

REGULAR REVIEW

The Medical And Surgical Management Of Chronic Anal Fissure

JP Garner, M McFall, DP Edwards

ABSTRACT

Major advances in our understanding of the mechanisms involved in chronic anal fissure have allowed the introduction of many new medical therapies for this condition. The literature about current treatment modalities licensed for anal fissure and those novel therapies still under evaluation has been reviewed. These new treatments are examined in the context of traditional surgical management of the disease and a future treatment algorithm suggested.

Introduction

Anal fissure is a common condition constituting approximately 10% of referrals to a colorectal clinic (1), the majority of patients being between 20-39 years of age (2) and as such can be a common problem in servicemen. Traditionally treatment has been surgical and, whilst very successful, up to about 5% of patients have reported long-term or permanent impairment of continence. Recently major advances have been made into elucidating neurotransmission in the anal sphincters and the pathophysiology of anal fissure. Consequently many novel medical therapies are now being evaluated, and the indications for surgery are being re-evaluated. Although anal fissure is associated with many other disease processes such as tuberculosis, Crohn's disease and HIV

infection, only the management of idiopathic fissure is discussed in this article.

Clinical Features and Pathophysiology

Anal fissure is slightly commoner in men and is most common between the ages of 20 and 39 years (2). It characteristically presents with pain on defaecation which often lasts for a number of hours after passage of the motion and is associated with small amounts of bright red rectal bleeding. The fear of pain leads to an unwillingness to defaecate and the patient becomes constipated, which exacerbates the situation. Examination reveals a boat shaped mucosal defect usually in the midline posteriorly, distal to the dentate line, as shown in Figure 1. There is secondary anal sphincter spasm and there is often associated perianal itching from mucous discharge. At this stage further examination of the anorectum by proctosigmoidoscopy is usually impossible and, if a fissure is identified, this should not be attempted.

The vast majority of fissures are acute and settle with minimal intervention within a few weeks. These fissures usually consist of loose connective tissue without induration or visible muscle fibres and without a sentinel pile. Up to 70% of acute fissures will heal without intervention and Frezza *et al* reported that 90% of acute fissures heal with

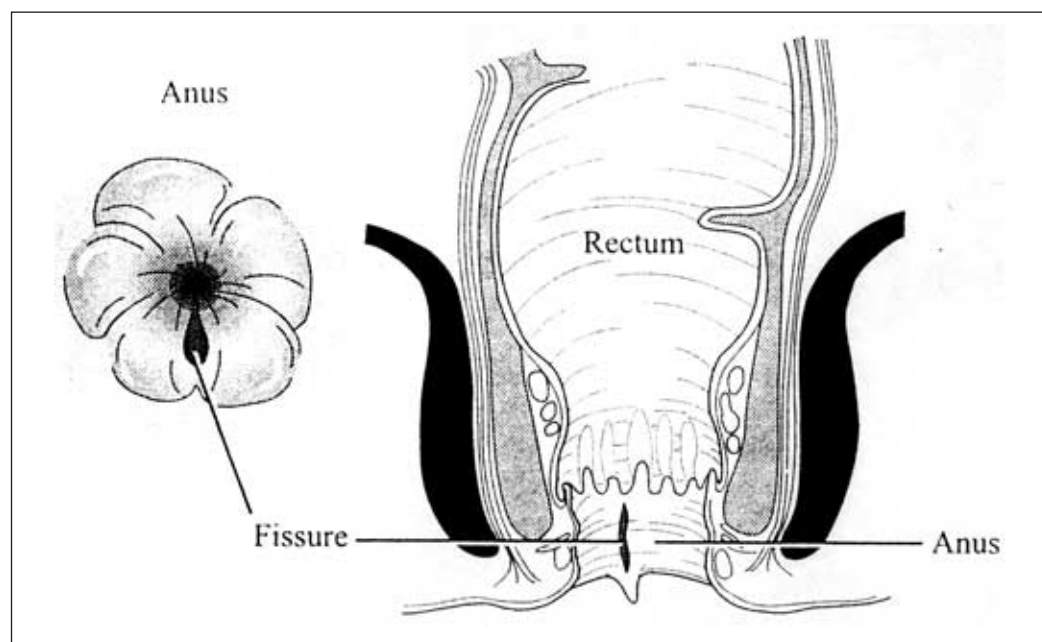


Fig 1. Typical chronic posterior anal fissure showing proximal extent below the dentate line and a "sentinel pile".

Maj JP Garner
MRCSEd RAMC
Specialist Registrar
Email: garners@dialstart.net

Mr M McFall FDS
RCS(Eng) FRCS(Eng)
Specialist Registrar

Maj DP Edwards ChM
FRCSEd (Gen.Surg)
RAMC
Consultant Colorectal
Surgeon, Department of
Colorectal Surgery,
Frimley Park Hospital,
Portsmouth Road,
Frimley, Camberley,
Surrey, GU16 7UJ

conservative treatment measures only (*vide infra*) (3).

If a fissure does not heal within 3 months it can be termed chronic. This is characterised by indurated edges to the fissure with white fibres of the internal anal sphincter (IAS) visible in the base. There is characteristically a skin tag associated with such chronic fissures (the 'sentinel pile') due to progressive perianal oedema. The underlying physiological derangement is an elevation in the resting anal canal pressure due to internal sphincter hypertonia. In healthy volunteers the mean anal canal resting pressure is approximately 85 cm H₂O (4,5). In comparison mean pressure in those with chronic fissure is significantly higher, in the order of 110cm H₂O (4). Sphincter hypertonia is greatest in the posterior anal canal where the vascular supply is poorest and recently laser doppler flow studies have demonstrated that there is an associated marked decrease in mucosal blood flow in the area of a chronic fissure (5). In essence a chronic fissure is an ischaemic ulcer.

Neurotransmission in the Anal Sphincters

Most of the gut circular smooth muscle relaxes under the influence of non-adrenergic non-cholinergic transmitters and it has been demonstrated that the sole end-mediator of IAS relaxation is nitric oxide (6). Internal sphincter excitation is in part mediated by alpha-1 adrenergic receptors and studies have shown that it may contribute up to 50% of the resting anal tone (7). Internal sphincter relaxation is mediated by muscarinic cholinergic receptors and this probably occurs in the longitudinal muscle layer of the anal canal rather than the IAS *per se* (8). In addition, up to 30% of resting pressure may be contributed by the striated muscle of the external sphincter. It is this understanding of the physiology and neurotransmission of the anal canal musculature that has resulted in the introduction of many medical therapies currently under evaluation.

Assessment of the Anal Sphincters

Endoanal Ultrasound (EAUS)

An elongated 10 MHz ultrasound probe is passed into the anal canal giving detailed images of the integrity of both the internal and external sphincters. It may be used intra-operatively to identify the length of the IAS and guide the length of sphincterotomy. This technique may be particularly useful in women who have a shorter sphincter, especially multiparous women who may already have a degree of subclinical obstetric sphincter injury. In addition, any patient who has impaired sphincter function pre-operatively or has had previous perianal surgery should be considered for EAUS

assessment. Additionally, in patients who remain symptomatic following surgery, EAUS will allow an assessment of the extent of previous sphincterotomy. Given that anal fissure can be an intensely painful condition, outpatient EAUS can be difficult - application of local anaesthetic gel helps.

Anal Manometry

In its simplest form, the pressure in the anal canal can be assessed using either a water-perfused system or a solid state transducer placed in the anus. The length of the sphincter can be estimated by a pull-through technique identifying the region of high resting pressure.

Conservative Treatment

All patients should be advised to avoid constipation and eat a relatively high fibre diet with plenty of liquid. In addition bulking laxatives such as ispaghula husk with osmotic agents such as lactulose may be used to maintain soft bulky stools and so avoid straining. Stimulant laxatives such as senna should be avoided. Excessive wiping with toilet paper tends to exacerbate the discomfort and the use of a bidet or a shower after bowel action is to be preferred. Topically applied local anaesthetic agents often help, as do steroid creams, but unfortunately although amelioration of symptoms is often achieved, fissure healing is less frequent and recurrence is common (2).

Medical Treatment Options

The medical therapies under evaluation hold much promise. Their appeal lies in the fact that they do not inflict permanent damage on the IAS and any side effects are transient. Such treatment has been termed '*chemical sphincterotomy*'. Isolation of nitric oxide as the mediator of IAS relaxation focussed research on the use of nitric oxide donors such as glyceryl trinitrate (GTN) applied topically at the anal verge, beginning with Kennedy's report in 1993 of a reduction of 14% in mean resting anal pressure and healing in 46%. (9)

Nitrates

GTN

GTN, an organic nitrate, is a nitric oxide donor, which is readily absorbed transcutaneously and has been extensively evaluated in the treatment of cardiac disease. Nitric oxide binds to the Fe 2+ moiety of the haem molecule of guanylate cyclase in the smooth muscle cell and increases the levels of the second messenger cGMP. This in turn may produce hyperpolarisation and relaxation of the smooth muscle cell by alteration in the potassium channels of the cell wall (10).

GTN, usually applied as a 0.2% paste to the perianal skin, has been demonstrated to increase anodermal bloodflow (11,12) and

reduce mean anal resting pressure (10,11,13). Unfortunately headache is a common side effect of GTN treatment and is experienced in up to 78% of patients (14) with typically up to 20% discontinuing treatment due to severe headache (15).

The efficacy of GTN has been compared with placebo in five randomised controlled trials, shown in Table 1 (11,13,16-19). These trials have demonstrated healing rates of up to 84%, at least in the short term. Follow up of over two years has demonstrated that 59 to 75% of patients will continue to be free of symptoms (13,20). Combined results of the GTN versus placebo trials yields an absolute risk reduction in the requirement for surgery of 32% with the use of GTN and a number to treat of three patients to avoid one operation. Three randomised trials of GTN versus internal sphincterotomy have also been reported (15,21,22). The results, shown in Table 2, reveal lower healing rates with GTN but useful symptom control was still achieved.

Table 1: Healing rates reported in randomised trials of the use of GTN in the treatment of anal fissure compared with placebo.

	GTN Healed / No. (% healed)	Placebo Healed / No. (% healed)
Lund & Scholefield (11)	26 / 38 (68)	3 / 39 (8)
Kennedy <i>et al</i> (13)	20 / 43 (46)	7 / 43 (16)
Chaudhuri <i>et al</i> (16)	7 / 10 (70)	2 / 9 (22)
Altomare <i>et al</i> (17)	29 / 59 (49)	31 / 60 (52)
Tander <i>et al</i> (18)	26 / 31 (84)	6 / 17 (35)
Carapeti <i>et al</i> (19)	23 / 35 (66)	11 / 35 (31)

Table 2: Randomised trials comparing GTN with internal sphincterotomy.

	GTN Healed / No. (% healed)	Internal Sphincterotomy Healed / No. (% healed)
Richard <i>et al</i> (15)	12 / 44 (27)	35 / 38 (92)
Zuberi <i>et al</i> (21)	24 / 37 (65)	11/12 (92)
Oettle (22)	10 / 12 (83)	12/12 (100)

GTN treatment may fail for a variety of reasons. Patients must be adequately instructed in the method of application since topical application will deliver a variable dose of active ingredient to the affected area. Some patients require a higher concentration of GTN to achieve adequate reduction in mean anal resting pressure, and tachyphylaxis seems to be a problem with some patients (10,19). Patients should be informed that treatment might take up to eight weeks to be effective.

Calcium Channel Blockers

Calcium channel blockers have been used for many years in coronary heart disease because blockade of the calcium channel produces smooth muscle relaxation in the arteriolar

wall. They have also been used with success for the treatment of lower oesophageal spasm by the same mechanism. They thus appeared a logical candidate to be used for anal fissure where smooth muscle hypertonia is the underlying cause. A variety of drugs and modes of administration have been tried.

Diltiazem

Carapeti *et al* in 1999 showed that both oral and topical diltiazem reduced the maximal anal resting pressure by between 17 and 28% with topical dosing having greatest effect (23). Neither dosing method gave rise to side effects in their healthy volunteers. They have subsequently shown healing of a chronic fissure in 67% of patients with twice daily topical application of diltiazem cream without side effects (24). In a similar study, Knight *et al* (25) observed overall healing rates with topical diltiazem of 59 out of 67 patients over a total of 4 months treatment. There were no reported side effects. The down side was the high recurrence rate of 14 out of the 41 patients available for follow up to a maximum of 67 weeks. Seven had only minor symptoms but no fissure and 7 had recurrent fissure. One underwent surgery and the remaining 6 had repeated successful chemical sphincterotomy (3 with GTN). Jonas *et al* (26) compared oral versus topical diltiazem in a prospective trial with a total of fifty patients. They compared reductions in maximum anal resting pressures and healing. The topical group achieved greater reductions in anal pressure and also greater healing rates (38% in the oral group versus 65% in the topical group). Significantly more side effects occurred in the oral group and Jonas concluded that topical diltiazem was an effective treatment for chronic anal fissure achieving healing rates comparable to GTN but without side effects.

Nifedipine

Cook *et al* used 20mg of oral nifedipine twice daily in two small cohorts, one of healthy volunteers and one of chronic fissure patients (27). In the volunteer group they produced a reduction in anal resting pressure of between 28-35% over 5 days. Patients achieved slightly greater reductions in pressure from a higher starting point. Nine out of 15 patients had their fissure healed at 8 weeks with a further 3 patients free of symptoms. Side effects included mild headache in 4 patients and flushing in 10. No patients reported postural hypotension although diastolic pressure was reduced for the first 4 weeks of the study. Side effects were well tolerated. They concluded that oral nifedipine is well tolerated and effective.

Alpha-1 adrenoreceptor blockers

Indoramin

Preliminary work using indoramin has shown that this alpha-1 adrenoreceptor

blocker reduces resting anal pressure in both healthy volunteers and patients with anal fissure to a level comparable with other chemical sphincterotomies (4). No clinical trials to assess healing rates have been performed but the authors suggest that this may be another new agent for healing chronic anal fissures.

Cholinergics

Bethanecol

Carapeti also demonstrated that bethanecol, a cholinomimetic, also reduces anal pressure and heals chronic fissure (60% at 8 weeks - no reported side effects) (24).

Botulinum Toxin

Botulinum toxin Type A (BT) is produced by the anaerobic bacterium *Clostridium botulinum*. It binds to presynaptic cholinergic nerve terminals, is internalised and thence inhibits release of acetylcholine at the neuromuscular endplate producing functional denervation. Within two days of exposure new axon terminals begin to sprout and regenerate the motor end plate.

BT has been used therapeutically since the 1980s. Initially it was used in the treatment of conditions such as strabismus and focal dystonias including blepharospasm but its indications have since widened considerably and the first proctological use of BT was in the treatment of anismus in 1988 (28).

In 1993 Jost and Schrimck reported the use of BT in the treatment of anal fissure, injecting 2.5U either side of a chronic anal fissure (29). Pain relief occurred within 24 hours and the fissure healed in 12 weeks. Over the course of the following 4 years they updated their reports and in 1997 published the results of 100 patients in which they achieved primary healing in 79 patients at 6 months follow up (30). In this series 7 patients had incontinence to flatus for two weeks post injection and two women suffered faecal incontinence for 1 week afterwards. All patients regained full continence.

The mechanism of action of BT in anal fissure healing is not entirely clear. The terminal neurotransmitter of the IAS is nitric oxide and cholinergic innervation causes sphincter relaxation, so the mechanism of cholinergic blockade causing IAS relaxation remains unknown. It may be that BT works on the striated external sphincter muscle, which contributes about 30% of resting tone, although studies have shown normal squeeze pressures in these cases.

The ideal dosage and site of administration of BT are not yet confirmed. It is injected using an insulin syringe with a 27 gauge needle. Espi showed 15U to be superior to 10U (31) but other studies have advocated 20U (32). Some authors have claimed direct injection into the internal sphincter is the method of choice, although in practice confidently needling the internal sphincter is

difficult. Consequently, most surgeons compromise by attempting to inject bilaterally into the intersphincteric space.

There is only one randomised trial of BT against placebo which showed healing in 73% of toxin compared to 13% of placebo treated patients at 2 months (32). Unfortunately the study was small (30 patients) and despite randomisation the control group had an older population of men than the treatment arm.

A direct comparison of GTN and BT in a randomised trial showed superior healing rates with BT (96 % compared to 60% at 8 weeks) with less adverse effects in the BT group (0 versus 5) (33). Surprisingly, during 15 months follow-up, there were no relapses, suggesting patients with acute fissures may have been inadvertently included in the study.

Surgical Treatment Options

The traditional treatment to reduce tone in the anal sphincter has been the anal dilatation in which 4 fingers are gradually inserted into the anus under deep general anaesthesia and gently separated thus breaking the fibres of the internal sphincter in a radial fashion. The risks to continence of this approach are obvious and have been estimated at 30% for temporary incontinence (34) and up to a 10% risk of permanent faecal incontinence (35). It has consequently fallen out of favour with most surgeons.

Surgical division of the IAS sphincter relieves hypertonia and allows increased mucosal blood flow and healing (5). Historically this was performed in the posterior midline with concurrent excision of the fissure (36). This approach has been shown to have high rates of incontinence (37) and often leaves a keyhole shaped defect in the posterior midline (38). The preferred procedure is the lateral internal sphincterotomy, which can be performed by either an open or closed technique. In the open technique a short circumferential incision is made just inside the cutaneous margin of the anal canal overlying the intersphincteric groove. This allows the mucosa to be lifted off and the intersphincteric groove to be cleared, leaving the IAS isolated before division under direct vision. Traditionally the IAS was divided up to the level of the dentate line but division only for the length of the fissure is now commonly practised, particularly in women who have a shorter sphincter, thus aiming to reduce the rate of post-operative incontinence. The closed technique utilises a stab incision in the 3 o'clock position. A scalpel is then inserted into the intersphincteric groove with blade parallel to the IAS before being rotated 90° and the blade advanced through the fibres of the IAS towards the index finger of the operator placed in the anal canal. The fibres

of IAS can be felt to give way as division takes place. The results are excellent with 95% of fissures healed at 3 weeks (39). Long-term follow up however reveals that a small but significant number of patients may report minor incontinence to flatus or suffer faecal soiling (40).

In difficult or recurrent cases, there is a place for excision of the fissure and coverage of the defect by an advancement flap. This has been shown to be safe and effective in a series of 40 cases by Leong and Seow-Choen (41) with no cases of impaired continence. This type of procedure is also ideal for those less common fissures associated with normal or low canal pressures where any procedure to lower anal canal pressure would be illogical.

Medical or Surgical?

Lateral Internal Sphincterotomy remains the most effective and rapid means of curing chronic anal fissure with rates of healing of 95% at 3 weeks. In comparison, chemical sphincterotomy has achieved healing rates of 80% in the best series but in general healing rates of only 50 - 60% are reported with much longer healing times. Current first line treatment for chronic idiopathic fissure in the UK is medical, with lateral sphincterotomy reserved for recalcitrant cases. The potential benefits of surgical sphincterotomy with regards to success rates and healing times should however be borne in mind when treating patients in a Service context as a serviceman may be better served by a quick, reliable cure rather than prolonged medical therapy with uncertain results.

The Future

Chemical sphincterotomy is an effective and well-tolerated treatment modality that has many advantages. It is repeatable, not permanent and causes no anatomical damage to the anal sphincter mechanism. Currently, only GTN is licensed for use in anal fissure, as a topical 0.2% ointment. Topical diltiazem is the subject of a phase 3 trial for first line medical therapy as it appears to have a superior side effect profile to GTN. Second line treatment, after either GTN or a calcium channel blocker may include BT injection.

Anorectal investigation with EAUS (with or without anorectal manometry) and surgical referral will be indicated for those few patients that fail to respond to medical treatment. Then, evaluation of the sphincters prior to lateral sphincterotomy, possibly with EAUS guidance of sphincter division should be recommended. Advancement flaps are indicated if a fissure persists or recurs after adequate sphincterotomy or after maximum medical therapy in patients with evidence of pre-existing sphincter injury. With a greater understanding of the physiology of the anal sphincters and the licensing of drugs to modify its action, it is likely that the

management of the majority of patients with anal fissure will move to the primary care setting.

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