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A pilot comparative study of fissurectomy/diltiazem and fissurectomy/botulinum toxin in the treatment of chronic anal fissure

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Abstract: Background: Treatment of chronic anal fissure (CAF) by fissurectomy with botulinum toxin A (BTA) injection results in a healing rate of greater than 90%. BTA injection, however, can cause incontinence and perianal sepsis. The decrease in sphincter pressure following topical treatment with 2% diltiazem cream (DTC) is comparable to that following BTA injection but with potentially fewer complications and at less cost. We report the shortterm results of a pilot study comparing fissurectomy with BTA and fissurectomy followed by DTC for the treatment of CAF. Methods: The recorded outcomes of CAF following treatment with the two methods were analysed retrospectively. Patients underwent either fissurectomy followed by injection of 40 U BTA into the internal sphincter (group A) or fissurectomy followed by the perianal application of DTC twice daily for 8 weeks (group B). Symptom resolution and treatment side effects at the initial follow-up were compared. Results: Demographics, fissure characteristics and the number of multiparous women between the two groups were comparable. At a median follow-up of 12 weeks (range 8-20 weeks), the two groups had similar rates of complete symptom resolution (group A, 25/28, 89.3%; group B, 19/23, 82.6%; $p=0.7739$), with minor side effects. Conclusions: In this small pilot study fissurectomy combined with chemical sphincterotomy resulted in high short-term fissure healing rates. The study also suggested that fissurectomy followed by 8 weeks of topical DTC may be as good as fissurectomy with BTA injection in the treatment of CAF. A prospective study, adequately powered to determine the significance of differences is needed

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A pilot comparative study of fissurectomy/diltiazem and fissurectomy/botulinum toxin in the treatment of chronic anal fissure

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between the two groups were comparable. At a median follow-up of 12 weeks (range 8–20 weeks), the two groups had similar rates of complete symptom resolution (group A, 25/28, 89.3%; group B, 19/23, 82.6%; $p=0.7739$), with minor side effects. **Conclusions** In this small pilot study fissurectomy combined with chemical sphincterotomy resulted in high short-term fissure healing rates. The study also suggested that fissurectomy followed by 8 weeks of topical DTC may be as good as fissurectomy with BTA injection in the treatment of CAF. A prospective study, adequately powered to determine the significance of differences is needed.

Key words Fissure-in-ano · Botulinum toxin · Chemical sphincterotomy · Diltiazem · Treatment

Introduction

The gold standard for healing rates in the treatment of chronic anal fissure is lateral sphincterotomy [1]. Despite the high healing rates associated with the procedure, the recognized risk of incontinence continues to prompt a shift from surgical to medical means of reducing internal anal sphincter (IAS) resting pressure to achieve fissure healing [2–4]. Medical agents include topical glyceryl trinitrate (GTN), calcium channel blockers such as topical diltiazem cream (DTC) and more recently, botulinum toxin A (BTA) injection into the IAS.

Diltiazem has been shown, both in oral and topical form, to reduce resting anal pressure in patients with anal disease, and when utilized as treatment for fissures, results in a healing rate of approximately 70% [5–7]. It acts by calcium channel inhibition thus relaxing smooth muscle. This results in vasodilation and increased blood

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flow as well as anal sphincter relaxation. The oral preparation, however, results in a more significant change in blood pressure and the topical 2% preparation may be preferred [8].

More recently, BTA injection into the IAS has also been shown to decrease mean resting pressure and has proved efficacious in the treatment of chronic anal fissures [9–14]. Development in the understanding of this drug's mode of action suggests that it binds rapidly to the neuromuscular junction and prevents the release of acetylcholine. Repeat administration of the toxin A may, however, result in antibody production in up to 10% of patients. Such patients will then develop resistance to further treatment. The results of treatment may also decrease over the long term [14, 15].

All the treatment modalities discussed above will have nonresponders who may require additional treatment. It may not be necessary to proceed immediately to surgical sphincterotomy.

In 2002, Engel et al. [16] successfully tested the hypothesis that chronic fissures unresponsive to medical treatment should be regarded as areas of unstable scar tissue in an environment of reduced tissue perfusion resulting from IAS spasm. In a prospective study of 17 patients who had failed topical isosorbide dinitrate (IDN) treatment for chronic anal fissures, a 100% fissure healing rate was achieved when fissurectomy was combined with further topical 1% IDN applied four to six times daily. The patients were followed up initially for 6 weeks after the procedure. A further long-term telephone follow-up at a median 29 months showed no recurrence, presumably of symptoms.

This hypothesis was further supported by a subsequent study of fissurectomy combined with BTA injection, which showed a 93% fissure healing rate at 16 weeks follow-up [12]. BTA is, however, relatively costly and there is emerging data on complications of incontinence and perianal sepsis with its use [10, 17–19]. Recent newspaper reports of complications following its use for cosmesis have resulted in patients questioning its utilization and asking for alternatives (*International Herald Tribune*, 25 January 2008; *HeraldNet*, Washington, 20 August 2008).

In the present study, we compared the results of fissurectomy followed by topical 2% DTC with those of fissurectomy combined with BTA injection in the treatment of anal fissures that had already failed to respond to medical management.

Methods

The outcomes of treatment in all patients with medically resistant chronic anal fissures who had undergone either

fissurectomy followed by 8 weeks of topical perianal DTC or fissurectomy combined with BTA injection was studied retrospectively. All patients in this study had failed previous treatment for at least 6 weeks with either topical GTN or 2% DTC. Failed treatment was defined as recurrent or unchanged anal pain and/or bleeding assessed and attributed to chronic anal fissure. At the time of treatment all patients had clinically evident chronic fissures characterized by fibrotic edges with or without a sentinel pile and hypertrophic anal papilla, and associated with pain and/or bleeding at defaecation. The choice of pharmacological adjunct to fissurectomy was based on clinicians' preference based on their experiences and past and newly implemented hospital procurement policy.

All patients underwent day-case general anaesthetic procedures between January 2005 and June 2006 inclusive.

Group A patients underwent surgical knife excision of the fibrotic fissure edges and, where present, the associated sentinel pile. The fissure base was curetted, avoiding damage to the internal sphincter muscle. BTA (BOTOX; Allergan, Marlow, UK) was then injected into the IAS on both sides of the fissure (20 U per side, total 40 U). Group B patients underwent similar fissurectomy, but after the procedure were provided with 2% DTC (Anoheal; SLA Pharma, Watford, UK). They received written instructions to squeeze 1 inch (2–2.5 cm) onto the tip of a finger and apply the cream to the perianal margin and into the anal canal twice daily for 8 weeks. The cream was supplied as 30-g tubes with each tube expected to last about 4 weeks. Patients in both groups were discharged home the same day with Fybogel (one sachet twice daily for 6 weeks and 15 ml lactulose twice daily for 6 weeks). No other topical or oral agents such as metronidazole were prescribed.

All patients underwent clinic follow-up at a median of 12 weeks after surgery (range 8–20 weeks). A consultant surgeon or a supervised senior registrar in the clinic assessed outcome. This involved direct questioning to establish the persistence or resolution of pain and/or bleeding at defaecation. Gentle eversion of the anal margin was performed to assess fissure healing. Grades or degrees of fissure healing were not included as end-points in this study due to its subjective nature. In the same vein, complete symptom resolution with a near-healed fissure would not necessarily mandate further intervention; hence the omission of visual evidence of fissure healing as an end-point. Incontinence was not formally assessed by the use of standardized tools or investigation.

All patients with symptoms and signs of failed treatment were offered further treatment with either DTC for a further 6 weeks or lateral sphincterotomy.

Statistical analysis

Differences in demographic and fissure characteristics were compared using the Mann-Whitney, chi-squared and Fisher's exact tests, and differences in outcome expressed as percentages were analysed using Fisher's exact test.

Results

Over the period studied, 51 patients with medically resistant anal fissures were treated either by fissurectomy combined with BTA injection (group A, $n=28$) or by fissurectomy followed by 2% DTC (group B, $n=23$). There was no statistically significant difference between the groups with respect to age, gender or fissure characteristics or, among the females, multiparity (Table 1). None of the patients had inflammatory bowel disease.

At initial follow-up, there was no statistically significant difference between the two groups with respect to patients who were completely symptom-free (group A, 25/28, 89.3%; group B, 19/23, 82.6%; $p=0.7739$). Of the three symptomatic patients in group A with persisting symptoms of anal pain and/or bleeding, all were observed to have unhealed fissures. Two patients were offered, and accepted, topical 2% DTC treatment for a further 6 weeks. One of these patient was completely symptom-free at the end of that period. The other two patients in this group therefore eventually underwent lateral sphincterotomy. In group B, all of the four symptomatic patients were observed to have unhealed fissures and were offered further topical 2% DTC. Two of these patients were completely symptom-free after a further 6 weeks of treatment. The other nonresponders did not attend further scheduled clinic follow-up sessions.

Two patients from group A complained of minor passive postdefaecatory faecal soiling lasting about 2 weeks during treatment whereas three patients in group B complained of pruritus ani, which resolved on completion of treatment.

There were no incidences of perianal sepsis or haematoma following BTA injection in this study, nor were there any reports of headache or dizziness with DTC use.

Discussion

This study demonstrates that fissurectomy followed by a short course of twice-daily topical 2% DTC may be as good as fissurectomy combined with BTA in the treatment of medically resistant fissure-in-ano at short-term follow-up. It also suggests that high rates of fissure healing can be achieved if fissurectomy is combined with the pharmacological sphincterotomy modalities investigated.

Chemical sphincterotomy shares the same goal as lateral sphincterotomy without its possible long-term side effects. It reduces the IAS spasm found with anal fissures, resulting in a decrease in the mean IAS resting pressure and an improvement in the arteriolar blood flow to the posterior commissures of the lower anal canal [20–22], thus logically creating an environment that would promote healing of anal fissures.

Fissurectomy alone has been used to treat anal fissures in children with success [23], but there are no published studies on the use of fissurectomy alone as treatment of anal fissures in adults. In the study in children of fissurectomy, which was followed by a period of prescribed gentle laxative use, a fissure healing rate of 81% was achieved. This may suggest that the clinically significant component of the presented therapy is fissurectomy. In the absence of a fissurectomy-alone arm in this comparative pilot study, we can only surmise at this possibility. A few studies have investigated the use of fissurectomy with posterior midline internal sphincterotomy with acceptable results [24–27]. However, Melange et al. found a 27% incidence of incontinence for flatus or liquid stool and a 9.2% incidence of passive soiling after the use of this technique [28]. This has historically made clinicians wary of the use of this combined modality. In performing fissurectomy in our prac-

Table 1 Demographic and fissure characteristics of 51 patients with medically resistant fissure-in-ano

	Fissurectomy/BTA ($n=28$)	Fissurectomy/2% DTC ($n=23$)	<i>p</i> value
Age (years)			
Median	43.5	41	NS ^a
Range	23–46	25–52	
Male/female	13/15	12/11	NS ^b
Anterior/posterior fissures	4/24	3/20	NS ^c
No. of multiparous females	3	1	NS ^b

^aMann-Whitney *U*-test ($p<0.05$)

^bChi-squared test ($p<0.05$)

^cFisher's exact test ($p<0.05$)

tice, utmost care is taken to avoid injury to the internal sphincter fibres. Theoretically, fissurectomy alone would not address IAS spasm, a most plausible reason for ischaemia and nonhealing seen in chronic fissures, and a possible cause of the debilitating postdefaecatory anal pain associated with anal fissures. Fissurectomy, however, creates fresh wound edges, creating in essence an acute fissure. This manoeuvre would promote primary wound healing, an approach utilized in other areas of surgery. When combined with chemical sphincterotomy, both possible reasons for fissure chronicity are addressed and this may explain higher fissure healing rates seen in studies of the treatment of chronic anal fissures utilizing both approaches [16, 29], and in this reported study.

Topical DTC has been shown to be superior to the oral form with fewer side effects and better fissure healing rates. Its lower side-effect profile, as well as early resolution of pain during its use, promotes compliance [8, 30], an added benefit that allows patients to complete the treatment. We found no complications such as headache or dizziness following DTC use in this cohort of patients.

BTA, on the other hand, only requires a single injection, thus eliminating the issue of compliance. However, it may be perceived as expensive, with a 100-U vial costing £143.92. The retail cost of a 30-g tube of 2% DTC is £49.92 in our hospital trust. Since an opened vial has to be discarded when even only 40 U have been used, one way to overcome the issue of cost would be to schedule theatre lists such that at least two patients requiring BTA injection are listed. However, two tubes of DTC as utilized in this study still costs less for an initial course.

BTA has also been reported to result in perianal sepsis and sustained minor incontinence, which may persist until the toxin's effects have worn off by neuronal degeneration [10, 17]. There is one case report of long-term faecal incontinence after BTA injection [18]. Short-term side effects of BTA injection such as transient incontinence to flatus and liquid stool, pain on injection and haematoma are also well documented, but other longer-term side effects are unknown [19]. Fortunately, we observed no perianal haematoma or sepsis after BTA injection in this study.

Sustained lowering of resting IAS pressure after BTA injection is also an obvious advantage, but therein lies its weakness: any significant incontinence not acceptable to a patient cannot be reversed until the effect of the drug subsides. This risk is eliminated with a twice-daily application of topical DTC which although short-acting, has also been shown to achieve up to 5 hours of sustained reduction in mean resting IAS pressure in one study [31],

much longer than the duration of the effect of GTN with which a significant decrease in resting pressure lasting only 90 minutes has been reported [32]. In the present comparative study as well as in the authors' early experience with these treatment modalities, no clinically reported incontinence was found. This may reflect the inconstancy of that side effect of BTA, as well as its unpredictability.

It is interesting to note that two more patients in group B were successfully treated with a further course of 2% DTC. Also interesting to note were the failed patients in group A who responded to DTC. It is unlikely that this was related to the fissurectomy, but the authors would suggest that the success of 2% DTC after previous BTA treatment could merely be a cumulative effect of the two treatments.

None of the patients who failed treatment with DTC had anterior fissures, a finding that is at variance with the observation of Griffin et al. that a high percentage of anterior fissures failed treatment with DTC [33]. However, their patients did not have the benefit of fissurectomy and this surgical component of treatment may play a significant role in healing of anterior chronic fissures.

Minor transient passive faecal soiling occurred in two patients (7.1%) after BTA injection. This is comparable to observed incidences documented in the literature. Both patients who experienced soiling were male and had had banding of haemorrhoids more than 12 months prior to presentation. At initial presentation, none of these patients had complained of faecal incontinence. No formal incontinence assessment tools were, however, applied as symptoms had resolved significantly at follow-up. The authors can only surmise that the faecal soiling was due to sustained lowered internal anal sphincter pressure from BTA injection. The absence of faecal soiling or incontinence amongst the DTC group is difficult to explain. The authors would suggest that the less-prolonged duration of sphincter relaxation with DTC compared to BTA could explain this. Between applications, a fluctuating degree of sphincter tone recovery could be providing a certain degree of continence; however, this is open to debate. Pruritus ani occurring with topical DTC, as observed in 13% of patients in group B, could have been a local effect of the moist application rather than a true side effect of the medication. This was also transient.

Although the median study follow-up period of 12 weeks may seem short, this study evaluated initial outcome only. As well as being a retrospective study without planned long-term follow-up, this aspect of the study reflects the practical aspects of management in a busy colorectal service. Other limitations of this study could be said to include its retrospective nature, nonrandomiza-

tion of patients and noninclusion of visual fissure healing as an end-point. The two former issues are inherent to retrospective studies and cannot be avoided. However, they do not detract from the thought-provoking nature of the study results. For the pathology in question, and considering the numbers of subjects studied in the published papers referenced, the number of patients in this report is not considered to be unduly small. This study cohort would be a reasonable cohort size for a pilot study. A larger prospective study with long-term end-points would be desirable to confirm this study's findings. However, sample size and power calculations suggest that the numbers needed, based on equivalence of the modalities being investigated, would be prohibitive.

In conclusion, even though this was a retrospective study with a small cohort of patients, the authors feel that significant issues have been raised. Firstly, the results suggest that fissurectomy followed by 8 weeks of topical treatment with 2% DTC may result in as high a healing rate as fissurectomy combined with BTA in the treatment of chronic anal fissures, without its risks. It has acceptable side effects, which would aid compliance with treatment. Secondly, our results, in addition to the published data on fissurectomy as an adjunct to chemical sphincterotomy, suggest some of the highest treatment rates for chronic anal fissures, except for surgical sphincterotomy. These modalities of treatment may become the standard for nonsphincterotomy treatment of fissures. The subgroup of patients most likely to benefit and who should be considered for such treatment may be those with chronic anal fissures with abundant scar tissue and those in whom surgical sphincterotomy would be better avoided. A larger prospective randomized comparison of these treatment modalities, powered to detect significant differences, is needed with long-term follow-up to assess recurrence.

Conflict of interest statement The Authors declare that they have no conflict of interest related to the publication of this article.

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Invited comment

In this issue Arthur and colleagues report a pilot study comparing symptom resolution after combined fissurectomy-diltiazem and fissurectomy-botulinum toxin in the treatment of chronic anal fissure. Interestingly, in both groups more than 80% of the patients were completely symptom-free after 12 weeks. The authors concluded that both treatment strategies do not differ in terms of healing rate.

The treatment of chronic anal fissures is still challenging. Conservative treatment with topical nitrates or calcium channel blockers is often unsatisfactory. Although lateral internal sphincterotomy is still the surgery of choice for refractory anal fissures this procedure is accompanied by a considerable risk of incontinence [1]. Today, increased tonicity of the internal sphincter is blamed for anal fissures. Tonic contraction of the internal anal sphincter is mediated by sympathetic innervations, and the sphincter stays in a state of partial contraction relaxing in response to rectal distension. Several reports have documented elevated resting anal pressures in patients with fissure, with values above 90 mmHg. Additionally, the elevated anal pressure causes ischaemia of the posterior commissure and reduces the anodermal blood flow. The combined concept of sphincter spasm and reduced anodermal blood flow explains how surgical disruption of the internal anal sphincter

allows the fissure to heal (anal pressure decreases with a rise in anal blood flow) [2, 3].

From this background the use of botulinum toxin is reasonable and justified. Botulinum toxin in the treatment of chronic anal fissures in nonsurgical settings and in combination with fissurectomy has been reported to show promising results in terms of healing rates [4, 5]. Fissurectomy, as a wound debridement, removes the bradytrophic scar tissue and supports wound healing. The additional injection of botulinum toxin decreases the tonus of the internal anal sphincter temporarily leading to an increased anal blood flow. The effect of botulinum toxin is similar to that of surgical sphincterotomy without the disadvantage of anatomical disruption of the internal anal sphincter. However, botulinum toxin is extremely expensive and its use is not without risk. Besides temporary incontinence for air and stool, other side effects have been reported, including necrotizing fasciitis, generalized muscular weakness, perianal thrombosis and the possibility of antibody production [3].

From this study two important questions in the treatment of chronic anal fissures arise. First, is the usage of botulinum toxin for chronic anal fissures overrated? Second, does fissurectomy without combined treatment achieve similar healing rates? We do not have the final answers yet and are looking forward to prospective randomized trials comparing fissurectomy alone versus combined strategies.

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