% of cases. However, there is a risk of both immediate (8-30%) (2,3) and long-term (4) incontinence.

Pharmacological treatments based on nitric oxide donors and calcium channel blockers are effective in 50% and 65-95% of patients, respectively (2). Botulin toxin A (BTA) is another option that achieves a healing rate of 43% (5,6). This poor result is probably related to the presence of fibrosis accompanying CAF (7-10). Isolated fissurectomy is used in pediatric patients (11) but is not routinely used in adults. In adult patients, the combination of fissurectomy and topical treatment with isosorbide dinitrate achieved 100% healing. Thereafter, some studies have demonstrated a healing rate of 50-95% with the use of fissurectomy associated with BTA (9,10,12-17).

The objective of the present study was to assess healing of the anal fissure in patients with CAF and sphincter hypertonia using a combination of BTA injection and fissurectomy. LIS was considered as a therapeutical option in these cases due to a

previous unsuccessful treatment with topical nitroglycerin (NTG). The secondary objectives were the assessment of continence and the need of subsequent LIS.

PATIENTS AND METHODS

Patients

A retrospective study was performed between 1999 and 2017. The study protocol was approved by the Clinical Research Ethics Committee of the hospital. Patients with a persistent anal fissure and sphincter hypertonia after treatment with daily topical applications of NTG for at least eight weeks that was confirmed by physical examination were included in the study. In addition, dietetic measures with stool softeners, an increased liquid intake and hygienic measures were performed.

CAF was defined as the presence of a longitudinal tear in the distal anal canal, with fibrosis and induration of the margins and also visible smooth muscle fibers in some cases. Atypical fissures (multiple, irregular) or fistulas associated with abscesses, grade II and IV hemorrhoids, chronic inflammatory bowel disease and malignant diseases were excluded. Fissures after obstetric trauma were also excluded. Neither age nor the risk of fecal incontinence in multiparous women was considered as an exclusion criteria. One patient who had undergone LIS eight months before was included as healing was never achieved and there was marked sphincter hypertonia without a history of incontinence. Although manometric studies were considered in this patient, the clinical condition made anorectal manometry difficult to perform. However, manometric studies were not performed as in other studies, due to anal pain and sphincter hypertony that was present in all patients.

The main objective of the study was to assess healing of the fissure, defined by a complete epithelization on physical examination. Secondary objectives included the assessment of fecal continence using the Jorge and Wexner scale (18) and the need of a subsequent LIS. The Wexner test was performed in the outpatient clinics at the end of the study in 2018, with the exception of six patients that were asymptomatic and refused to attend a hospital visit, therefore it was performed by telephone.

The following data were recorded: age, sex, duration of symptoms and location of the fissure (anterior or posterior). Cut-off points for age and the duration of symptoms

were established as the mean age and one year, respectively, as there is an increase of recurrences after the cut-off of one year (19). All patients with an unsuccessful treatment with BTA and fissurectomy were offered repeat treatment with NTG, or repeated BTA and fissurectomy or LIS.

Technique

Procedures were performed with the patient in the lithotomy position under sedation and local anesthesia in the first six patients or regional anesthesia in the remaining cases, due to organizational reasons. BTA (Botox®, Allergan Inc., Irvine, CA, USA) at 33 or 50 units in three and 51 patients, respectively, was diluted in 0.25 ml of saline. A 29 G needle was used in the 12 o'clock and 6 o'clock positions (relative to lithotomy) for injection in the internal anal sphincter. A fissurectomy was also performed, which consisted of curettage of the chronic scar tissue until granulation tissue was seen laterally and at a depth until the fibers of the internal anal sphincter were exposed.

Follow-up

Patients were discharged on the same day of the procedure with non-opioid analgesic treatment and recommendations for local care of the wound and dietary fiber supplements. They attended the outpatient clinics without a specific time schedule, depending on the clinical status of each patient until healing. Follow-up controls were not always performed by the attending surgeon and all patients were reevaluated at the end of the study in 2018. Healing was assessed by smooth eversion of the anal margin and the degree of healing was not established.

Statistical analysis

The PASW Statistics 18® statistical software was used for data analysis. All variables had a normal distribution, thus continuous data were expressed as the mean and range and categorical data as frequencies and percentages. The Student's t test was used for the comparison of quantitative variables and the Chi-square (χ^2) test or the Fisher's exact test were used for the comparison of qualitative variables. Statistical significance was set at $p < 0.05$.

RESULTS

Of the 54 patients initially eligible for the study, two were excluded. One patient was lost to follow-up and the other was subsequently diagnosed with Crohn's disease. Of the 52 patients finally included in the study, there were 36 (70%) females and 16 (30%) males, with a mean age of 49 years (range 22-75). The fissure was located in the mid-anterior line in ten patients and in mid-posterior lithotomy position in the remaining 42 cases. The mean duration of symptoms was ten months (range 2-44 months). Complications included small bleeding and discrete hematomas, as well as transient gas incontinence. There were no cases of infection.

Healing was achieved in 49 (94%) patients, with a persistent symptomatic fissure in three (6%) cases. LIS was performed in these three patients due to the decision of the patient after insisting on the use of NTG. After initial healing in 49 patients and a mean clinical follow-up of 62 months (range 13-104), 23 recurrences developed in 18 patients (37%) after five to 83 months of follow-up (mean 27 months). Five cases of fissure recurrence occurred within the first year of intervention, nine cases between the first and second year and nine cases after the second year. A single recurrence was recorded in 14 patients, two recurrences in three and three recurrences in one case. All cases were initially treated with NTG. Of these 18 patients, healing after topical treatment was achieved in eight and a repeat further treatment with BTA and fissurectomy was required in three cases. One patient is currently under treatment with NTG after a recurrence after 83 months. Another patient developed periodic recurrences that are being treated with NTG as other associated therapies were refused by the patient. Five patients required LIS. In the patients with fissure recurrence, only 28% required LIS (5/18). Sphincterotomy was avoided in 85% (44/52) of the total number of patients treated (Fig. 1).

Differences between pre-treatment and post-treatment scores of the Jorge and Wexner scale were not found in the overall series of patients. Changes in the scores were not observed between pre-treatment and post-treatment values in 47 cases. Whereas there was a mild improvement in two cases (pre- and post-treatment 1 to 0 and 2 to 0, respectively). A mild worsening was observed in two cases (pre- and post-

treatment 0 to 2 and 1 to 2, respectively) and a marked worsening (from 0 to 101) in a case in which LIS was performed. There were no statistically significant differences between patients with and without fissure recurrence according to gender, age, location of the lesion or previous duration of symptoms (Table 1).

DISCUSSION

There is currently no consensus on the therapeutic strategy for this disease (20). The technique of LIS that was introduced by Notaras (21) continues to be the gold standard for the management of CAF. The use of "tailored" LIS that is limited to the length of the fissure has been associated with a decrease of incontinence but also has an increased level of recurrences (2). BTA is usually a second-line treatment option. Sphincter relaxation caused by BTA lasts two or three months (22) but it does not act on the chronic tissue of the fissure.

Engel et al. (8) combined these therapeutic strategies, treating CAF with fissurectomy and topical diltiazem, with a reported healing in 100% of cases. Subsequently, Lindsey et al. (9) used an injection of BTA with fissurectomy, with good results in 93% of the patients. Further studies have shown the usefulness of this strategy in 50-95% of cases (10,12-17) after failure of topical treatment, with a range consistent with a 94% success rate in our series. A further advantage of the combination of BTA and fissurectomy is the avoidance of the lack of adherence to treatment and the possible adverse effects associated with topical therapies (5). In this line, Barnes et al. (17) proposed fissurectomy and BTA injection as the first-line treatment in cases of clearly established CAF, with induration and fibrosis.

In the present study, treatment was started with 33 U of BTA in two injections, subsequently increasing to 50 U. The use of 20 to 100 U has been reported in published series (10,12-17). In general, the injection is performed in the internal anal sphincter (8,10-14), although other clinicians prefer the intersphincteric space (13). Most studies used BTA (9,12-17), except for Witte at al. (10), where Dysport® was used, which is a variety of BTA with a procurement process different from Botox®. However, a recent meta-analysis did not show differences in the healing rate depending on dose, type of formulation, site and the number of injections per session

(23).

Recurrences develop in 37% of the patients (18/49). In different studies, the recurrence rate varies between 0% and 14% (9,10,12,15-17), except in one study that reported 50% (13). However, the mean follow-up of these series was 3-33 months, which is shorter than the 62 months follow-up of the present study. Poorer results with the follow-up time have been demonstrated (24). In fact, of the 23 cases of recurrence in our study, most cases developed after the first and second year of follow-up. Thus, these data suggest that studies with a short follow-up may not detect all recurrences. However, most cases were resolved with conservative medical management and 28% of patients with recurrence required LIS (5/18). The good results obtained with a second course of treatment with combined BTA and fissurectomy have also been confirmed by other studies (12,17). On the other hand and in agreement with other studies (9,22), significant differences in outcome with regard to gender, age, site of fissure or duration of previous symptoms were not observed. Significant differences in the incontinence scale before and after treatment with BTA and fissurectomy were not found either. With the exception of a patient who required LIS after failure and also presented marked continence deterioration (Wexner score pre-treatment 0 and post-treatment 10).

Other relevant complications were not recorded, except for transient incontinence after treatment. This has also been reported by other studies that describe the occurrence of limited bleeding and infections that were successfully managed with medical treatment (9,10,12-17). However, episodes of sepsis, hemorrhage and fistula have been reported after LIS (15,16,25), as well as early (8-30%) (2,3) and long-term (4) incontinence.

It should be noted that there are other sphincter-sparing procedures. Patti et al. (26) performed a study of 48 patients with CAF, and an advancement flap associated with BTA injection was performed in 22 patients with hypertonia. A 92% healing rate was achieved, although dehiscences occurred in 6%. Renzo et al. (27) used pneumatic balloon dilatation in 24 patients with CAF, with a healing rate of 83% without effects on continence. However, prospective studies that assessed different techniques are necessary to clarify the variability of the result published in the literature.

Currently, the therapeutic algorithm for the management of CAF proposed by the Spanish Society of Coloproctology is used (5). However, we include this option in patients with a failure of conservative treatment and associated hypertonia. Finally, LIS was only necessary in eight patients of the 52 patients included in the study. This was performed in three cases after an initial failure and in five cases after recurrences treated medically. Thus, LIS was avoided in 85% of the patients. Even though it did not reach the therapeutic "gold standard" of the LIS for CAF, our technique allowed the avoidance of the potential complications of LIS.

The limitations of the study include the retrospective design and the lack of a control group. Furthermore, follow-up visits were not scheduled at fixed time periods due to the high work load within our service. However, healing was confirmed at final discharge and in 2018. Despite these limitations, we believe that the present results support the therapeutic usefulness of the combination of botulin toxin A injection and fissurectomy as a reasonable alternative for the treatment of CAF, after two months of topical treatment in the presence of sphincter hypertony. It is a simple and safe procedure. However, prospective randomized studies that compare this treatment modality with fissurectomy alone and LIS are warranted.

AUTHORSHIP

All authors have participated in the design of the study, critical revision and approval of the final draft.

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Table 1. The relationship between recurrence and clinical variables

Clinical variables	*Healing n/N (%)*		*p value**
Gender	*Male*	*Female*	0.743
	10/15 (67)	21/34 (62)	
Mean age (years)	*≤ 48.6*	*> 48.6*	0.864
	18/28 (64)	13/21 (62)	
Duration of symptoms	*≤ 12 months*	*> 12 months*	0.195
	27/40 (68)	6/9 (45)	
Fissure localization	*Anterior*	*Posterior*	0.595
	5/9 (56)	26/40 (65)	

* Chi-square test and Fisher's exact test.

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Fig. 1. Flowchart showing of the results of the study. LIS: lateral internal sphincterotomy; GTN: glycerin trinitrate.

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