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Medical and Surgical Treatment of Chronic Anal Fissure: A Prospective Study

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Abstract
The aim of this prospective study was to assess the efficacy of different medical treatments and surgery in the treatment of chronic anal fissure (CAF). From 1/04 to 09/06, 156 patients with typical CAF completed the study. All patients were treated with 0.2% nitroglycerin ointment (GTN) or anal dilators (DIL) for 8 weeks. If no improvement was observed after 8 weeks, patient was assigned to the other treatment or a combination of the two. Persisting symptoms after 12 weeks or recurrence were indications for either botulinum toxin injection into the internal sphincter and fissurectomy or lateral internal sphincterotomy (LIS). During the follow-up (19±8 months), healing rates, symptoms, incontinence scores, and therapy adverse effects were prospectively recorded. Overall healing rates were 65.3 and 96.3% after GTN/DIL or BTX/LIS. Healing rate after GTN or DIL were 39.8 and 46%, respectively. Thirty-six patients (23.1%) responded to further medical therapy. Fifty-four patients (34.6%) underwent BTX or LIS. Healing rate after BTX was 81.8%. LIS group showed a 100% healing rate with no morbidity and postoperative incontinence. In conclusion, although LIS is far more effective than medical treatments, BTX injection/fissurectomy as first line treatment may significantly increase the healing rate while avoiding any risk of incontinence.

Keywords Chronic anal fissure · Surgery · Botulinum

Introduction

The cause of anal fissure is still unknown, but hypertonia of internal anal sphincter (IAS) associated with the passage of hard stools is likely one of the main factors implied. As a matter of fact, an elevated mean resting pressure of the IAS (measured during anorectal manometry) is the most consistent finding in patients with fissures. Lateral internal sphincterotomy (LIS) has proved highly effective in curing anal fissures in a number of randomized clinical trials[1–8], with success rates higher than 90%. Although LIS is currently considered the "gold standard" of treatment, it encompasses an overall risk of incontinence, which can be as high as 10%, as estimated in a systematic review of randomized surgical trials.[9] Hence, the interest, in the last two decades, in seeking new medical treatments is directed at lowering the tone of the IAS. Glycerin trinitrate (GTN), botulin toxin, and topical calcium channel blockers are all known to be able to lower the IAS tone. The efficacy of GTN has been evaluated in several randomized studies and although the overall healing rate for GTN estimated in a meta-analysis of the published randomized trials[10] is about 50%, it is established as a first line therapy in many centers because of convenience, safety, and costs. The main drawbacks of GTN treatment are recurrence, tachyphylaxis, anal burning, hypotension, and the risk of headache that can be so severe to cause many patients to abandon therapy. The botulinum toxin is injected directly into the IAS and produces a "chemical sphincterotomy." It appears to be the

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ideal agent to overcome the side effects of GTN, as it produces the same reduction of the anal sphincter resting pressure as GTN, there are no compliance issues, and adverse effects are infrequently reported. A meta-analysis of randomized clinical trials comparing medical treatments to placebo or surgery[10] has shown that GNT, botulinum toxin, and surgery have overall response rates of about 55, 65, and 85%, respectively, whereas the placebo healing rate is about 35% across all the studies. Medical treatment seems therefore a reasonable first line therapy for most patients with chronic anal fissure (CAF). Second-line use of botulinum toxin seems to heal only 50% of fissures resistant to.[11] It is likely that the fibrotic nature of chronic fissures resistant to GTN is not resolved by chemical sphincterotomy alone. Fissurectomy alone is not currently used in adults, but its combination with botulinum toxin injection has been recently used with success to treat fissures resistant to medical treatment.[12,13] with healing rates higher than 90%. The aims of our study were the assessment of the efficacy of different medical treatments, fissurectomy, and botulinum toxin injection, and LIS in lowering the anal sphincter tone and healing CAFs, and the development of a treatment algorithm for patients with CAF.

Material and Methods

Between January 2004 and September 2006, 156 consecutive patients with CAF were enrolled in the study. Diagnosis was made according to history and physical exam. CAF was defined by duration of symptoms longer than 3 months and the presence of a skin tag, a sentinel pile or fibrosis at the margins of the fissure. Exclusion criteria included atypical CAF associated with grade III/IV hemorrhoids, previous anal surgery, incontinence, inflammatory bowel disease, infection, or cancer. Patients with coexisting medical conditions requiring calcium channel blockers and oral, sublingual, or transdermal nitrates were also considered ineligible for this study.

During the outpatient visit, a complete explanation of the disease and the medical treatment options, benefits, and side effects were given to the patient.

After this, patient was assigned to an 8-week course of medical therapy with either 0.2% GTN or anal dilators (DIL) according to his/her preference. Patients of GTN group were instructed to apply the ointment twice a day to the edge and just inside the anal canal (morning and evening) after a warm sitz bath. The amount of crème to be applied was shown during the outpatient visit. If patients experienced side effects, he was instructed to use a finger glove for application or to reduce the amount to be applied.

Patients of DIL group were instructed to use an anal dilators set (Dilatan, Sapi Med, Alessandria, Italy) as follows. To ease the DIL introduction, after being heated for 15 min in water, patients lubricated the DIL with a preparation gel (Dilatan crema, Sapi Med, Alessandria, Italy) and introduced it fully into the anal canal and maintained the position for 10 min twice a day (morning and evening). Patient was invited to repeat this procedure for 3 weeks starting with small diameter dilators (20–23 mm), followed by medium size dilators (23–27 mm) and ending with the large (32 mm).

The primary end-point was fissure healing at last follow-up. Secondary end-points were symptomatic improvement, need for LIS, and side effects. Improvement was defined as absence of pain or bleeding. Healing was defined as complete epithelialization of the fissure base. Those patients in which no improvement in symptoms was observed after 8 weeks were crossed to the other treatment (either GTN or DIL) or switched to a combination of the two for additional 4 weeks. Botulinum toxin injection in the IAS associated to fissurectomy (BTX-F) or LIS were offered to patients who did not benefit from the 12-week treatment course with GTN or DIL or a combination of them, after full information about the risks and the benefits of either procedure. Patients with non-healed or recurrent CAF who refused surgery were offered a further medical treatment. Anorectal manometry was performed before either one of the procedures.

Either fissurectomy/Botox injection or LIS were performed in a day-surgery setting under sedation and local anesthesia in lithotomy position. Before surgery, all patients had a limited bowel preparation with one Sorbiclis (Sofar S.p.a, Milan, Italy). An Eisenhammer speculum was gently inserted, avoiding excessive sphincter dilatation. Fissurectomy was performed by minimal excision of the fibrotic edges of the fissure and curettage of its base just back to fresh, normal, non-fibrotic tissue. If present, the sentinel pile was excised with cutting diathermy. Once fissurectomy was performed, 25 U of botulinum toxin (Botox, Allergan, Milan, Italy) were injected as follows. A volume of 1.6 ml of saline solution was mixed into a 100-U vial of botulinum toxin, and 0.4 ml aliquot (equal to 25 U) was drawn up into a 1-ml syringe with a 27-gauge needle and injected equally into the IAS at 3 and 9 o'clock.

LIS was performed using the open technique with partial division of the IAS in the lateral position using coagulation diathermy. In all cases, fissurectomy was performed as previously described.[13]

Patients in both groups were discharged on the same day and stayed on a high-residue diet and stool softener for 7 days. A non-narcotic analgesic was also prescribed as needed, and patients were advised to take regular warm sitz baths. Patients were seen in outpatient clinic after 1 week and therefore at 1-, 2-, 3-, and 12-month intervals. Independently of these scheduled appointments, patients

were seen on request. Information about fissure healing, symptoms, complications, and adverse effects were prospectively collected. Wexner incontinence score was used to assess continence after the procedures.

Differences between treatment groups were evaluated by chi-square test.

Results

Patients' demographics, fissure characteristics, and treatment failures are shown in Table 1.

Median follow-up was 19±8 months ranging from 3 to 33 months.

Overall fissure healing after medical treatment with either GTN or DIL was observed in a total of 102 (65.4%) patients.

Figure 1a shows healing rates after 12 weeks treatment with GTN or DIL alone as well as recurrences and overall healing rates at the end of the study. Fig. 1b shows healing rates, recurrences, and overall healing after the switch. Healing after 12 weeks was observed in 52.7% of the patients for the GTN only group and in 50.8% of the patients for the DIL only group without significant differences. Recurrence rate after 12 weeks treatment was 24.5% for GTN only group and 9.4% for DIL only group respectively (p=0.09).

In particular, healing with no recurrence was observed in 37 out of 93 patients (39.8%) treated with GTN alone and in 29 out of 63 patients (46.0%) who underwent anal dilation only. In most of the patients, healing time ranged from 8 to 12 weeks after treatment course. No significant difference was noted between the two groups in terms of time to healing (p=0.1).

Seventy-five patients (48.1%) experienced non-healing or sudden recurring disease within the first 8 weeks observation period. Of those, 33 patients (previously treated with GTN) were switched to DIL and 22 (previously treated with DIL) to GTN for additional 4 weeks. The remaining 20 patients accepted a combined GTN/DIL treatment.

A total of 36 patients (23.1%) responded to this further medical therapy, and overall healing rate raised significantly from 42.3 to 65.4% (p=0.03). In particular, at the end of this further 4 weeks treatment, GTN after DIL resulted effective in 68.2% of the treated patients (15 out 22) and DIL after GTN in 36.4% (12 out of 33) (p=0.02). Of the 20 patients treated with combined DIL/GTN, 14 responded with healing (70%) (p=0.02 vs DIL and 0.90 vs GTN). During the follow-up recurrence rates were 16.7% for DIL after GTN, 7.1% for combined GTN/DIL, and 14.3% for GTN after DIL, with no significant differences among groups. Fig. 1b shows definitive healing after this further medical treatment. Definitive healing was observed in 10 out of 33 patients treated with DIL after GTN (30.3%), in 13 out of 22 patients treated with GTN after DIL (59.1%), and in 13 out of 20 patients treated with combined GTN/DIL (65%). Combined GTN/DIL and GTN after DIL treatments were similar in terms of definitive healing and significantly better than DIL after GTN treatment (p=0.003).

At the end of the study, overall medical treatment success was 60.2% (56 out of 93 patients) and 73% (46 out of 63 patients) respectively for patients initially treated with GTN or DIL. No significant differences were observed between the groups.

Overall incidence of GTN side effects was 12.8% (15 patients), mostly mild headache (9 patients) and *pruritus ani* (6 patients). Five patients (4.2%) discontinued therapy and were switched to DIL.

A total of 107 patients were treated with DIL (63 patients as initial treatment and 44 patients after GTN treatment) and 12.1% interrupted the DIL course (13 out 107) because of

Table 1 Patients' Demographics, Fissure Characteristics, and Treatment Failures Resume

	GTN	DIL	GTN/DIL	BOTOX/fissurectomy	LIS
Number	93	63	20	22	32
Mean age (years)	37	41	39	34	43
Sex (M/F)	42/51	29/34	8/12	10/12	11/21
Fissure position					
Post	74	49	13	19	28
Ant	14	11	5	2	3
Both	4	3	2	1	1
Other	1	0	0	0	0
Sentinel pile *N*/%	61/65.6%	39/61.9%	14/70%	15/68.2%	27/84.4%
Single treatment (12 weeks) success *N*/(%)	49/93 (52.7%)	32/63 (50.8%)	NA	NA	NA
Recurrence	12/49 (24.5%)	3/32 (9.4%)	NA	NA	NA
After cross-over healing *N*/%	12/33 (36.4%)	15/22 (68.2%)	14/20 (70%)	NA	NA
Recurrence	2/14 (14.3%)	2/15 (13.3%)	1/14 (7.1%)	NA	NA
Overall success *N*/%	47/93 (50.5%)	42/63 (66.7%)	13/20 (65%)	18/22 (81.8%)	32/32 (100%)

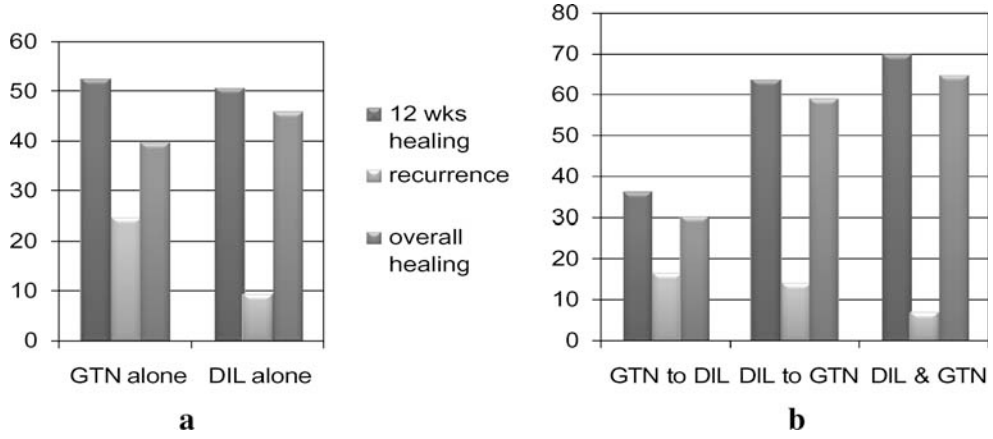

Figure 1 Healing after 12 weeks, recurrence rates, and overall definitive healing after single medical treatment (**a**) and after the switch (**b**). Data is expressed as percentage of treated patients.

severe discomfort. After non-healing or recurrence, surgery was offered to 53 patients (34%). One patient refused either botulinum treatment or surgery, and further medical treatment was offered with minimal beneficial effect. Of the remaining 52 patients, 22 underwent fissurectomy/Botox injection and 30 to LIS. Healing was reported in 18 out of 22 (81.8%) patients after fissurectomy/Botox injection. This percentage was significantly higher compared to GTN alone course (p=0.008), to DIL alone treatment (p=0.02) or to overall combined/cross-over groups (p=0.01). One patient (4.5%) experienced transitory flatus incontinence. Non-healing was observed in one patient (4.5%) and recurrence in 3 (13.6%). Two out four subsequently required LIS because of recurrent disease (one patient) or failure of therapy in promoting fissure healing (one patient) and had complete healing. The remaining two patient refused further surgical treatment and remained on periodical medical treatment.

All 32 patients treated with LIS showed complete healing with no morbidity or postoperative incontinence.

Comparing the different treatment groups, there were no significant differences in terms of healing rates between males and females, presence or absence of sentinel pile, or previous GTN or/and DIL treatment.

Discussion

The most recent theories on etiopathogenesis of anal fissures have focused on increased tonicity of the IAS, which contains smooth muscle fibers whose contraction is controlled by neural influences and myogenic mechanisms.[14,15] IAS contraction is mediated by increased cytosol calcium levels. Nitric oxide serves as the main neurotransmitter in the IAS causing relaxation of the muscle fibers.[15] Numerous clinical evidences pointed out the role of an elevated resting pressure of the IAS in patients with anal fissures.[16,17] Factors causing IAS hypertonia are not well understood, but a significant role in perpetrating the muscle spasm is played by the trauma caused by the passage of hard stools on the mucosa.[18] Spasm of the sphincter not only promotes constipation (thus setting up a vicious cycle) but also leads to compression of the terminal arterioles supplying the mucosa of the anal canal.[19] Impaired blood flow in this already poorly perfused area prevents fissure healing.

Since the introduction of the posterior internal sphincterotomy by Eisenhammer[20] in 1951, CAF has been managed with surgery once conservative measures failed. The more safe lateral sphincterotomy, popularized by Notaras[21] in 1969, has until recently been the mainstay of treatment to reduce the pathologically raised pressure profile within the anal canal. Despite that surgery is highly efficacious and succeeds in curing CAF in more than 90% of patients (often exceeds 95% with high patient satisfaction), postoperative impairment of continence is not uncommon.[10,15] The incidence is not well documented and varies between 0 and 35% for flatus incontinence, 0 and 21% for liquid incontinence, and 0 and 5% for solid stool incontinence.[22–25] As indicated by Nelson in a recent systematic review of randomized surgical trials, the overall risk of incontinence is about 10%,[9,10,26] mostly to flatus without any specification of the duration of this problem (transitory or permanent). However, it is a common belief that the risk of permanent incontinence is about 1%. Nonetheless, this does not take into account normal weakening of the sphincter with age and the possibility of future anorectal surgery, radiation, or obstetrical trauma. Therefore, the risk of incontinence after LIS should be considered lifelong, to an often young, otherwise healthy person.

To minimize this risk, several authors have tried a more limited division of internal sphincter, a tailored or controlled sphincterotomy, but additional remarkable data is needed.[27,28]

In the late 1990s when alternatives to surgery were sought because of risk of incontinence, costs, and time for recovery, newer medications directed at relaxing increased sphincter tone or enhancing mucosal blood flow were investigated. These included nitroglycerin ointment, calcium channel blockers (either given as tablets or topically), and recently, injection of botulinum toxin.

GTN causes sphincter relaxation by acting as a nitric oxide donor and improves anodermal perfusion.[29] Topical calcium channel blockers like diltiazem and nifedipine induce IAS by decreasing cytosolic calcium concentration.

Despite that early trials (including both acute and chronic fissure) of conservative medical treatments showed overall healing rates and pain relief close to surgery, usually results with medical treatments are only marginally better than placebo or conservative therapies alone (fiber, Sitz baths, and topical lidocaine) with healing rates between 36 to 68% and relapses rates as high as 35%.[30,31] According to Nelson's meta-analysis, a marginal advantage in using GTN (55%) over placebo (35%) exists, but no statistical difference was found comparing GTN to either botulinum toxin or calcium channel blockers.

We used GTN ointment in addition to conservative approaches (fiber and Sitz bath) as first line treatment because of its safety, convenience, and cost. The dosage and number of applications previously reported ranges from 0.2 to 0.5% and from twice to four times per day.[32,33] Dose escalation or use of a transdermal patch has not been shown to improve the healing rate.[34,35] The principal side effect is headache, seen in up to 50% of patients and less commonly anal pruritus.[31,36–38] Hence, compliance issues are observed in up to 72% of patients, and about 20% of patients will discontinue therapy.[26,35,39]

As 0.2% dosage seems to be as effective as 0.5% dosage, with less side effects, we decided to offer a 0.2% twice a day treatment. Our healing rate after GTN alone treatment was close to 40% increasing to only 50.5% when DIL course was added. We also observed a 24.5% recurrence rate, significantly higher compared to DIL use only or combined GTN/DIL. In our series, the incidence of side effects associated with GTN application was lower (12.8%) than the common incidence of at least 20–30% reported in literature. Only 4% of the patients discontinued the therapy and were switched to DIL. Surprisingly, in our series, the most common reason to discontinue GTN therapy was anal pruritus, observed in 5% of patients.

We believe that the low incidence of side effects and good compliance to treatment program showed by our groups of patients is the result of reduced number of applications (twice a day) and the accuracy of instructions given to the patient at the time of the outpatient visit.

The rationale for the use of anal dilators (DIL) is the finding that they induce muscle relaxation with consequent reduction in sphincter hypertonia. Moreover, blood flow is improved in the IAS, thus favoring fissure healing. When the DIL is heated, the relaxing effect is enhanced.[38] Short-term healing rates are reported as high as 95% when used in combination with GTN, with about 10% reduction after 2 years follow-up. However, little evidence on the efficacy of anal dilators is present in the literature. Recently, Schiano et al.[38] reported healing rates of 75% with DIL only and 93.7% with combined GTN/DIL treatment. In our experience, the DIL-only treatment was associated with a 46% healing rate, slightly superior to GTN use only. However, recurrence rate was significantly lower.

When DIL group was switched to GTN because of non-healing, the success rate increased to 66.7% significantly higher than the success rate of 50.5% observed when GTN course was followed by DIL. We explain this difference with a shorter healing time observed with GTN compared to DIL course that needs few weeks of applications of different size dilators. A 4-week DIL course may not be sufficient to significantly increase the healing rate after GTN, thus reducing the likelihood of surgery. An indirect evidence of this is observed in patients simultaneously treated with DIL and GTN who showed a definitive healing rate of 65% with a very low recurrence rate (7%). This result might be indicative of a possible synergic effect of the two. Schiano et al. reported a 93.5% healing rate; however, our follow-up was longer. In our experience, DIL use is safe, healing rates are comparable to GTN treatment, but compliance is lower. In our experience, 12.1% of the patients interrupted the DIL course because of severe discomfort preferring "less invasive" approaches. The reluctance in using DIL after GTN failure and the reduced compliance may also explain the low healing rate observed in this group.

Injection of botulinum toxin into the internal sphincter produces a temporary chemical sphincterotomy that allows fissure healing.

The botulinum toxin is believed to act at the postganglionic level reducing noradrenaline output from sympathetic neural terminals in the internal sphincter and possibly also by reducing myogenic tone in this tissue.[28] A single botulinum injection is well tolerated, with minor side effects, thus eliminating non-compliance issues. It reduces maximum resting pressure by a similar proportion to that of GTN (25–30%)[39] over a 2- to 3-month period of time.[22]

The most common side effect is transient incontinence to flatus (up to 10%) or feces (up to 5%).[40]

Recurrence are common but may be easily treated with a good rate of healing even if up to 20% of patients will need LIS.[26,41,42]

There is no consensus on dose, site, or number of injections.[43] However, a dosage between 20 and 25 U, and anterior injection seems more effective and causes no additional side effects.[14,15,37] A transient decrease in mean squeeze pressure can also be observed when higher doses are used.[40,44] Conversely, higher doses are not proven to be more effective.[45]

Despite that early trials have shown healing rates as high as 90% for acute and chronic fissures, the enthusiasm

was tempered by the disappointing results on CAF. Lindsey et al.,[11] in a prospective study of 40 patients with GTN-resistant fissures treated with 20U of botulinum, reported a healing rate of only 43%. Similarly, Minguez et al.[46] did not show healing rates as high as surgery after botulinum injection with a 42 months follow-up, while Arroyo et al. [47] and Mentes et al.[48] observed 1-year recurrence rates after botulinum injection approaching, respectively, 50 and 40%. Higher healing rates are observed if botulinum is given early, before the chronic fibrosis of the fissure is established.[39] As botulinum injection treats only the internal sphincter spasm, Lindsey et al.[22] have proposed to add fissurectomy to chemical sphincterotomy, reporting a healing rate of 93% for medically resistant CAF. In a more recent study, Scholz et al.[12] reports excellent results with implementation of the fissurectomy–Botox injection technique, which proved to be effective in treating fissure recurrences, too.

Fissurectomy enhances healing by removing the fibrotic fissure edges, unhealthy granulation tissue at the base, and the sentinel pile when present.[22]

We adopted this novel sphincter-sparing procedure as second line treatment after failure of GTN and/or DIL course. We observed a long-term healing rate of 81.8%, significantly higher than the one reported after all other approaches. Along with Lindsey et al, we believe that fissure healing is significantly higher with fissurectomy–botulinum toxin injection compared to medical treatment alone because with this treatment, we are able to address both elements of chronic fissure, chronic fibrosis, and internal sphincter spasm. We observed a single case of transitory incontinence, and our data confirm the safety of this treatment. The main drawback of this approach is the need of an operating theater and the costs. Although four patients of this group experienced fissure recurrence or non-healing, with two requiring subsequent LIS, fissurectomy and botulinum injection reduces significantly the need of LIS. The paucity of minor side effects associated to the good healing rates indicate that botulinum injection/fissurectomy may be used as first line approach for selected CAF even without previous medical treatment. Along with Lindsey et al., our study confirms that medical treatment alone for chronic, well-established fissures might be inappropriate, merely delaying definitive fissure healing.[13] Features of chronic fissure such as a fibrotic tissue, skin tag, or sentinel pile predict poor healing with medical therapy, and disappointing results of medical therapies for CAF, often similar, or just superior to placebo in different clinical trials, strengthen this observation. As a consequence of our experience and literature evidence, we believe that BTX/fissurectomy should be offered as first line treatment for patients with typical CAF even without previous medical/conservative treatments. Patients at high risk for anal incontinence, young female patients, and patients with previous anal surgery can also be treated with BTX/fissurectomy. Botulinum toxin injection associated to a gentle fissurectomy seems to be very safe, reducing greatly the likelihood of surgery and abolishing the risk of incontinence. The main drawback of BTX/fissurectomy is the need of surgery and the costs. However, we believe that the prompt and excellent healing rates (close to LIS) and the absence of severe side effects or complications might justify the costs.

Failure of BTX/fissurectomy or recurrence indicate the need of LIS.

Our study confirms that LIS represents the most effective approach to CAF. Although transitory postoperative incontinence can been observed in up to one third of patients, in our experience, we did not incur in any. Nonetheless, we did not observe any permanent incontinence. Although the proximal extent of the LIS continue to be a topic of debate, in our experience, by 'tailoring' the amount of sphincter to be divided to the length of the fissure, the risk of incontinence is minimized and the fissure healing achieved. To enhance and accelerate healing, we also believe that an accurate fissurectomy should always be added to LIS.

Conclusions

Although surgery (LIS) may be appropriately offered without a trial of pharmacological treatment after failure of conservative therapy as indicated by the "Practice parameters for the management of anal fissure", being incontinence as a lifelong risk, a step-wise approach would be appropriate and a trial of topical GTN and/or DIL should be offered. However, as refractory CAF with fibrotic tissue may heal with fissurectomy and botulinum injection only, abolishing the risk of incontinence, this approach should also be offered especially if patients are reluctant to undergo LIS or at high risk for incontinence. Moreover, according to our experience, this approach as first line medical treatment seems to be rational, safe, and effective, but further data is needed.

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