



## Pathophysiology of Chronic Anal Fissure: Current Understanding and Clinical Applications

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### Introduction

The pathophysiology of chronic anal fissures is not completely understood but likely involves an initial trauma resulting in sphincter hypertonicity and local ischemia which spirals into an unending fluctuating pattern of pain, spasm, worsening hypertonicity, and ischemia. Traditionally, treatments for chronic fissures have been aimed at decreasing the hypertonicity of the internal anal sphincter (IAS), albeit by innumerable means and methods. The lateral internal sphincterotomy (LIS), first suggested by Eisenhammer (1) in 1951 has been considered the gold standard and has been practiced relatively unchanged for almost 40 years. Reports of incontinence and a better understanding of the pathophysiology of this condition have led to a search for non-surgical agents to treat chronic fissures. In this review article, we will focus on the current level of understanding with regard to the pathophysiology and clinical implications of chronic anal fissures. Fissures occurring off of the midline are usually associated with other systemic conditions including inflammatory bowel disease, cancer, tuberculosis, AIDS, and other sexually transmitted diseases and will not be considered in this paper, nor will the management of acute fissures.

The exact definition of what constitutes a chronic fissure varies in the literature but is generally characterized mediated by the duration and appearance. Lindsey et al. (2) have suggested a standard definition: "the presence of visible transverse internal anal sphincter fibers at the base of an anal fissure of duration not less than 6 weeks." This definition appears to be reasonable although many authors, including us, use 4 weeks as a cut-off for acute fissures. Chronic fissure patients will describe a deterioration cycle of recurrent pain, fear of defecation precipitating worsening constipation, and even more severe pain. On physical exam, an acute fissure will appear to be a mere crack in the epithelium, typically beginning at the anal verge and traveling proximally along the anal canal toward the dentate line. Over time, a number of factors occur precipitating the well-known secondary clinical features of a chronic fissure. The distal epithelium can become edematous and fibrotic resulting in a sentinel tag or pile at the distal margin, often indistinguishable from a typical hemorrhoidal skin tag. Similar changes at the proximal margin may result in a hypertrophied anal papilla. Chronic inflammation and fibrosis result in fibrotic lateral edges and exposed IAS fibers at the base (3).

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## Section I : Pathophysiology of chronic anal fissures

The anatomy and physiology of the IAS have been extensively studied over the last 20 years, and although much has been elucidated and hypothesized, the cause of chronic anal fissures is not yet entirely understood.

Most agree that the inciting event for an acute fissure is local trauma, usually by a hard stool to the anoderm, resulting in an overstretching and tearing of the squamous epithelium of the anal canal. The traditional hypothesis for the persistence of acute fissures and the development of chronicity was based mostly on pragmatic observation and not scientifically proven data based on the observation that pain caused IAS spasm. In this scenario, and acute fissure would result from an initial trauma, followed by a worsening cycle of severe pain producing IAS spasm and hypertonicity which precluded the fissure from ever healing primarily. An 'overshoot' effect was proposed in which patients with chronic fissures were more likely than controls to have episodes of prolonged hypertonicity following rectal distention and that every bowel movement would continue to hamper healing (4). Additionally, the role of psychological stress was suggested to play a role (5). Although these hypotheses made intuitive sense for many years, clinical experimentation and anecdotal observation did not support this theory. Keck et al. (6) used computer-generated anal profiles to map the IAS and found that resting pressures among patients with chronic fissures were unaffected by the subjective experience of pain. Also, the lack of any data in multiple randomized trials suggesting pain relief alone can heal fissures any better than placebo or nitroglycerin (NTG) ointment implied that relief of spasm alone will not bring about fissure healing. Although sphincteric spasm as an entity is undoubtedly present and painful, mounting evidence from 1986 to 1996 supported a more complex and multifactorial nature of chronic fissures.

The increasing use of standardized anorectal manometry in a number of studies began to question whether a hypertonic IAS was the effect of pain or the very milieu upon which acute fissures go on to develop chronic changes.

Initial manometric studies in the 1960s and 1970s varied with respect to the association of increased IAS resting pressures and anal fissure. Inconsistent methods and results left unanswered whether pain induced spasm or if the spasm was preexisting. In 1986, Gibbons and Read (7) attempted to settle the issue by using a systematic approach that

compared 6 chronic fissure patients with 14 normal controls using a standardized system with multiple probe sizes.

They reported that fissure patients had significantly elevated resting pressures which persisted over time, and they made a number of conclusions which were novel at the time and were confirmed over the next 20 years. They were the first to suggest that chronically elevated IAS tone is the primary inciting event in the non-healing of acute fissures and further hypothesized that the hypertonic sphincter creates microvascular hypertension and subsequently causes a relative ischemia to the lining of the anal canal. Limited perfusion pressures of the anoderm were equated to those of the lower extremities in patients with severe peripheral vascular disease, and they concluded that chronic fissure patients suffer from anal canal claudication and ischemic ulceration. They also equated the built-up edges of lower extremity arterial ulcers which represent the area of best available blood supply to the sentinel tag and hypertrophied anal papilla representing the in-growth of new tissue at the areas of greatest perfusion proximally and distally.

In 1989, Klosterhalfen et al. (8) reported their work on postmortem angiographic examination of the inferior rectal arteries; they found that small perforating branches pierce the intermuscular septa perpendicular to the muscle. Lateral branches approaching perpendicularly toward an ellipse would be expected to have the weakest flow at the edges of the ellipse. This was confirmed in this study when there was found to be little or no contact at the posterior midline producing a zone of relative ischemia.

Over the next 10 years, a number of researchers would report anorectal manometric studies before and after lateral internal sphincterotomy (LIS). Among them, Chowcat and co-workers (9) reported a decrease in resting anal pressure of 50% maintained for 4-6 years. Although evidence was mounting for a new hypothesis of hypertonicity-driven ischemia, the link between manometry, ischemia, and healing had not been made. In 1994 seminal work by Schouten et al. (10) put the controversy at rest by combining anorectal manometry and laser Doppler flowmetry and examining chronic fissure patients before and after LIS. In their first report, they established that not only at the posterior midline blood supply was significantly lower than anywhere else in the anal canal, but that at the posterior midline, specifically,



the IAS resting pressure was inversely related to the blood flow. Subsequently, they reported on 27 patients with chronic anal fissure who had manometry and laser Doppler studies before and 6 weeks following LIS, then compared results to 27 controls. Consistent with other reports, maximum resting pressure was significantly higher in the fissure population than controls, and blood flow was proportionately decreased as well. In 24 of 27 patients who healed within 6 weeks, a 35% IAS resting pressure decrease was seen with a concurrent 65% increase in anodermal blood flow at the posterior midline.

The second report by Schouten et al. (11) in 1996 defined the 'ischemic' hypothesis of chronic anal fissure by correlating the preoperative IAS hypertonicity, relative anoderm ischemia, and fissure non-healing with postoperatively normal IAS resting pressure, increased anoderm perfusion, healed fissures by 6 weeks. This newfound understanding not only explained the benefit of LIS in permanently decreasing the resting tone of the

IAS, but also opened up a number of new avenues with which to medically treat chronic anal fissure. These new methods no longer aim at pain relief, but rather attempt to chemically manipulate the sphincter in order to decrease the hypertonic state. The IAS is controlled by three separate neurological impulses.

The first is the intrinsic myogenic tone, a poorly understood network under the control of calcium channel cell signaling.

The autonomic nervous system contributes sympathetic control which is generally considered to be the main stimulus for the tonic contraction of the sphincter, responsible for the main component of IAS resting pressure and inhibitory parasympathetic control responsible for relaxation. Lastly, the enteric nervous system controls a non-adrenergic, non-cholinergic system in which nitric oxide acts as a local vasodilator and is responsible for additional relaxation.

The nitrergic system appears to dominate over the cholinergic one with regard to relaxing the IAS (12).

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## Section II: Modern clinical management

Conservative treatment of acute fissures with warm sitz baths, high fiber diets with psyllium or other appropriate supplements, stool softeners, and use of either lubricating or locally anesthetic ointments as needed will heal up to 80%, albeit with significant recurrence rates.

Although the general goal of these measures is to break the cycle of hard stools, pain, and subsequently worsening constipation, sitz baths have actually been reported to decrease resting IAS pressure (13). A decrease in recurrence rate has been reported when a high fiber diet is continued indefinitely. The success of these basic measures is well established with acute fissures, and most patients will self-treat acute fissures without seeking medical care. However, patients are often seen for the first time with established chronic disease.

At this stage, many of the above mentioned treatments will be ineffective and clinical judgment is required to assess the appropriateness of initial conservative management versus more active treatments.

The choice for starting with more invasive treatment should depend on the severity of symptoms, the duration of the problem, and the completeness of response that the patient may have already had. Treatment of chronic fissures can be divided into two main categories, surgical and medical.

More than 50 years after the initial report by Eisenhammer, lateral internal sphincterotomy (LIS)

remains the gold standard. Although there are refinements and adjustments and the ongoing debate of open vs. closed technique, LIS is the procedure of choice for surgical management of chronic anal fissures. The medical treatment of fissures has tried to replicate surgery by inducing a 'chemical sphincterotomy'. Innumerable regimens, doses, medications, and delivery routes have been investigated and no one medical treatment has taken the lead in the medical fight against chronic fissures.

Prior to the 1950s, the need for definitive sphincterotomy was realized, yet while cutting the sphincter fibers seen at the base of the fissure would often heal the fissure, the high fecal soilage rates and incidence of keyhole deformities made this technique unpopular. In 1951 Eisenhammer (1) was the first to recommend division of the IAS in a lateral position away from the fissure. Originally recommending an 80-100% division of the IAS in 1951, Eisenhammer later revised his technique to a lesser division up to the dentate line (14). The closed technique was first described by Notaras (15) in 1971.

The open technique involves the open identification and division of the IAS through a small perianal incision, while the closed subcutaneous technique is performed through a stab incision in the intersphincteric groove which may be guided by the surgeon's finger.



In the largest case-controlled retrospective study of 549 patients by Garcia-Aguilar et al. (16), no significant difference was seen between the open and closed techniques. In our reported experience of 976 patients, 420 had unilateral LIS (292 open and 128 closed) (17).

We too found no significant differences between individual type of surgery and outcomes. In the largest prospective randomized series by Wiley et al. (18), 79 patients were randomized to an open or closed arm performed by a single surgeon.

Follow-up was blinded to the type of procedure performed; 96% of fissures healed, and 6.8% of patients had some incontinence at 1-year follow-up. There were no significant differences between the two techniques, with regard to pain, healing, recurrence, or incontinence. A recently updated meta-analysis of surgical techniques undertaken by Nelson (19) encompassed 3475 patients in 24 studies. Open and closed LIS were equally efficacious with regard to recurrence and associated morbidity, and there is no compelling evidence to suggest one technique over the other.

Over the last two decades, two major factors have pushed the development of non-surgical treatment options, namely the rising cost of OR time and the perceived risk of incontinence following LIS. The medical treatment of chronic anal fissures has consisted of multiple measures aimed at producing a chemical sphincterotomy. Nitric oxide donors, calcium channel blockers (CCB), and Botulinum toxin (Botox) remain the most well studied agents although recent reports using a number of other compounds have shown promising results as well.

Direct comparison between studies of different agents is difficult due to the unreliability and unpredictability of absorption rates and dosages when using topical and injectable agents. As mentioned above, IAS tone is regulated by a number of different mechanisms. The more thorough understanding of these complex interactions on sphincter tone as previously elucidated has allowed for a rational and structured approach toward the medical treatment of chronic anal fissures.

As mentioned previously, the major determinant of IAS tone are the nitric-oxide regulated enteric neurons located in Auerbach's and Meissner's plexus. Nitric oxide produces an inhibitory influence on sphincter tone producing relaxation. The ability

of topical nitric oxide donors to reduce chronic hypertonicity has been thoroughly investigated. The local administration of nitric oxide donors usually in the form of nitroglycerin (GTN) paste has been extensively studied against placebo, LIS, and Botox. In a recent Cochrane meta-analysis (20), nine prospective randomized trials of GTN vs. placebo were examined which showed a not significant decrease in non-healing (OR 0.73, 95% CI 0.56-1.08). Randomized multicenter trials from Canada (21) and England (22) comparing GTN to LIS showed highly significant increases in healing rates 90% and 100% versus 30% and 54%, respectively, with no incidences of fecal or fatal incontinence. GTN has an undeniable safety profile with respect to incontinence, but the incidence of dose-limiting headaches as high as 72% (23) and the general lack of efficacy in long-standing disease limits its usefulness to acute fissures and/or early chronic fissures as first line therapy in patients not wishing to proceed directly to surgery.

Additional debate persists in the literature regarding the ideal dosing, strength, and frequency of use for GTN. As a whole, CCBs appear to be as good as, if not superior to, GTN with regard to healing rate and recurrences, and definitely have a better safety profile. Additionally, CCBs may be equivalent to LIS with regard to initial healing, but larger studies and longer follow-up periods are needed.

CCBs and topical nifedipine, in particular, seems ideally poised to replace GTNs as a first-line medical treatment for patients who do not wish to proceed immediately with surgery.

Known for its potent inhibitory effect on cholinergic neurons, Botox should actually potentiate IAS contraction and cause anything but smooth muscle relaxation. Yet multiple studies have revealed that Botox does indeed reduce IAS mean resting pressures. Although the exact mechanism is incompletely understood, an elegant study of porcine sphincter muscle by Lindsay et al. (2) has shed some light on the subject. They have suggested that Botox may actually directly inhibit the release of neurotransmitters from adrenergic nerves.

These intrinsic nerves are responsible for the baseline contractile response and mean resting pressure. This is as opposed to the effect of GTN and CCBs on the nitric oxide mediated relaxation response.

## Conclusion

As the pathophysiology of chronic anal fissure has been better characterized, the search for the best chemical sphincterotomy has produced a number of treatments with varying degrees of success. The surgical treatment, however, remains the gold standard with the most important decision of either open or closed being a personal one with little or no effect on outcomes. The choice of first line treatment is based upon a number of factors; there is no single option suitable for every patient or every instance. Robert T. Madoff (24) summarized it best in a recent commentary, "For patients who have tolerable pain...risk-averse...to any change in

continence, a trial of pharmacologic therapy using either a topical...or Botox injection is a logical first choice. For patients with impaired continence, chronic diarrhea, or known sphincter injuries, LIS is generally contraindicated and all reasonable alternative therapy should be used. If surgery is required, an anal advancement flap is...preferred. For patients with severe, unrelenting pain, or for those willing to accept a small risk of significant incontinence for the fastest available pain relief, highest likelihood of healing and lowest rate of recurrence, LIS can and should be offered in the first instance."

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