Botulinum Toxin A Injection in ISDN Ointment-Resistant Chronic Anal Fissures

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Key Words

Anal fissures · Botulinum toxin A

Abstract

Background: In the treatment of chronic anal fissures (CAFs), surgical sphincterotomy is more commonly being replaced by chemical sphincterotomy. After the good results of our pilot study including 32 patients, we now describe the effect of botulinum toxin A (BT-A) in a consecutive series of 100 patients with isosorbide dinitrate (ISDN) ointment-resistant CAFs. **Methods:** From October 2002 until August 2005, 100 patients (52 males, 48 females) with a median age of 45 (20–79) years were treated with an injection of 40–100 IU BT-A (Dysport®, Ipsen, The Netherlands) in the internal anal sphincter. **Results:** After a median follow-up of 10 (4–38) months, 77 of the 100 CAFs (77%) were cured. 20 patients were given a second injection, 1 a third and 1 a fourth injection. In 11 patients a fissure recurred (14%). In 1 patient (1%) there was temporary incontinence due to flatus. **Conclusion:** With an early response rate of 77% and an overall success rate of 66%, BT-A injections appear to be effective in patients with ISDN ointment-resistant CAFs if initial non-responders are retreated. These results are in concordance with the results of our pilot study. It is a simple technique with little or no side effects, that does not compromise future treatments. Its place in the first-line treatment of CAFs should be investigated further.

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Introduction

An anal fissure is an acute longitudinal rupture or a chronic ulcer of the anodermis. Symptoms are pain during and after defecation and bright red anal blood loss. Acute fissures normally heal spontaneously. However, fissures that exist for more than 6 weeks with features of chronicity (indurated edges, sentinel pile, hypertrophied anal papilla) are unlikely to heal with conservative therapy [1, 2]. This study is restricted to chronic anal fissures (CAFs).

Localization of preference of chronic fissures is the posterior commissure (90%). Blood flow to the posterior commissure is supplied by end arteries passing through the internal anal sphincter before reaching the posterior commissure. Therefore, the perfusion of the posterior commissure is lower than blood flow at the other quadrants of the anal canal. Furthermore, a direct relationship has been demonstrated between internal anal sphincter pressure and anodermal blood flow to the posterior commissure. Patients with CAFs are known to have higher resting pressures of the internal anal sphincter with inadequate short relaxations. This internal sphincter hypertonia compresses the end arteries passing through the internal sphincter causing ischemia of the anodermis of the posterior commissure. A CAF can thus be regarded as an ischemic ulcer [2–5]. Central in the therapy for CAFs is therefore the lowering of internal anal sphincter resting pressure. For many years, manual anal dilatation was considered an effective treatment, but because of the

Table 1. Number and dosage of BT-A injections

Dosage	Injection			
	No. 1	No. 2	No. 3	No. 4
40 IU	34	13	1	–
60 IU	66	13	3	–
80 IU	–	13	1	3
100 IU	–	–	1	–

high risk of uncontrolled tearing of sphincter muscle resulting in incontinence, this method was replaced by the more controlled lateral sphincterotomy, which until recently was regarded as the golden standard in the treatment of CAFs. However, this effective method also holds considerable risks of permanent sphincter damage, with incontinence due to flatus occurring in 0–36%, soiling in 0–21%, and fecal incontinence in 0–5% [1, 6–10].

Nowadays, a deeper understanding in the pharmacology and physiology of the anal sphincter has led to the development of pharmacological methods to temporarily and reversibly reduce internal anal sphincter resting pressure to aid the healing of the fissure. This is called chemical sphincterotomy. The best known agents are the local nitric oxide (NO) donors glyceryl trinitrate (GTN) and isosorbide dinitrate (ISDN). Calcium channel blockers have also been shown to be effective. Botulinum toxin A (BT-A) is a new development in the treatment of CAFs. By injecting BT-A in the internal anal sphincter it temporarily reduces internal anal sphincter resting pressure, allowing fissures to heal [11–14]. After the promising results of 32 patients in our pilot study [15], we now evaluate the effect of BT-A injections in the first 100 consecutive patients with CAFs.

Patients and Methods

In the period October 2002 until August 2005, a prospective trial was conducted in our hospital to evaluate the effect of BT-A injections in patients with ISDN ointment-resistant CAFs. 100 patients (52 males, 48 females) with a median age of 45 (20–79) years were consecutively included. Criteria for inclusion were the existence of a CAF that had not healed by treatment with ISDN ointment during 6–8 weeks, or where treatment with ISDN ointment could not be completed due to its side effects. In 90 patients treatment with ISDN ointment had no effect, 8 patients ended ISDN ointment treatment because of headaches and 2 patients were unable to apply the ointment as frequently as prescribed.

Anal fissures were classified according to localization – dorsal, ventral or other. 93 patients had a dorsal fissure, 5 had a ventral fissure, 1 had fissures both dorsally and ventrally, and 1 had a fissure located somewhere else. Of the 100 patients, 26% were also diagnosed with hemorrhoids, 5% were diagnosed before with a perianal abscess, 3% with anal polyposis, 3% with perianal fistulas, 2% with constipation, and 1 with Crohn's disease.

The treatment was performed in the lithotomy position under general or spinal anesthesia in daycare. A BT-A injection (Dysport®, Ipsen, The Netherlands) was given in the ventral part of the internal anal sphincter. The site of injection was determined by palpation of the internal sphincter. Manual anal dilatation was avoided and no anal retractor was used. The first 34 patients received an initial injection of 40 IU (0.2 ml) BT-A, the following 66 patients received an initial injection of 60 IU (0.3 ml) BT-A.

Follow-up evaluation was standardized with visits planned at 3 and 6 weeks postoperatively and longer if necessary. Patients were asked if symptoms (pain/blood loss) persisted or disappeared and if they had experienced any changes in continence. A physical examination was performed to evaluate healing of the CAF. When symptoms persisted, a second injection was given after 6 weeks. When there was no change of symptoms after the first injection, a second injection dosage was elevated with 20 IU (0.1 ml). When there was some but not enough relief of symptoms after the first injection, a second injection with the same dosage as in the first injection was administered. When the second injection had only an inadequate or no effect, a third and fourth injection could be given in the same way, with a maximum dosage of 100 IU (0.5 ml) BT-A per injection. 61 patients received one, 33 patients two, 3 patients three, and 3 patients four injections of BT-A (table 1). Our median follow-up is 10 (4–38) months after the first injection.

Results

After a median follow-up of 10 months, 77 of 100 (77%) patients were symptom-free at follow-up and in these patients the fissure was healed at physical examination. Of these 77 patients, 55 needed only one injection, 20 patients two, 1 three and 1 four injections of BT-A. Of these 77 patients, 13 received one injection of 40 IU and 42 with 60 IU of BT-A; 10 received a second injection of 40 IU, 9 with 60 IU, and 1 with 80 IU of BT-A; 1 received a third injection of 40 IU, and 1 a fourth injection of 60 IU BT-A (table 2).

When the 10 patients that did not complete the ISDN ointment treatment are excluded, the healing rate remains 70/90 (78%).

Of the 77 patients that became symptom-free and showed healing of the fissure at follow-up, a fissure recurred in 11 patients (14%). Eight of 11 patients eventually healed (1 with a fissurectomy and 7 with BT-A again) and 3/11 persisted (1 chose no further therapy and 2 were waiting for another BT-A injection).

In 23/100 patients, BT-A injections had no effect; symptoms persisted and at physical examination the fissure showed no healing. Of these 23 patients, 10 eventually healed with other therapies, such as fissurectomy or fissurectomy combined with BT-A injection, and 1 patient was sent to a dermatologist because of perianal skin problems where he was successfully treated. In 12 of 23 patients, fissures persisted. Of these 12 patients, 3 chose no further therapy, in 5 patients symptoms persisted despite other therapies and 4 were awaiting other therapies. No patients were lost to follow-up.

Complications were seen in 1 female patient (1%), who experienced flatus incontinence temporarily during the first 3 weeks postoperatively. She became symptom-free after two injections of 40 IU BT-A under spinal anesthesia. No other changes in continence were reported when patients were asked at follow-up visits. Constipation during follow-up was avoided by prescribing Macrogol to all patients during the first weeks postoperatively.

Discussion

Our study shows that 77% of patients with CAFs that do not respond to application of local NO donors or where local NO donors are not tolerated because of the side effects or inability to apply the ointment as frequent as necessary, can still heal by injecting BT-A in the ventral part of the internal anal sphincter. This result is in accordance with the result of our pilot study with 32 patients, where 75% became symptom-free [15]. With an early healing rate of 77%, our overall response rate is 66%, because in 11 patients an anal fissure recurred. We found a higher healing rate than was described in a recent study by Lindsey et al. [7], where only 43% of GTN ointment-resistant CAFs healed with second-line BT-A injections.

The oldest and best known pharmacological agents for the treatment of CAFs are NO donors. The local application of GTN ointment, the most frequently used NO donor, gives a temporary reduction of anal resting tone. The most used dosage is 0.2%, applied topically 2–3 times daily during 6–8 weeks. Healing rates of CAFs with GTN ointment vary from 30 to 88% in the literature. Higher dosages do not improve outcome [1, 5, 6, 16–19]. Comparable results are described for ISDN ointment [20, 21]. Headache, the main side effect from local NO donors, is reported in 10–72% of patients at a dosage of 0.2% GTN, and this percentage increases with higher dosages [1, 5, 17]. Patient compliance is essential in this treatment because the short duration of action of NO donors man-

Table 2. Number and dosage of BT-A injections in patients who became symptom-free

Injection	Symptom-free				total
	40 IU	60 IU	80 IU	100 IU	
No. 1	13	42	–	–	55
No. 2	10	9	1	–	20
No. 3	1	–	–	–	1
No. 4	–	1	–	–	1
Total	24	52	1	–	77

dates frequent application. In two large randomized trials a recurrence rate of up to 35% is described [16, 22]. Despite the side effects, high recurrence rate and patient compliance, treatment with local NO donors is in many centers first-line therapy, because of the safety, simple application and low costs.

A second category of pharmacological agents with sphincter tone-lowering capacities are the calcium channel blockers, such as nifedipine and diltiazem. They lower anal resting tone by inhibiting the influx of calcium ions in smooth muscle cells. Local application favors oral treatment because of a better effect on anal resting tone, a higher healing rate (65 vs. 38%) and fewer side effects [23]. Side effects of local application of diltiazem, such as perianal dermatitis and headaches, are rare. Nifedipine and diltiazem have an effect that is comparable to GTN, but cause fewer side effects with local application [1, 23–26]. Moreover, diltiazem heals 48–75% of GTN ointment-resistant CAFs [27, 28]. Little is known about the long-term effect of local calcium channel blockers, but initial results are promising.

A new development in the treatment of CAFs is the injection of BT-A in the internal anal sphincter. This is an exotoxin produced by the bacterium *Clostridium botulinum* and a potent neurotoxin, preventing the presynaptic release of acetylcholine by binding to the presynaptic nerve terminal at the neuromuscular junction inhibiting neuromuscular transmission [1, 2, 6, 29]. By causing temporary synaptic blockade, botulinum toxin has been shown to relax the internal anal sphincter when injected into it [30] or into the external anal sphincter [31]. By contrast, injection into the internal anal sphincter has no effect on the external anal sphincter. After initially injecting BT-A in the external anal sphincter [31], it was later advised to inject in the intersphincteric region or in the internal anal sphincter, to prevent paralyzing the ex-

ternal anal sphincter, which regulates voluntary anal continence and is not involved in the pathogenesis of anal fissures [2, 30, 32].

Injections in the ventral part of the internal anal sphincter give better results than injections in the dorsal part [33]. No manometric data were obtained in this study, but BT-A has already proven to lower anal resting pressures [11–14].

Several studies were conducted to establish the effect of BT-A in the treatment of CAFs. Healing rates vary from 43 to 83% with ≤ 15 IU BT-A and from 60 to 96% with ≥ 20 IU BT-A [2, 5, 6, 30–32]. Most studies used Botox®. In our study, we used Dysport®. A randomized controlled trial has shown that the efficacy and tolerability of the two different formulations of botulinum neurotoxin are indistinguishable [34]. The dosage of Dysport is 4 times the dosage of Botox [35]. The low injection volumes of Dysport (0.1 ml = 20 IU) prevent local pressure effects.

The most important side effect of BT-A is temporary incontinence, mainly due to flatus [1, 2]. This is reported in less than 9% of patients. Perianal thrombosis is described in the literature as a rare side effect [36]. We only saw temporary flatus incontinence in 1 patient; no complications or side effects were seen otherwise.

Few studies have compared the treatment of CAFs with NO donors to BT-A injections. A recent randomized controlled trial reports that locally applied GTN ointment is as effective as a single injection of BT-A in the ventral part of the internal anal sphincter. The healing rate at 3 months was 67% in the GTN group and 57% in the BT-A group; at 3 years the healing rate was 40 and 33.3%, respectively. 20% of the patients treated with GTN suffered from headaches, whereas no side effects were reported in the BT-A group [37].

Another study reports that BT-A is more effective than GTN in the treatment of CAFs [32]. Perhaps this is because of the more constant, continuous reduction in internal sphincter resting tone during 2 months in the treatment with BT-A, causing a much longer normotensive state of the internal anal sphincter than in the treatment with NO donors [7]. Other advantages of BT-A injections in the above NO donors are that the problems of patient compliance and regulating dosage are no longer an issue (because the treatment consists of one single injection, which can be administered in daycare) and that side effects are rare [1, 2, 7, 32]. No randomized controlled trials were conducted which compared BT-A with ISDN ointment. There are no studies in the present literature which have compared BT-A with local calcium channel blockers in the treatment of CAFs.

Little is known about the long-term effect of BT-A. A tendency of progressive recurrence over time with an overall healing rate at 3 years of 33–47% was described in three recent controlled clinical trials [37–39]. In our study, fissures recurred in 11/77 patients (14%). Recurrence rates in the literature vary from 0 to 42% with a follow-up of 6–42 months [6, 30, 35, 40, 41]. Our low recurrence rate may be caused by our relatively short median follow-up of 10 (4–38) months.

In this study, BT-A was tested as a second-line therapy in the treatment of CAFs. In our pilot study including 32 patients, 75% became symptom-free. They all were injected with 40 IU BT-A as a first injection dosage. Because we thought that a higher dosage might give a higher healing rate, we administered an elevated first injection dosage of 60 IU in the last 66 patients.

Not much literature exists about using this therapy as first-line treatment. The higher cost of BT-A has to be taken into account, but by clustering patients, costs can be kept low, because more than 1 patient can be treated with one flacon of BT-A. Because we thought that the injection would be painful, we treated patients in daycare in this study. Because of little pain reported by patients, we now give injections on an outpatient basis, which also lowers costs. To compare BT-A with NO donors and other pharmacological agents, such as calcium channel blockers, as a first-line therapy, more studies are required. We therefore started a randomized multicenter trial (the ISDYS trial) at our hospital, in which BT-A injections are going to be compared with ISDN ointment as first-line therapy for CAFs.

Conclusion

With an early response rate of 77% and an overall success rate of 66%, BT-A injections appear to be effective in patients with ISDN ointment-resistant CAFs if initial non-responders are retreated. It is a simple technique which does not require intensive patient compliance and has little or no side effects and might therefore also be a good alternative for locally applied NO donors in the first-line treatment of CAFs. Furthermore, the risk of permanent sphincter damage resulting in incontinence, as can be seen with surgical sphincterotomy, is avoided. Future treatments are not compromised. More research is needed to compare the effect of BT-A with other pharmacological agents in the (first-line) treatment of CAFs. This study shows that it is very effective as a second-line therapy when treatment with NO donors fails.

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