12
Benign Anorectal: Anal Fissure

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Epidemiology

An anal fissure, or fissure-in-ano, is an oval, ulcer-like, longitudinal tear in the anal canal, distal to the dentate line. Although the exact incidence is unknown, it is a common disorder, with equal gender distribution. Fissures can occur at any age, but are usually seen in younger and middle-aged adults. In almost 90% of cases, fissures are identified in the posterior midline, but can be seen in the anterior midline in up to 25% of affected women and 8% of affected men. An additional 3% of patients have both anterior and posterior fissures. Fissures occurring in lateral positions should raise suspicions for other disease processes, such as Crohn's disease, tuberculosis, syphilis, human immunodeficiency virus (HIV)/ acquired immunodeficiency syndrome (AIDS), or anal carcinoma (Figure 12-1).

Early, or acute, fissures have the appearance of a simple tear in the anoderm, whereas chronic fissures, defined by symptoms lasting more than 8–12 weeks, are further characterized by edema and fibrosis. Typical inflammatory manifestations of chronic fissures include a sentinel pile, or skin tag, at the distal fissure margin and a hypertrophied anal papilla proximal to the fissure in the anal canal. In addition, fibers of the internal anal sphincter (IAS) are often visible at the fissure base.

Etiology

The cause of anal fissure has been long debated. Trauma to the anal canal secondary to the passage of a hard stool is believed to be a common initiating factor. A history of constipation is not universally obtained, however, and some patients report an episode of diarrhea before the onset of symptoms.

The persistence of a fissure after any initiating event is associated with increased resting anal pressure—an observation first reported in the mid-1970s.[1,2] Physiologic studies using ambulatory manometry have confirmed the presence of sustained resting hypertonia in fissure patients.[3] Further observations have delineated an inverse relationship between anal canal pressure and perfusion of the anoderm. Ischemia was initially proposed as an instigator of fissure persistence by Gibbons and Read[4] in 1986. Later support was provided by angiographic studies of the inferior rectal artery in cadavers, which demonstrated a paucity of blood vessels in the posterior midline of the anal canal in 85% of those examined.[5] Schouten et al.[6] measured anodermal blood flow in healthy individuals using Doppler laser flowmetry, and found that the posterior midline had the lowest perfusion when compared with the other three quadrants. In addition, there was a significant inverse correlation between posterior midline anodermal blood flow and maximum resting anal pressure in a large cohort of patients that included normal controls and fissure patients. Those with fissures demonstrated the highest resting anal pressures and the lowest posterior blood flow of any group. Improvement in posterior midline blood flow was noted to occur after reduction of anal pressure with anesthesia. These same authors were able to demonstrate normalization of sphincter hypertonia and anodermal blood flow after lateral internal sphincterotomy (LIS) in anal fissure patients.

Symptoms

The clinical hallmark of an anal fissure is pain during, and particularly after, defecation. In acute fissures, pain may be short-lived, but it can last several hours or even all day in the presence of a chronic fissure. The pain is frequently described as passing razor blades or glass shards. Understandably, patients with anal fissures may often fear bowel movements. Rectal bleeding, although not uncommon, is usually limited to minimal bright red blood seen on the toilet tissue.

Diagnosis

Diagnosis is suggested by patient history and confirmed by physical examination. Most fissures are readily visible by simply spreading the buttocks with opposing traction of the

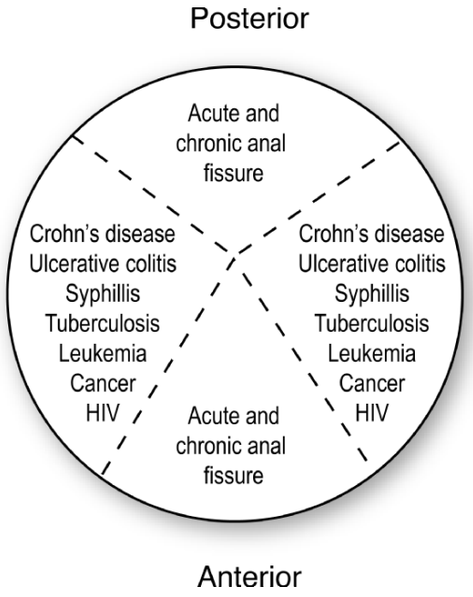

FIGURE 12-1. The location of anal fissure suggests their cause.

thumbs (Figure 12-2). Once the presence of a fissure is verified, further attempt to examine the anal canal with insertion of a finger or endoscopic instrumentation (anoscopy or proctoscopy) is not appropriate. Most patients are far too tender to justify such invasive evaluation, which should be delayed or deferred until symptoms have resolved.

Fissures may be frequently misdiagnosed as hemorrhoids by primary care providers. The differential diagnosis includes perianal abscess, anal fistula, inflammatory bowel disease, sexually transmitted disease, tuberculosis, leukemia, and anal carcinoma. Atypical fissures, such as those occurring off the midline, multiple, painless, and nonhealing fissures, warrant further evaluation, via examination under anesthesia and possible biopsy and cultures.

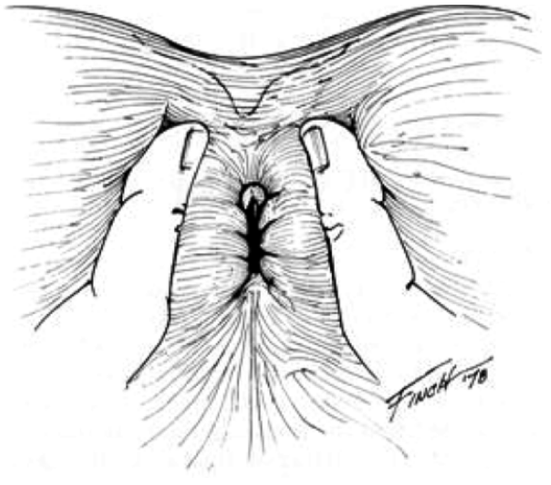

FIGURE 12-2. Examination revealing an anal fissure.

Management

Conservative

Almost half of all patients diagnosed with an acute fissure will heal with conservative measures, i.e., sitz baths and psyllium fiber supplementation, with or without the addition of topical anesthetics or anti-inflammatory ointments. In a retrospective review, Shub et al.[7] were able to demonstrate healing in 44% of fissure patients using psyllium fiber, sitz baths, and emollient suppositories. During a 5-year follow-up period, there were treatment failures in 27% of patients initially reported as healed. A second retrospective review almost 20 years later demonstrated similar findings. Hananel and Gordon[8] reported initial healing in 44% and recurrence in 18.6% of their fissure patients. Therapy consisted of bulking agents and sitz baths.

Jensen[9] has conducted two randomized, controlled trials examining the effects of unprocessed bran in both initial treatment and maintenance therapy of acute fissures. In the first, 103 patients with acute posterior anal fissures were randomized to receive lignocaine ointment (33), hydrocortisone ointment (35), or sitz baths and unprocessed bran (35) for 3 weeks, with symptomatic relief and fissure healing as endpoints. After weeks 1 and 2, patients treated with sitz baths and bran were found to have significant improvement in symptomatic relief as compared with the other two groups. By the 3-week endpoint, there was no symptomatic difference between the three groups; however, healed fissures occurred most frequently in the bran/sitz bath group (87%), when compared with patients receiving hydrocortisone (82.4%) or lignocaine (60%). In a double-blind, placebo-controlled trial, fissure recurrence was measured after 1 year in three groups. Significantly fewer recurrences (16%) were seen in patients receiving 15 g of unprocessed bran daily, when compared with 60% of patients receiving 7.5 g daily or 68% of patients on placebo.[10]

Operative Treatment

The primary goal in the treatment of a nonhealing anal fissure is to decrease abnormally elevated resting anal tone. Operative procedures, such as manual anal dilatation or internal sphincterotomy, have been advocated as initial modes of treatment because they produce permanent reductions in maximum resting anal pressures.

Anal Dilatation

Manual dilatation of the anus for anal fissure was first reported in 1964.[11] Ensuing endorsements have described a variety of means to enlarge the anal canal, such as the "four-finger method" and an assortment of instrumentation,

including rectal dilators and retractors. Inconsistencies with regard to technique, specifically extent and duration of sphincter stretch, have cast some doubt about true success rates of this procedure. Reports as recent as 1995, however, support the use of gentle anal dilatation as a "first management choice in the treatment of anal fissure."[12–15] In 1992, Sohn et al.[16] standardized the extent of anal dilatation using either a Parks' retractor opened to 4.8 cm or a pneumatic balloon inflated to 40 mm. These authors reported up to 93%–94% healing of anal fissures after these procedures, which were associated with relatively few complications.

Long-term outcomes of anal dilatation are sparse. Additional widespread criticism of the technique stems from reported complications of incontinence, secondary to diffuse sphincter damage. In a retrospective analysis by MacDonald et al.,[14] patient outcomes after manual anal dilatation were reviewed. Not only was dilatation unsuccessful in 56% of patients diagnosed with fissures, incontinence occurred in 27% of patients overall. Speakman et al.[17] performed endoanal ultrasound and anorectal physiology studies on 12 men with fecal incontinence after anal dilatation. Internal and external anal sphincter defects were identified in 11 and 3 patients, respectively. Sphincter defects after anal dilatation were also recognized by Nielsen et al.,[18] who reported minor incontinence in 12.5% of patients overall. Ultrasound was ultimately performed in 20 patients, 13 of whom had IAS defects. Deficits were identified in 61% (11/18) of the continent and 100% (2/2) of the incontinent patients.

One retrospective review comparing treatment outcomes of anal dilatation and lateral subcutaneous sphincterotomy was reported by Collopy and Ryan.[19] Questionnaires were sent to 160 patients who underwent either of the two procedures. Fissure recurrence and incontinence were reported less often in the sphincterotomy group. Early prospective, randomized trials did not support these findings.[20–22] In one study, recurrence and incontinence rates were equal between both groups[20]; in another, significantly worse after lateral sphincterotomy.[21] Four months after randomization in the trial by Marby et al., symptomatic improvement was reported in 93% after dilatation versus 78% after sphincterotomy ($P < .05$). During the same time period, recurrence rates were 10% after dilatation and 29% after sphincterotomy ($P < .02$). Later randomized trials demonstrated better functional results, in terms of incontinence, after lateral sphincterotomy.[23] Whereas recurrence rates were 3.5%–10% up to 1 year after lateral sphincterotomy, higher rates of 26%–30% were observed after anal dilatation.[22,24]

Lateral Internal Sphincterotomy

The use of internal sphincterotomy in the treatment of anal fissure was introduced by Eisenhammer[25] in the early 1950s. His initial approach through the bed of the fissure in the posterior midline often resulted in a scarred groove, or "keyhole deformity," as often referred today. The functional impairment that ensued resulted in incontinence to gas and/or stool for many patients. Lateral subcutaneous sphincterotomy was popularized by Notaras[26] in 1969, and was believed to be associated with less functional impairment. In a retrospective review of 300 patients, comparing LIS to fissurectomy and midline sphincterotomy, Abcarian[27] reported a low recurrence rate of 1.3% and no incontinence after LIS—his procedure of choice for uncomplicated anal fissures. Several retrospective studies support the use of LIS as the preferred operative method for the treatment of anal fissures.[28–30] Exceptional healing and low recurrence rates have invariably been reported, and LIS has emerged as the "gold standard" for the treatment of anal fissure[31] (Table 12-1).

Persistent incontinence to gas and stool has emerged as a major concern after sphincterotomy. Incontinence rates of up to 36% have been reported, but these vary widely among studies.[32–36] Much of this variation can be attributed to differences in definition and assiduousness of follow-up. Reasons for incontinence after LIS have been related to the type and extent of sphincter muscle divided. Sultan et al.[37] prospectively performed endoanal ultrasonography before and 2 months after sphincterotomy in 15 patients. IAS defects were identified in 14 patients. In 90% of the women examined, the defect comprised the full length of the sphincter. Incontinence to flatus was reported in 3 of 10 women, in whom *external* sphincter defects were found in 2. The authors concluded that the complete sphincter deficits observed in women were the consequences of lack of appreciation for shorter anal canals in this population and suggested that postsphincterotomy incontinence may be further lessened if external anal sphincter deficits are recognized preoperatively.

Littlejohn and Newstead[38] reported a retrospective review of 287 patients who underwent tailored sphincterotomy, i.e., division of the IAS for the length of the fissure, rather than to the dentate line. There were no reports of incontinence to liquid or solid stool. The incidence of urgency was 0.7%; gas incontinence, 1.4%; and minor staining, 35%. Pescatori et al.[39] reported the results of a prospective, randomized study of tailored LIS on the basis of preoperative manometry. When increased resting anal tone was not demonstrated preoperatively, fissurectomy with anoplasty was performed. For elevated anal pressures (70–90 mm Hg), the extent of sphincterotomy was 0.5–1.5 cm and up to 2.5 cm for higher pressures. Continence worsened in only 11% of patients, and recurrences were limited to 4% of patients after sphincterotomy.

Inadvertent division of the external sphincter during sphincterotomy affects overall healing rates as well. In a study by Farouk et al.,[40] ultrasound evaluations performed in patients with persistent fissures after sphincterotomy demonstrated a lack of internal sphincter defects in almost 70% of patients. External sphincter defects were identified, however.

Other technical variations that have influenced patient outcomes after LIS have been described (Figures 12-3 and 12-4).

TABLE 12-1. Results of LIS

Year	Author	n	Success (%)	Recurrence (%)	Incontinence (%)*	Follow-up (type)	Follow-up (mo)
1980	Abcarian[27]	150	100	1.3	0	C	NS
1981	Keighley et al.[107]	71	100	25	2	I, E	12
1982	Ravikumar et al.[108]	60	97	0	5	C	24
1984	Hsu and MacKeigan[28]	89	100	5.6	0	C	NS
1984	Jensen et al.[24]	30	100	3	0	Q, E	18
1985	Walker et al.[43]	306	100	0	15	I	52
1987	Gingold[109]	86	100	3.5	0	C	24
1987	Weaver et al.[20]	39	93	5.1	2.5	I, E	17
1988	Lewis et al.[41]	350	94	6	6	I	37
1988	Zinkin[110]	151	94.7	NS	NS	None	0
1989	Khubchandani and Reed[33]	717	97.7	NS	35.1	Q	52.9
1992	Kortbeek et al.[42]	112	95.5	NS	NS	I	1.5
1994	Pernikoff et al.[34]	500	99	2	16	Q	78
1994	Romano et al.[35]	44	100	0	9	E	8
1995	Leong and Seow-Choen[46]	20	100	NS	0	I, E	6.5
1995	Prohm and Bonner[111]	177	96	3.3	1.6	E	1.5
1995	Usatoff and Polglase[29]	98	90	20	18	Q	41
1996	Garcia-Aguilar et al.[32]	864	96	11	37.8	Q	63.5
1997	Hananel and Gordon[30]	312	98.6	1.4†	—	C	NS
1997	Littlejohn and Newstead[38]	352	99.7	1.4	1.4	C	9
1999	Nyam and Pemberton[36]	585	96	8	15	Q	72
2004	Wiley et al.[112]	76	96	NS	6.8	Q	12
2004	Parellada[113]	27	100	NS	15	E	2.5

C, chart review; E, examination; I, interview; Q, questionnaire; NS, not stated.
*Includes seepage and incontinence to flatus and stool.
†Recurrence and persistence combined.

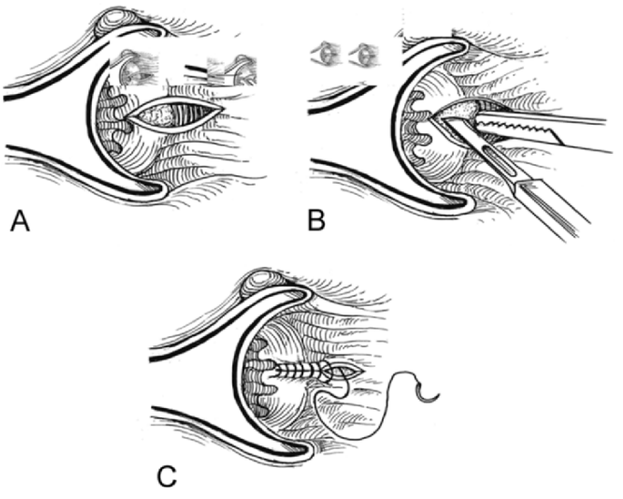

FIGURE 12-3. Open lateral internal anal sphincterotomy. **A** Radial skin incision distal to the dentate line exposing the intersphincteric groove. **B** Elevation and division of the internal sphincter. **C** Primary wound closure.

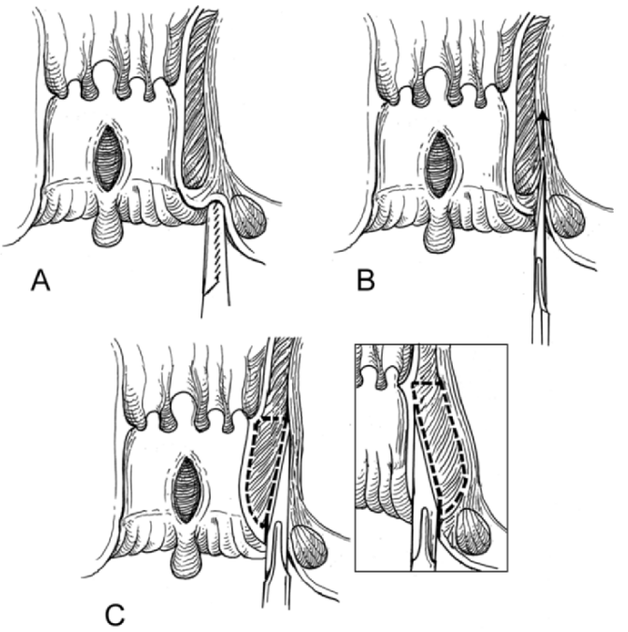

FIGURE 12-4. Closed lateral internal anal sphincterotomy. **A** Location of the intersphincteric groove. **B** Insertion of knife blade in the intersphincteric plane in performing a "blind" lateral subcutaneous internal anal sphincterotomy. **C** Lateral to medial division of the IAS (insert: medial to lateral division of the muscle).

With regard to open or closed sphincterotomy, several retrospective analyses[41] and at least one randomized trial[42] report similar rates of initial healing and fissure recurrence. In these studies, incontinence to flatus or stool occurred in 15%–17% of patients overall. Although there was no significant difference in *acute* complications in another randomized study, long-term persistent complications were more frequent in the open (55%) than the closed (20%) sphincterotomy group in retrospective review.[43] In a separate study, in which the degree of continence after open versus closed sphincterotomy was assessed by questionnaire, closed internal sphincterotomy was again favored. A significant difference was reported with regard to postoperative incontinence to gas (27.6% versus 30.6%), stool (3.1% versus 11.3%), and seepage (16.1% versus 26.7%).[32]

Excision of hypertrophied anal papillae and fibrous anal polyps has been advocated by Gupta and Kalaskar.[44] In a randomized trial, patient satisfaction was rated as excellent or good after removal of these structures in 84% of patients, compared with 58% of patients whose polyps and papillae were left intact. In a separate prospective study, earlier wound healing rates were achieved with primary closure after LIS, as compared with healing by secondary intention.[45]

Advancement Flaps

One prospective trial of the use of advancement flaps for chronic anal fissures has been conducted to date.[46] When patients were randomized to receive LIS or advancement flap, there was no significant difference between healing rates (100% in the sphincterotomy group versus 85% in the flap group, $P = .12$). Incontinence was not observed in either group.

Medical Management

Sphincter Relaxants

Increasing concerns with long-term complications associated with the operative management of anal fissures has led to the development of "chemical sphincterotomy," aimed at reducing mean maximum resting anal pressures, without permanent sphincter injury. Preparations have included: 1) various nitrate formulations, including nitroglycerin (NTG) ointment, glyceryl trinitrate (GTN), and isosorbide dinitrate (ISDN); 2) oral and topical calcium channel blockers, including nifedipine and diltiazem (DTZ); 3) adrenergic antagonists; 4) topical muscarinic agonists, i.e., bethanechol; 5) phosphodiesterase inhibitors; and 6) botulinum toxin (BT). However, there is increasing controversy in this area. Whereas one recent review concluded "first-line use of medical therapy cures most chronic fissures cheaply and conveniently,"[47] a systematic review of the literature published at the same time concluded "medical therapy for chronic anal fissure . . . may be applied with a chance of cure that is only marginally better than placebo . . . [and] far less effective than surgery."[48]

Topical Nitrates

The IAS is a smooth muscle whose tone is affected by both intrinsic myogenic properties and extrinsic neural influences. Nitric oxide is the predominant nonadrenergic, noncholinergic neurotransmitter in the IAS. Release of nitric oxide results in IAS relaxation. Exogenous nitrates release nitric oxide in vivo and have been used as nitric oxide donors.

Studies by Loder et al.[49] and Guillemot et al.[50] demonstrated decreased resting anal pressure with 0.2% GTN. This led to a series of retrospective and prospective reports, as well as randomized trials, supporting the use of various nitrate preparations in the treatment of anal fissures (Table 12-2). An early clinical trial in 1997 by Bacher et al.[51] randomized 35 patients with acute and chronic anal fissures to receive either 0.2% NTG ointment or 2% lidocaine gel for 4 weeks. After 1 month, the healing rate was 80% for patients receiving NTG (11 of 12 acute and 5 of 8 chronic fissures), which was significantly higher than the 40% healing rate reported for patients receiving topical lidocaine (5 of 10 acute and 1 of 5 chronic fissures). Manometry was performed on the 28th day of treatment. Overall maximum resting anal pressures were found to decrease from a mean of 110 to 87 cm H_2O, although this difference was not observed for patients with chronic fissures or patients receiving lidocaine ointment. The authors postulated that the persistence and recurrence of chronic anal fissures was secondary to lack of sphincter tone reduction.

Subsequent randomized, placebo-controlled trials have attempted to determine whether higher doses of NTG ointment promote healing and lessen recurrence in chronic anal fissures. Carapeti et al.[52] found no difference in chronic fissure healing between patients randomized to receive an 8-week treatment of either 0.2% GTN 3 times daily or 0.2% GTN titrated in 0.1% increments (to maximum of 0.6%). Higher dosing did not result in accelerated healing. Patients treated actively with either GTN preparation demonstrated 67% healing rate, compared with 32% in those receiving placebo. Bailey et al.[53] and Scholefield et al.[54] reported similar findings when patients with chronic anal fissures were randomized to receive placebo, 0.1%, 0.2%, or 0.4% GTN ointment 2–3 times daily. In the study by Bailey et al., there were no significant differences in fissure healing among treatment groups. In fact, healing rates were approximately 50% for all groups, including placebo.[53] Scholefield et al. also demonstrated similar healing rates among all groups (37.5% for placebo, 46.9% for 0.1% GTN, 40.4% for 0.2% GTN, and 54.1% for 0.4% GTN) with no significant improvement over the placebo response.[54]

Additional randomized, placebo-controlled trials have demonstrated comparable healing rates of 46%–70% in patients with chronic anal fissures after application of 0.2% GTN ointment 2–3 times daily for 4–8 weeks. Supportive data have included statistically significant decreases in pain scores and maximal anal resting pressures in patients treated with GTN as compared with placebo. In a study by Altomare et al.,[55] 132 patients with chronic fissures were randomized to receive

TABLE 12-2. Randomized trials of NTG therapy

Year	Author	n	Treatment	Follow-up	Success (%)
1997	Lund et al.[114]	80	0.2% GTN bid	8 wk	68
			placebo		39
1997	Oettle[56]	24	0.2% GTN tid	4 wk	83.3
			LIS		100
1997	Bacher et al.[51]	35	0.2% GTN 2% lidocaine	4 wk	80
					40
1999	Kennedy et al.[115]	43	0.2% GTN	4 wk	46
			placebo		16
1999	Carapeti et al.[52]	70	0.2% GTN tid		
			0.2% GTN tid (titrated to 0.6%)	8 wk	67
			placebo		32
2000	Altomare et al.[55]	132	0.2% GTN bid	4 wk	49.2
			placebo		51.7
2000	Zuberi et al.[60]	42	0.2% GTN	8 wk	66.7
			10mg NTG patch		63.2
			LIS		91.7
2000	Richard et al.[58]	82	0.2% GTN	6 mo	27.2
			LIS		92.1
2001	Evans et al.[57]	65	0.2% GTN tid	8 wk	60.6
			LIS		97
2001	Chaudhuri et al.[116]	19	0.2% GTN bid	6 wk	70
			placebo		22.2
2002	Libertiny et al.[59]	70	0.2% GTN	2 y	45.7
			LIS		97.1
2002	Bailey et al.[53]	304	0.1%, 0.2%, and 0.4% GTN bid/tid placebo	8 wk	50% across board
2003	Scholefield et al.[54]	200	0.1%, 0.2%, and 0.4% GTN bid/tid placebo	8 wk	46.9, 40.4, 54.1, 37.5

GTN, glyceryl trinitrate; NTG, nitroglycerin; LIS, lateral internal sphincterotomy; bid, twice daily; tid, three times daily.

0.2% GTN or placebo bid for 4 weeks. These authors confirmed the effects of GTN on anodermal blood flow and sphincter pressure, but unlike similarly designed trials, they demonstrated no significant difference in healing rates between GTN and placebo (49.2% versus 51.7%). They concluded that the use of GTN as a substitute for surgery should be discouraged.

Several simultaneous randomized trials whose treatment arms consisted of 0.2% GTN and LIS support the findings of Altomare et al. Although initial healing rates during 4- to 8-week evaluation periods were similar to those in placebo-based trials (and up to 83.3% in a study by Oettle[56]), healing rates were far superior for LIS (91.7%–100%). Evans et al.[57] demonstrated healing in 20 (60.6%) of 33 patients treated with GTN, in comparison to 26 (97%) of 27 patients treated with sphincterotomy. Of the patients initially treated with GTN, 12 eventually underwent sphincterotomy for persistent fissures. Of the 20 patients whose fissures healed with GTN treatment, nine developed recurrences. The authors acknowledge that GTN will heal the majority of fissures, but concluded "a significant minority have little improvement and require conventional surgical treatment."[57] Richard et al.[58] also found LIS "superior to topical NTG . . . in the treatment of chronic anal fissure, with a high rate of healing, few side effects, and low risk of early incontinence." After 6-week follow-up in a multicenter, randomized, controlled trial, 89.5% of patients in the LIS group compared with 29.5% in the NTG group had complete healing of fissures. At 6 months, fissure healing had occurred in 92.1% versus 27.2% in the LIS and NTG groups, respectively. Side effects were observed more frequently in patients treated with NTG (28.9%), compared with LIS (84%).

Although findings were similar in other randomized, controlled trials, conclusions still favor the use of GTN. Libertiny et al.[59] randomized 70 patients with chronic anal fissure to receive 0.2% GTN or LIS. Only 16 of 35 patients initially treated with GTN healed without recurrence during 24-month follow-up, in contrast to operative cure in 34 of 35 patients treated with LIS. The authors concluded that chemical sphincterotomy with GTN should be the initial treatment in patients with chronic anal fissure, and despite its effectiveness, LIS should be reserved for treatment failures. Zuberi et al.[60] similarly concluded that GTN ointment and NTG patch were effective treatment options in patients with anal fissures. In their study of 42 patients, healing rates were 66.7% in patients receiving 0.2% GTN, 63.2% for those receiving a 10-mg NTG patch applied at a distance from the fissure, and 91.7% in patients who underwent LIS. Their findings support the use of GTN as a first line agent in chronic anal fissures, as the difference in healing rates was not statistically significant between groups.

Other nitrate preparations have been used in the treatment of anal fissures. A prospective, uncontrolled study by Schouten et al.[61] demonstrated reduction in anal pressure and improvement in anodermal blood flow in patients with chronic anal fissure treated with ISDN. The authors demonstrated an 88% fissure healing rate after 12 weeks. Two randomized, placebo-controlled trials confirmed these findings. Werre et al.[62] were able to achieve healing in 17 of 20 patients (85%) with chronic anal fissure treated with ISDN for 5 weeks, as compared with 6 of 17 patients (35.3%) who received placebo. Tankova et al.[63] subsequently reported fissure healing in 80% of patients actively treated with mononitrate for 3 weeks, compared with 22% of the control group. In a dose finding study, Lysy et al.[64] found that 2.5 mg of topically applied ISDN 3 times daily resulted in a greater reduction in maximum anal resting pressure than 1.25 mg. By 1 month, 34 patients (83%) were able to achieve complete healing of their fissures. During the mean follow-up period of 11 months, six healed patients had fissure recurrence, which responded to additional treatment with ISDN.

Endogenous nitric oxide donors, such as L-arginine, have also been shown to be effective in relaxation of the anal sphincter. Preliminary in vivo studies in rats have demonstrated a decline in sphincter pressure with administration of 10 mg L-arginine rectally. This effect was reversed with the use of L-arginine antagonists. In a placebo-controlled trial, 46% reduction in resting anal pressure was observed 5 minutes after topical application of L-arginine, and maintained for 2 hours. The decrease in pressure observed in the placebo group was not significant.[65]

Despite these encouraging results regarding initial healing rates with topical nitrates, concerns about long-term outcomes and adverse reactions have limited their use. In studies summarizing long-term follow-up, recurrence rates up to 35% have been documented. For example, in a retrospective study by Dorfman et al.,[66] of 31 patients treated with 0.2% GTN bid, only 67% were compliant with treatment. Although there was an overall healing rate of 56%, recurrence occurred in 27% of patients initially healed. More than 75% of patients had side effects, including headache in 63% and lightheadedness in 52% of patients. In a nonrandomized, prospective trial, Graziano et al.[67] demonstrated a 67% recurrence rate for chronic fissures during a 9-month follow-up period. Patients were treated with a 2-week course of 0.25% NTG, which produced headache in 77% of patients actively treated.

Side effects have invariably been reported in randomized, controlled trials as well. Mild headaches were described by Bacher et al.[51] in 20% of patients receiving 0.2% GTN. Altomare et al.[55] reported that 34% of chronic fissure patients treated with GTN had headaches and nearly 6% of patients had orthostatic hypotension. Carapeti et al. reported headaches in 72% of patients receiving GTN versus 27% of controls receiving placebo.[52] In the L-arginine study, no side effects were noted during the study period.[65]

Calcium Channel Blockers

The effect of nifedipine on the anal sphincter was first evaluated by Chrysos et al.[68] in a prospective, controlled trial in 1996. Anorectal manometry was performed on 10 patients with hemorrhoids and/or anal fissure and 10 controls before and 30 minutes after receiving 20 mg of sublingual nifedipine. Anal resting pressure was reduced by almost 30% in both groups. This study set the stage for further prospective, clinical trials examining the efficacy of nifedipine and other calcium channel blockers in treating anal fissures. Carapeti et al.[69] investigated the use of topical DTZ in the treatment of anal fissure, after a prior randomized trial demonstrated that the majority of fissure patients treated with GTN developed headaches. After application of 2% DTZ gel 3 times daily in 10 patients, 67% obtained healed fissures after 8 weeks of treatment. No headaches or side effects were reported.

Further prospective trials substantiated these findings. Knight et al.[70] also evaluated the effects of 2% DTZ gel in 71 patients and were able to achieve healing in 75%, after 9 weeks of treatment. An additional 8 weeks of treatment was administered to incompletely healed fissures in 17 patients, 8 of whom healed. Side effects were reported in five patients overall: four with perianal dermatitis and one with headache. Agaoglu et al.[71] demonstrated 60% healing in patients treated with 20 mg of oral nifedipine twice daily. Headache was reported in only one patient. Ansaloni et al.[72] reported even more encouraging results regarding efficacy of 6 mg of oral lacidipine and warm sitz baths. At 2 months' follow-up, 90.4% of patients treated healed without evidence of fissure recurrence; however, 33% of patients had side effects.

Randomized, controlled trials comparing topical nifedipine gel with a combination of topical lidocaine and hydrocortisone gels have also demonstrated superiority of nifedipine in the treatment of anal fissures. Antropoli et al.[73] randomized 283 patients to either receive 0.2% nifedipine gel every 12 hours or 1% lidocaine/1% hydrocortisone gels. Complete healing occurred in 95% of patients receiving nifedipine, as compared with 50% of controls. Perrotti et al.[74] similarly randomized 110 patients with anal fissure to receive 0.3% nifedipine gel with 1.5% lidocaine or 1.5% lidocaine with 1% hydrocortisone twice daily. Of the 52 patients treated with nifedipine, 94.5% healed completely versus 16.4% of controls. During 1-year follow-up, three of the 52 patients healed with nifedipine had recurrent fissures; two healed after additional treatment. No side effects were observed in either study.

Jonas et al.[75] performed a randomized, controlled trial to ascertain whether different routes of administration had similar healing rates. The authors randomized 50 patients to receive 60 mg of oral DTZ or 2% topical DTZ gel twice daily. Complete healing occurred in 38% of patients taking oral treatment versus 65% of patients using topical therapy. Side effects were reported in 33% of patients treated orally.

Although long-term follow-up studies are lacking, several randomized, controlled trials comparing calcium channel

blockers and nitrates have been performed. Kocher et al.[76] randomized 61 patients with chronic anal fissures to receive 0.2% GTN or 2% DTZ. After 6–8 weeks of treatment, 21 of 29 patients in the GTN group and 13 of 31 in the DTZ group experienced side effects. Therapeutic efficacy was similar between both groups. In the GTN group, 25 of 29 patients (86.2%) were healed or improved, compared with 24 of 31 patients (77.4%) in the DTZ group ($P = .21$). Bielecki et al.[77] also found equal healing rates between topical 0.2% GTN and 2% DTZ, as well as fewer headaches with 2% DTZ (0% versus 33% with 0.2% GTN). In a prospective, double-blind trial by Ezri and Susmallian,[78] 52 patients were randomized to receive topical GTN or nifedipine. The healing rate was higher ($P < .04$) with nifedipine (89%) as compared with GTN (58%). Side effects occurred more frequently ($P < .01$) with GTN (40%) than nifedipine (5%), a finding that was similar to the other trials. Recurrences within a 6-month period were common in both groups: 31% for GTN and 42% for nifedipine. Based on these study results, topical calcium channel blockers appear to be as effective as topical nitrates, with fewer side effects. Initial data suggest that long-term recurrences may be similar between both treatment groups, but further studies are warranted. Currently, topical calcium channel blocker preparations are not commercially available in the United States.

Adrenergic Antagonists

The effect of alpha-1 adrenergic blockade on anal sphincter pressure has been studied in two prospective trials. Pitt et al.[79,80] administered 20 mg of indoramin, an alpha-1 blocker, to seven patients with chronic anal fissure and six healthy controls. Reduction in anal pressure was observed in both groups: 35.8% in patients with fissure and 39.9% in those without. In a placebo-controlled trial, 23 patients with chronic anal fissure were randomized to receive 20 mg of indoramin or placebo twice daily.[79] Although a 29.8% reduction in maximum anal resting pressure was observed 1 hour after active treatment, healing occurred in only 1 patient (7%), despite 6 weeks of therapy. That patient developed a recurrence within 3 months. In the placebo group, 22% of patients achieved healing, although no significant change in anal pressure was observed. The trial was not completed because of lack of efficacy.

Cholinergic Agonists

Carapeti et al.[81] documented reduced anal sphincter pressure using bethanechol in a dose-finding study. Using increasing concentrations of bethanechol gel in healthy volunteers, they demonstrated a 24% reduction in maximal anal resting pressure using 0.1% dose. In a subsequent study, they reported fissure healing in 9 of 15 patients treated with 0.1% bethanechol gel 3 times daily for 8 weeks.[69] Maximum resting sphincter pressure was significantly lower after treatment ($P = .02$) compared with pretreatment values. No side effects were reported.

Phosphodiesterase Inhibitors

Early work by Jones et al.[82] has demonstrated an in vitro effect of increasing concentrations of various phosphodiesterase inhibitors on internal sphincter tone. This may spark future clinical trials in the treatment of anal fissure.

Botulinum Toxin

Botulinum Toxin (BT) is an exotoxin produced by the bacterium *Clostridium botulinum*. When injected locally, BT binds to the presynaptic nerve terminal at the neuromuscular junction, thereby preventing release of acetylcholine and resulting in temporary paralysis of skeletal muscle. Its mechanism of action on smooth muscle, such as the internal sphincter, has been evaluated in recent animal studies. In a series of experiments, Jones et al.[83] injected BT into porcine anal sphincters, which responded with decreased mean anal resting pressure in subsequent manometric studies. Strips of sphincter muscle were then isolated and examined in vitro. Application of electrical field stimulation and nicotinic agonists resulted in increased myogenic tone, which was blocked by guanethidine and attenuated by BT injection. These findings suggested that the predominant effect of BT on the IAS is sympathetic blockade.

BT injections can be given easily, on an outpatient basis, and are well tolerated. The commercial availability of BT has prompted several prospective trials examining its efficacy in the treatment of anal fissure (Table 12-3). An early placebo-controlled trial randomized 30 patients to receive either two injections of 20 U BT-A or saline.[84] After 2 months, complete healing occurred in 11 of 15 patients (73.3%) receiving BT and 2 of 15 patients (13.3%) receiving placebo. Subsequent BT injections were offered and given to 10 patients in the control group; there were seven healed fissures. Repeat BT injections (25 U) were given to four treatment failures, all of which healed after 2 months. No recurrences were observed during 16 months' follow-up. In a randomized trial comparing BT and lidocaine pomade in the treatment of anal fissure, Colak et al.[85] demonstrated superiority ($P = .006$) of BT in 62 patients, with complete epithelialization in 70.58% of patients in the BT group versus 21.42% in the lidocaine group.

The dose of BT injected is critical to successful healing in anal fissures. Siproudhis et al.[86] reported that a single 20-U injection of BT was not superior to that of placebo in a randomized, double-blind trial of 44 patients with chronic anal fissure. In a dose-finding study, Brisinda et al.[87] randomized 150 patients to two treatment arms. Initial treatment with 20 U of BT, followed by 30 U of BT for fissure persistence, was given to the first group, and 30 U of BT, followed by 50 U of BT, was given to the second group. One month after BT injections, there were no significant differences in resting anal pressures between the two groups; however, complete healing was more frequent in the second group (87%) than the first (73%). Fissures remained unhealed in two patients in the first, and three patients in the second group, despite additional BT

TABLE 12-3. Prospective BT trials

Year	Author	n	Treatment	Follow-up	Success (%)	Side effects
1998	Maria et al.[84]	30	BT 20 U (2 doses)			
			Saline	2 mo	73.3	
					13.3 (P = .003)	
1999	Brisinda et al.[90]	50	BT 20 U (2 doses)			
			0.2% NTG	2 mo	96	
					60 (P = .005)	20% headaches
2002	Colak et al.[85]	62	BT			
			Lidocaine	2 mo	70.6	
					21.4 (P = .006)	
2002	Brisinda et al.[87]	150	BT 20 U, 30 U			
			BT 30 U, 50 U	2 mo	89	
					96	
2003	Siproudhis et al.[86]	44	BT 20 U (1 dose)			
			Saline	4 wk	22.7	
					22.7	
2003	Mentes et al.[91]	101	BT 0.3 U/kg			
			LIS	12 mo	75.4	
					94 (P = .008)	16% incontinence

BT, botulinum toxin; U, units; LIS, lateral internal sphincterotomy.

injections. Temporary incontinence to flatus was reported in 6.6% of the second group only.

Optimal dosing of BT therapy was evaluated in a separate study by Madalinski et al.[88] Fourteen patients with chronic anal fissures resistant to topical nitrates and a subsequent 25-U BT injection were offered a second application of topical nitrates, which resulted in healing in only one patient. A higher dose of BT (50 U) was given to the 13 remaining patients and healing achieved in seven. The use of BT injections for GTN treatment failures was further supported in a prospective trial conducted by Lindsey et al.[89] Forty patients with chronic anal fissures despite GTN therapy were treated with 20 U of BT. Initial success, which included patients with symptomatic relief in the presence of an unhealed fissure, was observed in 29 patients (73%). Less than one-third of patients eventually underwent a surgical procedure. Transient incontinence was noted in 18% of patients. The authors concluded that BT should be considered as a second-line, and perhaps a first-line, agent in the treatment of chronic anal fissures before pursuing surgical options.

In a prospective, randomized trial, Brisinda et al.[90] directly compared BT injection and topical NTG as first-line agents in the treatment of chronic anal fissures. BT injections (20 U) were given on each side of the IAS and 0.2% NTG ointment was applied twice daily for 6 weeks. Fissures healed in 96% of the patients in the BT group and 60% of the patients in the NTG group. Moderate to severe headaches were reported in 20% of the NTG group, whereas no side effects were observed after BT injections. Regarding nonsurgical treatment of chronic anal fissure, the authors concluded that BT was more effective than NTG therapy.

There has been only one prospective, randomized trial to date comparing BT to LIS in the treatment of chronic anal fissures. Mentes et al.[91] reported the results of 61 patients receiving a total of 0.3 U/kg BT in two divided doses and 50 patients who underwent sphincterotomy. Fissure healing was evaluated at 1 and 4 weeks postprocedure, as well as at 2-, 6-, and 12-month intervals. Patients in the BT group had a second injection if healing was incomplete after 2 months. After 1 month, fissures were completely healed in 62.3% of patients in the BT group versus 82% of patients in the LIS group (P = .023). By 2 months, healing rates were 73.8% in the BT group and 98% in the LIS group (P < .0001). Six months after treatment, 86.9% of patients in the BT group had healed fissures. In the LIS group, two patients developed recurrences, decreasing the healing rate to 94%, not significantly different from the BT group. By 12 months, however, fissure recurrence in seven patients in the BT group resulted in a decrease in the overall healing rate to 75.4%, significantly lower than 94% rate still observed in the LIS group (P = .008). Anal incontinence, predominantly to flatus, was reported in 16% of patients in the LIS group. No side effects were observed with BT injections. Although initial success and fewer complications were found with BT therapy, long-term results were not as encouraging when compared with LIS.

Late recurrence rates 42 months after BT treatment of chronic anal fissures have been reported in a prospective trial by Minguez et al.[92] Only patients with complete healing 6 months after BT injections were included for reassessment in 6-month intervals. Fissure recurrence was demonstrated in 41.5% of patients. Stratification by various clinical parameters revealed that higher risks of recurrence were associated with anterior location, chronicity of disease (longer than 12 months), multiple injections, and dosage greater than 21 U. They comment that lack of recurrence cited in earlier reports by Maria et al. and Brisinda et al. may have been influenced

by their use of strict exclusion criteria, such as patients with anterior fissures. Furthermore, standard doses of BT were not used in all trials. Optimal dosing and appropriate patient selection remain uncertain.

Complications reported after BT injections of anal fissures have included perianal hematomas in 2 of 10 patients treated by Tilney et al.[93] and perianal thrombosis in early reports by Jost et al.,[94] although this has not been reproduced in his recent experience.[95]

Special Situations

Low Pressure Fissures

Unlike the classic anal fissures described previously, low pressure fissures are not appropriate candidates for operative sphincterotomy. Patients within this category include those with impaired continence and fissure recurrence after sphincterotomy. Anal fissures sustained after childbirth are also associated with reduced anal canal pressures. Corby et al.[96] prospectively studied 209 primigravid women with anal manometry 6 weeks before and after childbirth. Of those women, 9% developed postpartum fissures. Manometric evaluations demonstrated similar antepartum resting and squeeze pressures in women who developed fissure and those who did not. In addition, postpartum resting and squeeze pressures were decreased in both groups. For this group of patients, "surgical interference with the anal sphincter mechanism should be avoided."[96]

Optimal treatment of low-pressure fissures is unclear. Nyam et al.[97] reported the results of an island flap in 21 patients with preoperative median resting anal pressures and squeeze pressures significantly lower than controls or patients with high-pressure fissures. Sphincter defects were recognized ultrasonographically in 15 of 21 patients (71%). During an 18-month follow-up, all fissures healed and incontinence was not observed. The authors concluded that the island advancement flap "provides a useful alternative" for recurrent anal fissures, or low-pressure anal fissures, in which sphincterotomy "might jeopardize continence."[97]

Crohn's

The incidence of perianal Crohn's fissures varies widely among reports. In one retrospective review by Platell et al.,[98] symptomatic anal disease was documented in 42.4% of patients with Crohn's disease. More than one-quarter of those patients (27.6%) had anal fissures. In a separate analysis in which 3.8% of patients with Crohn's disease required surgery for perianal symptoms, Sangwan et al.[99] found that 31.8% had anal fissures. Fleshner et al.[100] specifically examined fissures in Crohn's disease and found 84% were symptomatic. Multiple fissures were noted in one-third of patients and only 66% were located in the posterior midline. Sweeney et al.[101] reviewed the natural history of Crohn's fissures in 61 patients, in whom anal fissure was the only anal pathology. Fissure healing occurred in 42 of 69 patients (60.8%) during medical treatment for Crohn's disease. Ten patients developed additional anal lesions. Six patients (9.8%) eventually underwent anorectal surgery.

Traditionally, anorectal surgery in patients with Crohn's disease has been approached with caution. Complications resulting in proctectomy and fears regarding postoperative incontinence, exacerbated by preexisting diarrhea, have precluded perianal operations in these patients (although impairment of continence after such operations has not been studied in this population). As a result, most authorities argue that initial treatment of Crohn's fissures should be focused on controlling diarrhea. If fissure persists despite conservative measures, examination under anesthesia and limited sphincterotomy should be performed. Currently, there are no data to support the use of topical sphincter relaxants or BT in the treatment of fissures in Crohn's disease.

Outcomes after surgery in patients with Crohn's fissures have been reported, albeit in small retrospective series. Wolkomir and Luchtefeld[102] reported uncomplicated wound healing in 22 of 25 patients. In the series by Fleshner et al.,[100] 88% of patients healed after anorectal surgery, compared with 49% of patients after medical treatment and 29% after abdominal surgery. Of treatment failures, perianal abscess or fistula was observed in 26% of patients.

Anal dilatation for Crohn's fissures has also been reported with some success. Isbister and Prasad[12] reported that "three patients with anal fissures and Crohn's disease were successfully managed by anal dilatation." Allan and Keighley[103] described improvement in 4 of 7 patients, in whom 1 became incontinent.

Human Immunodeficiency Virus

Distinction between HIV-associated fissures and HIV-associated ulcers is necessary for optimization of fissure management in this patient population. Fissures in HIV-positive patients have a typical appearance, whereas HIV ulcers are deep and broad based and can occur anywhere within the anal canal.[104,105] Early pessimistic reports of poor wound healing and high rates of incontinence after sphincterotomy for HIV-associated fissures may have been skewed by inclusion of HIV ulcers in the fissure group.[105] In addition, these data preceded the era of highly effective antiviral therapy. In fact, there is a paucity of current information on HIV-associated fissures, and no available data about risk of postoperative incontinence or use of topical sphincter relaxants or BT as treatment options.

Barrett et al.[106] reported fissure prevalence in 32% of HIV-positive patients. Although sphincterotomies were performed in 18 patients, specific outcomes were not reported. Viamonte et al.[104] compared alternative treatments for anal fissures in 33 HIV-positive patients. Ten patients were lost to follow-up.

Improvement was noted in 10 patients treated nonoperatively and in 12 of 13 patients who underwent LIS. Actual healing rates were not provided, but no cases of incontinence were observed.

Conclusions

Anal fissure is a common, symptomatic disorder. Diagnosis is often established by history alone, but is easily confirmed by physical examination without the need for additional instrumentation. After instigation by anal trauma, anal fissure is sustained by elevated resting anal pressure. Treatment of anal fissure has consequently been aimed at reducing anal tone.

Surgery has been highly effective, although alterations in continence have been documented. Although proponents of anal dilatation exist, LIS has been advocated as the operation of choice. Regarding nonoperative treatment options, the early GTN literature has been promising, but varies significantly with regard to rates of healing, relapse, and side effects. Topical calcium channel blockers have shown similar efficacy to GTN, but fewer side effects have been reported. In at least one randomized trial, BT demonstrated superiority to GTN, but long-term outcomes of BT have uncovered high fissure recurrence rates. In general, the success of medical therapies has been controversial, with lack of consensus demonstrably evident after dichotomous analyses in the recent literature: a review by Lindsey et al.[47] that determines that most chronic anal fissures are successfully treated by inexpensive medical therapies and a systematic evaluation by Nelson[48] that concludes that medical therapy offers only a slight advantage when compared with placebo, but is significantly inferior to surgery.

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