

Review Article**Chronic anal fissure: new approaches to chemical sphincterotomy***Mohammad Hassan Emami**, *Samar Sayedyahosseini***JRMS 2008; 13(3): 149-155**Definition of anal fissure**

An anal fissure is a split in the mucosa extending from the anal verge towards the dentate line. It was first recognized as a disease in 1934¹ and currently affects 10% of patients attending proctology clinics.² Fissures usually present with pain and small amounts of bright red rectal bleeding. Contrary to traditional teaching, a precipitating history of constipation is found only in a small percentage of patients (approximately 20%).³ Acute fissures usually heal with conservative management. Fissures lasting greater than two months with features of chronicity (sentinel skin tag, hypertrophied anal papilla, and exposure of the underlying internal anal sphincter or anal cicatrisation) are unlikely to heal with conservative management. Fissures due to an underlying disease (for example, perianal Crohn's disease where fissures are often multiple and situated laterally) are also unlikely to resolve with conservative management.³ Although most of the fissures are short-lived and heal spontaneously, those that persist and require intervention cause considerable morbidity in an otherwise healthy young population.⁴ Severely constipated individuals with anal fissure exhibit the same poor quality of life as patients with faecal incontinence.^{4,5}

Etiology

Recent studies have highlighted the role of increased internal anal sphincter pressure and

decreased anodermal blood flow in the pathogenesis of chronic anal fissures.³ The internal anal sphincter hypertonia seen in patients with an anal fissure has long been thought to be a secondary phenomenon, occurring after local trauma to the mucosa by for example, passage of hard faeces. In this scenario, subsequent sphincter spasm then leads to further constipation and so a vicious cycle is created. Traditional treatment (anal dilatation and internal sphincterotomy) aims to break this cycle by disrupting the internal anal sphincter. Recent research has shown the blood flow to the posterior midline of the anus is potentially deficient, being supplied by end arteries (mean arteriolar blood pressure 85 mmHg), which passes through the internal anal sphincter before reaching the posterior commissure.³ As the maximum resting anal pressure (MRAP) is usually greater than 90 mmHg in patients with fissures,⁶ such hypertonia will compress these end arteries and cause ischemia of the posterior commissure. Such a reduction in the posterior anodermal blood flow has been confirmed using laser Doppler flowmetry.⁷ Further evidence that the hypertonia is not secondary to pain arises from the demonstration that it is not relieved by the use of topical anaesthetics.⁸ This evidence supports the hypothesis that anal fissures are caused by internal anal sphincter hypertonia producing ischemia of the posterior commissure of the anus. This explains the presence of sphincter spasm,

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severe pain (ischemic in nature), predilection for the posterior midline, and poor healing. It also explains how surgery allows the fissure to heal by disrupting the internal anal sphincter and improving anodermal blood flow.

Previous treatments

Surgical sphincterotomy: Although acute anal fissures usually respond to conservative management, lateral internal sphincterotomy has been the treatment of choice for chronic anal fissures.⁹ Sphincterotomy was first described in 1835 and can be carried out using an open or a subcutaneous¹⁰ technique and under local or general anesthesia. Two large studies have demonstrated a 2.3%-3% failure rate at five years.^{11,12} The median time to fissure healing was 5.6 weeks, with incontinence for flatus occurring in 3%-36%, soiling in 4.4%-21%, and faecal incontinence in 0.4%-4.9%. The extent of sphincterotomy may influence the subsequent outcome (in terms of healing and incontinence) and it would appear reasonable to divide the sphincter for the length of the fissure.^{13,14} It has been suggested that open sphincterotomies are longer than closed ones,¹⁴ explaining why they have been shown to have a higher risk of incontinence than the closed technique.¹⁵ Various studies have shown lateral internal sphincterotomy to be superior to anal dilatation and posterior internal sphincterotomy¹⁶. Posterior internal sphincterotomy results in a keyhole deformity of the anal canal and a wound, which is slow to heal, presumably because of the inadequate blood supply.

Anal dilatation: Anal dilatation was first described in 1838¹⁷ and was popularised by Lord in the treatment of haemorrhoids.¹⁸ Lord's original eight finger dilatation was abandoned in favour of a more gentle four finger stretch for four minutes¹⁹ and more recently a standardised dilatation procedure using a Parks' retractor opened to 4.8 cm or with a 40 mm rectosigmoid balloon has been advocated in the treatment of chronic anal fissures.²⁰ Although anal dilatation results in successful healing of anal fissures comparable to lateral

internal sphincterotomy²¹⁻²⁵, there is no way to reliably standardise the procedure and both the internal and external sphincters can be disrupted or fragmented in an irregular manner^{26,27}. Retrospective²⁸ and prospective^{20,27} trials have shown that anal dilatation has a higher risk of incontinence than that of lateral internal sphincterotomy.

Novel approaches

Chemical sphincterotomy: Because of the disability associated with surgery for healing anal fissure and the risk of incontinence, medical alternatives for surgery have been sought. Most recently, pharmacologic methods that relax the anal smooth muscle, to accomplish what occurs in surgery, have been used to obtain fissure healing. Agents like nitroglycerin ointment,²⁹⁻⁴⁰ besides Botulinum toxin A,⁴¹⁻⁵³ isosorbide dinitrate,⁵⁴⁻⁵⁷ diltiazem,⁵⁸⁻⁶² bethanechol,⁶³ nifedipine,⁶⁴⁻⁶⁶ lidocaine,⁶⁷ L-arginin,⁶⁸ lacidipine,⁶⁹ alpha-1 adrenoceptor blockade,⁷⁰ and combinations of some of them⁷¹ are used as well as anal dilators and surgical sphincterotomy. Topical 0.2% glyceryl trinitrate (GTN) ointment probably is the most widely used first-line treatment.²⁹⁻⁴⁰

GTN

A nitric oxide donor: The mediator of the non-adrenergic non-cholinergic pathway stimulating relaxation of the internal sphincter has been shown to be nitric oxide.⁷²⁻⁷⁴ Application of topical nitric oxide donors has been demonstrated to reduce anal pressure.^{75,76} Such observations have generated an interest in the use of nitric oxide donors as a form of chemical sphincterotomy. A prospective, randomized, double blind, placebo controlled trial in 80 recruited patients with chronic anal fissures revealed a 68% (26/38 cases) healing rate at eight weeks when 0.2% GTN ointment was applied twice daily compared with an 8% (3/39 cases) healing rate for placebo⁷⁷. Healing correlated with a reduction in pain, reduced MRAP, and an improvement in anodermal blood flow. There was an 8% relapse rate at four months but, these three patients were suc-

cessfully retreated with GTN ointment and no further relapses were reported four months later. The median time to healing was six weeks, with 58% of patients developing headaches and one patient (2.6%) required surgery after stopping the treatment for this reason. There were no cases of incontinence. The MRAP has been shown to return to pre-treatment levels once the GTN was stopped.⁷⁸ A more recent prospective, randomized, double blind, placebo controlled trial in 70 patients with chronic anal fissures revealed a 65% (15/23 cases) healing rate at two weeks after an eight week course of 0.2% GTN ointment applied three times a day compared to 32% (7/22 cases) for placebo.⁷⁹ The median time to healing was eight weeks. Increasing the strength of GTN ointment to a maximum of 0.6% did not improve healing efficacy (16/23, 70%). GTN treatment caused a significantly greater reduction in MRAP compared with the placebo group but this was not associated with an improvement in anodermal blood flow. During a median follow up of nine months, symptomatic recurrence rates were 43% for the placebo group (3/7), 33% for the 0.2% GTN group (5/15), and 25% for the higher dose GTN group (4/16). Forty four percent of these recurrences were successfully treated with a second course of GTN. Seventy two percent of patients receiving GTN developed headaches, with no difference between the low and high dose groups (15/23 vs. 18/23, respectively). Temporary loss of flatus control was observed in 6/46 patients during GTN treatment, with no case of faecal incontinence. A smaller prospective, randomized, controlled trial using 0.2% GTN ointment applied three times a day showed a one month healing rate of 62.5% (five of eight patients with chronic anal fissure) compared with 20% (one of five patients) when 2% lignocaine was used.⁸⁰

Limitations of GTN: It has been suggested that tachyphylaxis may occur when GTN is used to treat anal fissure,⁸¹ just as it occurs in cardiovascular disease. Higher doses may overcome this problem as there is some evidence that the internal anal sphincter demonstrates a dose related response to the application of GTN.⁸² A potential problem with using GTN ointment outside of a trial setting may be poor compliance. A retrospective mail audit of 27 patients who were prescribed GTN ointment 0.2% twice daily reported a compliance rate of 67% with a healing rate of only 56% after three to 10 weeks of treatment.⁸³ Till now most drugs for treatment of anal fissure are used in oral form or in the form of cream or gele. The internal anal sphincter has a dose related response to some of them like GTN, so it requires high doses of the drug to achieve the desired response.⁸²⁻⁸³ The transient sphincteric relaxation effect of the pharmacologic agents such as GTN, makes them less effective than surgery.⁸³ Although we have different forms of GTN products, they do not show a long acting effect on relaxing and enhancing the perfusion of anal sphincter, because they are soon metabolized; Besides that, repeated application of the drug, during day and night, given the need of long period treatment, is not easily practical.

Conclusion

We think that, most difficulties with current usage of drugs are due to poor compliance of patients. It can be taken into consideration that new formulation and novel combination of GTN and other first line treatments in slow releasing forms, may lead to acceptable strategies in the management of chronic anal fissure.⁸⁴⁻⁸⁶ As authors' experience in this field, other clinical trials on the drug combination and slow releasing formulations are warranted to generate new data on the subject.^{87,88}

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