

Chapter 53

Pharmaceutical Manipulation of Chronic Anal Fissure

Kadhim Jawad, Waqar Al-Kubaisy, Ali Al Shaham, Suneet Sood and Yahya Mohammed Arpuin

Abstract Physiologically, it is the resting tone of the internal anal sphincter that chiefly interferes with the healing of the fissure. An anal fissure which does not heal with sitz baths and laxatives is a chronic anal fissure. Till now, the treatment for chronic anal fissures has been surgery in the form of anal dilatation or lateral sphincterotomy. Fissures heal in most patients, but a few develop transient or even permanent incontinence. There are exciting new advances in the form of chemical sphincterotomy, by the application of drugs that relax the sphincter. Glyceril trinitrate and isosorbide dinitrate relax smooth muscle. They promote healing in about half of patients, but often cause headaches. Consequently compliance is a problem. The calcium antagonists, nifedipine and diltiazem, also reduce anal pressure by 28 %, but healing rates are low. Botulinum toxin is the most promising of the agents used for chemical sphincterotomy. This toxin can be used to weaken smooth muscle in the gastrointestinal tract, for example in achalasia and infantile hypertrophic pyloric stenosis. Botulinum toxin injection near the fissure reduces anal pressure lasts for about 3 months. This allows the fissure to heal, thus eliminating the need for surgery. After injection of botulinum toxin, there is a decrease in resting anal pressure by 18–30 %. The injection relieves the pain almost immediately. Cure rates are over 60 %, and the procedure can be repeated. Botulinum toxin

K. Jawad (✉) · Y. Mohammed Arpuin

Faculty of Medicine, Universiti Teknologi MARA, Shah Alam, Malaysia
e-mail: kadhim_jawad@yahoo.com

Y. Mohammed Arpuin

e-mail: mayahya3@gmail.com

W. Al-Kubaisy

Faculty of Medicine, Universiti Teknologi MARA, Shah Alam, Malaysia
e-mail: waqar_abd@yahoo.co.uk

A. Al Shaham

General Surgery, Al Kindy Medical School, Baghdad, Iraq
e-mail: alialshaham@yahoo.com

S. Sood

Faculty of Medicine, Monash University, Melbourne, Australia
e-mail: suneetsood@yahoo.com

is a reasonable first-line alternative to surgery in the management of chronic anal fissure.

Keywords Botulinum toxin • Anal fissure • Glyceryl trinitrate • Lateral sphincterotomy

1 Background

An anal fissure is a longitudinal tear at the anal verge. It is caused by hard stools, and presents with fresh bleeding and anal pain during defecation. Acute fissures may respond to conservative management with sitz baths and laxatives (Ellis et al. 2006). Until now, surgery has been necessary for acute fissures that do not respond to conservative therapy and for chronic fissures. Fissures, therefore, are typically managed by surgeons. However, there are exciting new advances in nonoperative management that may well see this condition becoming a primarily medical disorder. This review discusses the current status of nonsurgical treatment for anal fissures.

2 Pathophysiology and Pathogenesis

In a patient with constipation, the passage of hard stools can injure the skin in the anal canal. Such injuries in most parts of the body would heal. Therefore, why does this injury not heal easily? The cause of this difficulty in healing is the internal anal sphincter (IAS). The IAS is a dense condensation of circular muscle fibers that form a complete ring around the anal canal. The IAS is in a state of tonic contraction state (except when defecating). It is the single most important contributor to anal resting pressure. In contrast, the external sphincter contributes little to resting anal pressure. The anal injury triggers a spasm of the IAS, increasing the resting anal pressure. This sphincteric spasm is fundamental in the pathophysiology of anal fissure. The degree of spasm in an anal fissure is sufficient to cause regional ischemia and hinder healing. Ninety percent of anal fissures occur at the posterior anus (Maria et al. 1998a, b) this part of the anus is less perfused than other sections of the anal canal. A permanently elevated resting pressure impairs the intrasphincteric blood flow. This results in ischemia to the anoderm and therefore hinders healing of the fissure (Fig. 1).

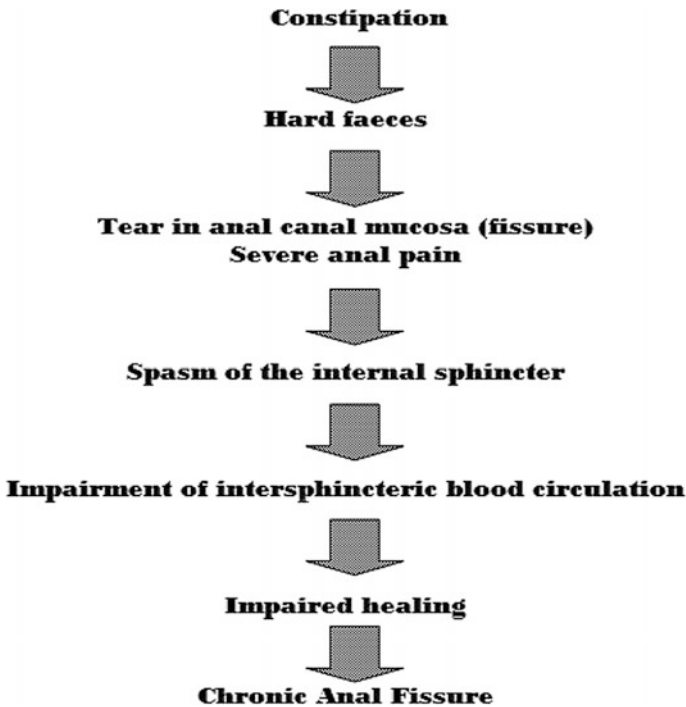


Fig. 1 The pathophysiology of development of a chronic anal fissure

3 Surgical Sphincterotomy

It follows that a relief of IAS spasm will improve the blood supply to the fissure area and result in healing. Indeed, the surgery of anal fissure is based on this concept. The two most popular procedures are anal dilatation and lateral sphincterotomy. In an anal dilatation, the surgeon stretches the sphincter so much that the IAS becomes paralyzed for several days. During a lateral sphincterotomy, the surgeon divides the lowermost fibers of the IAS. These fibers lose their spasm, and improve the blood supply with consequent healing of the fissure. After anal dilatation, fissures heal in 93 % of patients. Nevertheless, because of the sphincter damage, as many as 38 % of patients can have transient incontinence, and a small number of patients have a degree of permanent incontinence (Nyam and Pemberton 1999) Since anal dilatation may cause incontinence, many surgeons prefer lateral internal sphincterotomy, often considered the procedure of choice for anal fissure. The sphincterotomy is simple to perform, and provides immediate relief of pain. Healing occurs in 96 % of patients. Although incontinence is rare, it does occur, and may be permanent (Nyam and Pemberton 1999). Many studies show Some patients develop incontinence to flatus or faeces (Khubchandani and Reed 1989), (Littlejohn and Newstead 1997), (Hananel and Gordon 1997), (Mélange et al. 1992) as in table 1.

Table 1 The incidence of incontinence after lateral internal sphincterotomy

Authors	No.	Incontinence to flatus %	Incontinence to faces %	Incidence of soiling %
Nyam and Pemberton (1999)	487	6	1	8
Melange et al. (1992)	76	17	11	9
Khubchandani and Reed (1989)	829	35	5	22
Littlejohn and Newstead (1997)	287	2		1
Hananel and Gordon (1997)	312	1	1	1

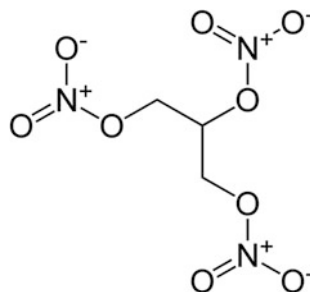
4 Chemical Sphincterotomy

Both anal dilation and sphincterotomy are associated with irreversible damage to the IAS and the possibility of long term incontinence. These side effects of surgery can be quite distressing, and therefore researchers have investigated nonsurgical methods of reducing IAS spasm. They have discovered drugs that reduce this spasm: these drugs help with healing of the fissure, but the sphincter paralysis is not permanent. The use of pharmacological agents for this purpose is called chemical sphincterotomy.

Glyceryl Trinitrate and Isosorbide Dinitrate

Glyceryl trinitrate (GTN) (Fig. 2) and isosorbide dinitrate relax smooth muscle. They reduce resting anal pressure, and consequently improve blood flow. Their vasodilatory effect may also help. The resting anal pressure falls after local anal application of GTN ointment. Immediately after the application of 0.2 % GTN, a significant rise to normal blood flow levels occurs (Kua et al. 2001). GTN ointment

Fig. 2 Glyceryl trinitrate (GTN)



promotes healing of anal fissures in 33–88 % of patients in different trials (Lund and Scholefield 1997). Moderate to severe headaches are common, and occur in about 80 % of patients (Richard et al. 2000) and compliance is a major issue (Altomare et al. 2000; Palazzo et al. 2000). These side effects, along with tachyphylaxis, limit the utility of topical GTN ointment in the treatment of anal fissure (Richard et al. 2000). The problems encountered with isosorbide dinitrate are similar to those with GTN.

Calcium Antagonists

Nifedipine and diltiazem are calcium channel blockers, and are effective in the management of selected patients with hypertension. Topical formulations of both nifedipine (Nyam and Pemberton 1999) and diltiazem, have been evaluated. The reduction in anal pressure is a modest 28 %, and the effect lasts for hours after application (Ellis et al. 2006). At present these drugs are not used in routine clinical practice for managing anal fissure (Antropoli et al. 1999).

Botulinum Toxin

Toxin is a lethal biologic neurotoxin released by *Clostridium botulinum*. It binds rapidly and strongly to presynaptic cholinergic nerve terminals, and prevents the release of acetylcholine into the neuromuscular junction (Westfall and Westfall 2006). This decreases the activity within parasympathetic and sympathetic cholinergic synapses, and produces a flaccid paralysis of skeletal muscle (Fig. 3). Botulinum toxin is a versatile tool and is used in disorders of striated muscles, e.g., spasmodic torticollis, strabismus, blepharospasm, and hemifacial spasm. The toxin can be used to weaken smooth muscle in the gastrointestinal tract as in achalasia and infantile hypertrophic pyloric stenosis. In the treatment of anal fissure, botulinum toxin has greater clinical potential than GTN or the calcium antagonists. Figure 3 shows the normal nerve function, the synaptic vesicle adheres to the cell membrane at the synaptic cleft and releases acetylcholine by exocytosis. The process of release of acetylcholine requires a complex of proteins, commonly known as SNARE proteins, consisting of VAMP—synaptobrevin, SNAP-25, and syntaxin. When botulinum toxin is administered, it attaches itself to the presynaptic nerve terminal and enters the cell by endocytosis. Botulinum toxin cleaves SNAP-25, and prevents the release of acetylcholine into the synaptic cleft, paralyzing the nerve.

The advantage of using botulinum toxin injections in patients with anal fissure is that the ensuing reduction in anal pressure lasts for 3 or more months. This prolonged relaxation of the IAS allows the fissure to heal, thus eliminating the need for surgery. When botulinum toxin is used for the management of other disorders, as in disorders of the face, its disadvantage is that the effect wears off, necessitating

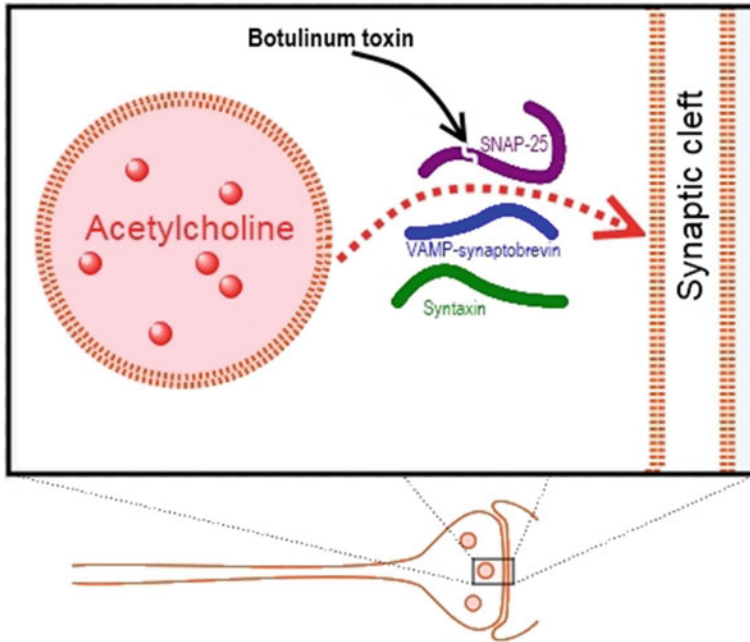


Fig. 3 The effect of botulinum toxin

reapplication. In the management of anal fissure this property is actually an advantage, since there is no risk of permanent incontinence (Mason et al. 1996). Typically, 0.4 ml of botulinum toxin is injected around the fissure in a saline solution containing 50 units/ml. Some patients may need re-injection after 2 months (Maria et al. 1998a). After injection of botulinum toxin, there is a significant decrease in resting anal pressure by 18–30 % (Maria et al. 1998b). The therapeutic effect of sphincter relaxation occurs within a few hours after injection, relieving pain almost immediately. Another benefit over surgery is that no sedation or local anesthesia is required during the procedure. Botulinum toxin should be used with caution in certain situations. The presence of abscesses in the area of injection constitutes a definite contraindication. Coagulation disorders and intake of anticoagulants are relative contraindications (Fernandez et al. 1999). A transitory incontinence for flatus occurs in about 3 % of patients (Maria et al. 1998b). It is natural to assume that botulinum toxin injection is dangerous because it is a toxin, but in fact it is very safe. Others show no temporary incontinence (Minguez et al. 1999) as shown in Table 2. When used for cosmetic purposes (e.g., facial disorders), side effects include bruising at the site of the injection are headache, respiratory infection, temporary eyelid droop, nausea, and an influenza-like syndrome. Injection for fissure in ano seems very safe and lacks systemic side effect.

In a randomized trial, Nasr et al. (2010) showed that fissure healing occurred in 25/40 patients after use of botulinum toxin, as compared to 36/40 patients after

Table 2 Treatment of chronic anal fissure using botulinum toxin injection in three large studies

Author	No.	Temporary incontinence (%)	Healing rate (%)
Maria et al. (1998a, b)	57	2	68
Fernandez et al. (1999)	76	3	67
Minguez et al. (1999)	69	0	63

lateral sphincterotomy. Recurrence rates were also lower following surgery. Unfortunately, five patients had incontinence, which persisted in two. Permanent incontinence does not seem to occur with the use of botulinum toxin.

We believe that botulinum toxin injection should be tried before surgery in patients with chronic anal fissure. Over 60 % of patients will heal without the morbidity or side effects of surgery. The injection can be repeated, and surgery is always an option in case the fissure still does not heal.

5 Conclusion

Although surgical sphincterotomy reduces anal tone and sphincter spasm and promotes fissure healing and it is effective treatment in fissure in ano, it is a surgical procedure, and is associated with cases of fecal incontinence and soiling. Therefore, pharmacological means to treat chronic anal fissure is an interesting alternative. GTN 0.2 % ointment has an efficacy of up to 68 % in healing chronic anal fissures, but it is associated with headache as a major side effect. Botulinum toxin injected into the anal sphincter healed over 60 % of chronic anal fissures.

The use of botulinum toxin appears to be effective for the treatment of chronic anal fissure. It is less expensive and easier to perform as an outpatient procedure and does not require anesthesia. No adverse effects or permanent sphincter damage resulted from the injections of the toxin. It might be considered also for patients with high surgical risks or in selected cases with high risk of future incontinence or patients to avoid surgery.

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