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REVIEW

Current evidence and new trends in anal fissure treatment

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ABSTRACT

An anal fissure is a benign and painful ulcer extending from the pectinate line to the anal margin. It leads to an increase in the resting pressure of the internal anal sphincter and the pressure within the anal canal, resulting in local ischemia and impaired wound healing. Anal fissures are mostly located in the posterior midline. They are primarily caused by local trauma to the anoderm, often due to the passage of hard stools, irritation from diarrhea, or anorectal surgery. For both acute and chronic anal fissures, several treatment options are available, and surgery typically reserved as a second-line option. Recent trends in first-line therapy prefer calcium channel blockers (CCBs) over topical glyceryl trinitrate (GTN), as they offer similar healing rates but are associated with fewer side effects and better patient's compliance. Lateral internal sphincterotomy (LIS) remains the gold-standard surgical treatment for this condition. Additionally, emerging therapies, such as platelet-rich plasma (PRP) application, adipose-derived regenerative cells (ADRCs), and percutaneous tibial nerve stimulation (PTNS), have shown promising results and they are gaining attention as potential alternatives for managing chronic anal fissures. The present narrative review aims to provide a comprehensive overview of current therapeutic approaches for anal fissures, evaluating their effectiveness in promoting healing and comparing them with guideline-based recommendations.

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An anal fissure (AF) is a benign and painful ulcer extending from the pectinate line to the anal margin.[1] As a result of AF, there is an increase in the resting pressure of the internal anal sphincter (IAS) and in the pressure of the anal canal leading to local ischemia and impaired wound healing.[2, 3]

The pathophysiology of AF involves multiple interrelated mechanisms.[2-4] The most common cause of AF is an anal trauma, due to the passage of hard stools or diarrhea, causing injury to the anal mucosa, leading to AF formation.[2] Chronic AFs are often associated with sustained spasms of the IAS, resulting in hypertonicity and increased resting anal pressure.[2] This spasticity impairs local blood flow to the anoderm, causing ischemia, and disrupting the healing process of fissures.[2] The reduced perfusion to the affected mucosal region, secondary to sphincter hypertonia, plays a key role in the chronicity of AFs.[3] Elevated anal pressure and diminished blood flow in the fissure area are fundamental factors contributing to its pathogenesis.[3]

Another factor responsible for AF development could be the IAS nitric oxide deficiency in the case of chronic AF, which may prevent

proper sphincter relaxation and perpetuate the spasm, thus contributing to the chronic nature of the condition.[4]

However, it is reported that AFs may be present in patients with sphincter hypotonia in the absence of any trauma or constipation.[5] For these reasons, the sphincter tone should be considered in the selection of appropriate treatment.[2-5]

AFs can be classified as typical (primary) or atypical (secondary).[6] Typical AFs are most frequently located in the posterior midline and primarily result from local trauma to the anoderm due to the passage of hard stools through the anal canal, irritation from diarrhea, and/or anorectal surgery.[1]

In contrast, atypical AFs may be present in other sites than the midline and they are often associated with the pathophysiological processes of other conditions, for example, Crohn's disease, tuberculosis, and sexually transmitted infections, which can present with similar symptoms of AF but are managed differently.[6]

AF is considered acute when it has a short duration with the resolution of symptoms within 6-8 weeks, and chronic when the lesion and symptoms persist after 8 weeks.[1]

There are multiple therapeutic options for managing this condition, with various algorithms proposed by different coloproctology associations or societies,[6-9] moreover new therapies recently have been proposed showing promising results.[10-12] However, often the choice for conservative or surgical treatment depends on the surgeons' preferences.[2]

This narrative review aims to thoroughly examine the existing literature on current treatments for AFs, assessing their healing rates, and evaluate, through national and international surveys, which therapies are most used. Additionally, the aim is to determine whether these treatments align with the recommendations outlined in current clinical guidelines.

Literature search

A narrative review was conducted searching the non-operative and operative treatment strategies for AF. The research was carried out in the PubMed and Cochrane databases using the following keywords: "acute anal fissure" OR "chronic anal fissure" AND "treatment" OR "conservative management" OR "surgery" OR "lateral internal sphincterotomy". Moreover, to include additional articles useful for the study, cross-referencing was made with included articles.

Inclusion and exclusion criteria

Articles written in English, Spanish, and Italian in which AF treatment is reported, and published between 2014 and August 2024, were included. Also, articles reporting both non-operative and operative management were included.

Comments, case reports, correspondence and letters to editor, editorials, conference articles, imaging studies, and studies involving animals were excluded.

Non-operative treatment

Non-specific non-operative treatment

This approach is particularly indicated for patients with acute AF and involves taking sitz baths with warm water to IAS relaxation, as well as making hygienic and dietary changes.[7] These changes include increasing fiber intake by modifying the diet or adding fiber supplements such as psyllium and using laxatives to soften stools.[8] Additionally, the recurrence of acute AF is significantly reduced when 5 grams of fiber were taken three times daily compared to placebo (lactulose) and 2.5 grams of fiber.[13] On the other hand, it is recommended to perform sitz baths at least twice a day and after each bowel movement, using warm water for 10 minutes.[8] This measure is primarily advised for analgesic purposes, as its efficacy as a curative treatment is controversial[14] (Table I).[6, 8, 15-18]

This treatment is internationally accepted having demonstrated significant improvement in the patients' symptoms with acute and chronic AF.[19-23] It is also one of the recommendations from the latest American Society of Colon and Rectal Surgeons (ASCRS) guidelines on AF management (strong recommendation based on moderate-quality evidence: 1B).[6]

However, most surgeons combined the above-

mentioned treatment strategy as the first therapeutic attempt with pharmacological treatment using oral or topical analgesic medications, corticosteroids or lidocaine, and ointments (calcium channel blockers or glyceryl trinitrate).[19]

Specific non-operative treatment

Topical glyceryl trinitrate

Topical glyceryl trinitrate (GTN) promotes IAS relaxation, aiming to break the pathophysiological cycle of chronic AF.[24] It is recommended to apply it two or three times daily directly on fissure.[24] This therapeutic option is considered unsuccessful if symptomatic relief or healing of the chronic fissure is not achieved within 6-8 weeks from the beginning of the treatment.[24] Regarding dosage, higher doses did not show an increased healing rates, hence the recommended dose is 0.2%.[24] Adequate use of this medication shown to resolve chronic fissures in up to 50% of cases.[24]

GTN can be used in combination with cryothermal anal dilators.[25] A randomized clinical trial was conducted to compare the use of 0.2% GTN combined with dilators with the use of 0.4% GTN alone.[25] The study concluded that the combination of GTN with dilators was superior to the administration of GTN alone, despite its higher dosage, and is proposed as an alternative for patients in whom isolated GTN has not been effective.[25]

However, it must be noted that a primary concern with this drug is its side effects, such as headache, which occur in up to 30% of patients, leading 20% of this group to discontinue or not comply adequately[6] (Table I).

Worldwide, its use is accepted, however, the current trend is shifting towards calcium channel blocker (CCB) medications.[19-23] CCBs have demonstrated similar efficacy in fissure healing without the associated side effects, thereby achieving better patient adherence and therapeutic outcomes.[19-22]

Recently updated guidelines for AF management advocate for its use as first-line therapy for chronic fissure management (strong recommendation based on moderate-quality evidence: 1B).[6]

Calcium channel blockers

Topical CCBs relax IAS through the inhibition of calcium entry into the cytoplasm of smooth muscle cells.[2, 26] This inhibition leads to muscle relaxation, reducing sphincter tone, which in turn alleviates pain and promotes fissure healing.[26] The two most used CCBs are topical nifedipine (0.2-0.5% gel) and diltiazem (2% cream).[27] Its use can be topical or oral, though topical application shows better results in terms of healing efficacy, and it is associated with fewer adverse events, although further studies are still needed.[27] Despite, it seems that differences in outcomes between nifedipine and diltiazem did not occur, most surgeons use nifedipine most frequently.[19]

Recent studies support the use of CCBs as an effective option for treating AF.[28] In clinical trials, the effectiveness of topical diltiazem was compared with GTN, showing that both treatments were effective, but with fewer side effects reported in the diltiazem group.[29] Similarly, a meta-analysis, reported that topical nifedipine has the advantage to present fewer adverse effects compared to surgical treatment.[29]

Moreover, this treatment is currently accepted as a first-line treatment for acute or chronic AF, in multiple international guidelines[6-9] and it is increasingly being used over topical nitroglycerin in many countries[19-23] (Table I).

The use of this drug as a first-line treatment in the management of chronic AF has a strong recommendation grade based on moderate-quality evidence: 1B.[6]

Potassium channel blockers it is another therapeutic option for AF treatment; however, its use is not popular among surgeons, due to it did not show as good results as other treatments in terms of healing.[19]

Operative treatment

Botulinum toxin

Botulinum toxin (BT), primarily known for its neuromodulatory effects, induces temporary paralysis of the IAS by inhibiting acetylcholine release at neuromuscular junction.[2] This relaxation reduces sphincter pressure, allowing for improved blood flow and facilitating fissure heal-

ing, as opposed to the case of chronic sphincter hypertonia.[8]

Several studies have consistently demonstrated the efficacy of BT in AF treatment, demonstrating that BT injections resulted in healing rates comparable to GTN and CCBs.[6, 15, 30] However, the use of BT as a second-line treatment for chronic AF is still debated.[5] Retrospective studies evaluating its use after failed topical nitroglycerin therapy showing greater symptomatic relief and the possibility of avoiding lateral internal sphincterotomy (LIS).[31] However, recently published meta-analyses comparing second-line therapies for chronic AF have demonstrated significantly higher healing rates with LIS compared to BT injection.[32] Nevertheless, BT is associated with a lower complication rate, such as incontinence, and it has proven to be a safer option[32] (Table I).

Moreover, standardized protocols for BT injected dose, number of injections, and site are still lacking.[33] In a recent meta-analysis, a comparison of the dose-response of BT has been reported, using doses ranging from 5 to 150 U, without correlation between dose and the AF healing rate.[34] Recent studies recommended small BT doses (20-60 U) due to it seems that small doses are effective as high doses, and it is associated with less risk of temporary incontinence.[6, 33] However, in literature, there is a lack of comparison studies.

Nowadays, endoscopic ultrasound-guided BT injection is emerging as a promising approach to chronic AF refractory to conventional medical treatment.[11] The use of endoscopic ultrasound guidance offers the advantage of precise localization, allowing for targeted BT administration, which may enhance therapeutic outcomes and minimize complications.[35]

Comparative data suggests that ultrasound-guided BT injection may be superior to the traditional endoscopic approach without ultrasound assistance, due to its increased accuracy.[35] However, further studies, particularly well-designed randomized controlled trials, are necessary to validate the efficacy and safety of this approach. These studies will be crucial in determining the role of ultrasound-guided BT injection in the management of refractory AF and could potentially influence future clinical practice guidelines.[11]

In clinical practice, surgeons typically reserve the use of BT for chronic AF refractory to GTN or CCBs with a high risk of fecal incontinence (FI), employing it as a second-line therapy.[19-23] However, the latest updated ASCRS guidelines suggest its use as a first-line treatment (grade of recommendation: 1B),[6] since recent studies have shown similar healing rates compared to drugs traditionally used as first-line therapy.[30]

Anal dilatation

Anal dilation is a treatment option for anal fissures that involves carefully stretching the anal canal to reduce IAS pressure.[19-23] This approach helps to improve blood flow to the affected area, promoting fissure healing and alleviating pain.[6, 19-23]

However, this approach is no longer widely used due to its associated risk of incontinence and experts have ceased recommending it as a treatment option.[6, 19-23]

A less aggressive option is controlled pneumatic balloon dilatation or anal stretching.[2, 36, 37] Pneumatic balloon dilation involves the insertion of a balloon into the anal canal.[2] Then the balloon is inflated to a specific pressure to control the IAS dilation, aiming to reduce the sphincter tone.[2, 36] This treatment could be a safe and effective alternative when compared to LIS, with similar healing rates and a lower FI incidence.[2, 36]

Another option for chronic AF treatment is manual anal stretching.[37] It involves the IAS dilation through the application of manual pressure by inserting one or two fingers into the anal canal, and in a controlled manner, applying pressure to stretch the internal anal sphincter.[37] This technique could be promising in terms of efficacy for AF healing, as demonstrated by a case series of 25 patients with a healing rate of 94% at 6 months, with a recurrence rate of 19% after one year, without FI.[37]

Lateral internal sphincterotomy

LIS has demonstrated a success rate ranging between 90% and 100%.[8] A systematic review reported LIS as the gold standard treatment of

chronic AF, with better results in comparison to other conservative and surgical treatments in terms of efficacy.[16] Additionally, this systematic review compared open and closed LIS, concluding that both are equally effective for chronic AF treatment, even if, a closed technique has fewer complications.[16]

Although LIS is generally safe, mild FI remains a concern.[38] However, recent studies have shown that the long-term incidence of incontinence is low, ranging between 2% and 16% with early and late incontinence rates ranging from 3.3% to 16%, and with incontinence for gas or soiling being more common than incontinence for liquid stool.[8, 16] Moreover, the current trend in surgical practice is to perform LIS tailored to the fissure length, rather than extended LIS to the dentate line.[35] This variation in technique has been shown to provide similar outcomes in terms of healing rates while significantly reducing the risk of FI[39] (Table I).

In current clinical practice, in the case of hypertonic sphincter, surgeons typically reserve the use of this technique as a second-line treatment for chronic AF refractory to GTN and CCBs, prioritizing it over other surgical alternatives or third line if the patient has a high risk of FI after administering BT as a second-line treatment.[19-23] However, a French survey reports fissurectomy with anal advancement flap as the surgical treatment of choice due to low-risk FI.[13] Finally, according to ASCRS guidelines, LIS may be indicated as a first-line treatment in patients without FI (grade recommendation: 1A).[6]

Fissurectomy with anal advancement flap

During fissurectomy the fibrous edges of the fissure are removed, along with the sentinel skin tag and the hypertrophied anal papilla often associated with fissures.[20] This procedure can be combined with an anal advancement flap (AAF).[17, 39] However, most literature supports LIS due to its lower recurrence rate and the absence of significant differences in FI outcomes when compared to isolated fissurectomy.[39] Various techniques for anoplasty are available, but all share the common

TABLE I.—*Summary of evidence.*[6, 8, 15-18]

Treatment	Short term effectiveness	Long term effectiveness	Fecal incontinence, %
Hygienic-dietary measures (*e.g.*, sitz bath, fiber supplements)[6]	60-80% effective in relieving pain and improving comfort. Sitz bath reduces pain and inflammation in acute anal fissure.	20-30% effective: regular fiber supplementation and good hygiene can reduce recurrence, but often insufficient for complete healing without other treatments.	Not reported
Glyceryl trinitrate[6, 8, 18]	50-60% effective symptom relief (within 4-6 weeks).	40-50% success rate after discontinuation. Higher relapse rates 30-50% recurrence after stopping treatment.	0.8
Calcium channel blockers[6, 8, 18]	60-80% effective reducing pain and promoting healing (similar to nitroglycerin).	50-75% effective with lower recurrence rate compared to nitroglycerin. Better tolerance, less relapse.	0.8
Botulinum toxin[6, 8, 15, 18]	60-80% effective with significant pain reduction and healing.	50-65.5% effective, with low recurrence rate. Some patients experience lasting relief after 1-2 injections.	3.3-15% risk of transient fecal incontinence. Most cases are mild and resolved after a few weeks. In rare cases, can be persistent but typically resolves with time.
Anal dilatation[18]	89.5% effective for healing.	Not reported	8.1
Internal lateral sphincterotomy[6, 8, 16, 17]	92-100% effective for pain relief and healing.	90-95% effective with high success rate and low recurrence rate.	2-16% of most cases are mild and transient, usually resolved within a few months (3.3% early fecal incontinence and 16% late incontinence).
Fissurectomy and anal advancement flap[8, 16, 18]	90-98% effective for healing, especially in cases of severe or complex fissures.	74.3-90% effective with a very low recurrence rate.	0-5% very low risk of incontinence.

principle of covering the fissure with either a skin flap or a rectal mucosal flap.[17, 40] The major benefit of this technique is the effectiveness, with success rates ranging from 81% to 100%, while preserving sphincter function and maintaining a low risk of FI (0.6%)[40] (Table I).

This technique is generally indicated in patients with a high risk of FI, or with normal/hypotonic sphincter, proving to be a safe approach with healing rates comparable to sphincterotomy.[2, 17] In fact, it is the preferred technique of the French group, surpassing LIS, for managing chronic AF that is resistant to conservative treatment.[6, 19-23]

Emerging therapies

Platelet-rich plasma

Platelet-rich plasma (PRP) is a blood-derived product with a platelet count three to five times higher than normal, and it can be used for reparative and regenerative purposes.[10] It has recently been introduced in the management of chronic AF, infiltrating PRP deeply into the base and edges of the AF, showing promising results.[41] In a prospective study involving 44 patients, the effectiveness of this emerging therapy was compared to topical GTN.[41] The results indicated that pain relief and healing rates were superior with this new therapy.[41]

Adipose derived regenerative cells

Adipose tissue is one of the most abundant sources of adult stem cells and other regenerative cells.[42, 43] When adipose derived regenerative cells (ADRCs) are administered to damaged or diseased tissue, they can release cytokines and growth factors that help regulate inflammation, enhance neovascularization, and stimulate the natural repair mechanisms through paracrine signaling.[42, 43] Additionally, ADRCs can influence the hosts "stem cell niche" by encouraging the recruitment of endogenous stem cells to the injury site and promoting their differentiation along the necessary lineage pathways.[43] These mechanisms play a key role in tissue regeneration and are critical for the healing process in chronic anal fissures.[43]

Liposuction was performed under local or general anesthesia, using abdominal wall subcutaneous fat.[43] ADRC was extracted with a closed automated medical device, and it is injected subcutaneously along the fissure edge and into IAS.[43]

This therapy has been administered for chronic AF treatment in a prospective study involving 8 patients, yielding promising results regarding the healing.[43]

Percutaneous tibial nerve stimulation

Percutaneous tibial nerve stimulation (PTNS) has gained interest as a therapeutic option for chronic AF due to its potential to alleviate pain and improve symptoms in patients with FI.[44] This approach emerged from clinical observations where patients suffering from both FI and AF reported significant pain relief and healing rates comparable to conventional treatments after receiving PTNS.[45]

The posterior tibial nerve, a branch of the sciatic nerve, can be stimulated peripherally to modulate neuromuscular reflexes and enhance anal sphincter function.[44] This appears to have a positive effect on the AF healing process.[44] By improving sphincter tone and local circulation in the anorectal area, this stimulation can help to reduce pain associated with fissure and promote tissue healing.[46]

A recent systematic review including 102 patients who underwent PTNS therapy reports a symptom resolution of up to 72% at 2 months and up to 73% at 6 months.[12]

In a randomized clinical trial, PTNS has been compared with NTG, showing a lower treatment discontinuation rate compared to NTG application, with a higher healing rate (up to 80% versus 60% for PTNS and NTG application, respectively).[47]

As a non-invasive therapy, PTNS has been well-tolerated by patients and represents a promising alternative, particularly for those seeking less invasive options compared to surgery.[17] However, while early results are encouraging, further studies are necessary to better understand its mechanisms of action, specific indications, and long-term outcomes in the treatment of chronic AF through posterior tibial nerve stimulation.[39]

Although PRP, ADRCs, and PTNS seem promising innovations for AF treatment, due to their limited use in a few patients and the poorly reported evidence in the literature, the available results must be evaluated with caution, since further prospective and randomized control trials are required to draw definitive conclusions.

Conclusions

Several therapeutic options are available for the treatment of acute and chronic AF, with surgery generally being reserved as a second-line approach. Current trends in first-line therapy favour the use of CCBs over GTN as they offer comparable healing rates while being associated with fewer adverse effects and improved patient's compliance. LIS remains the gold standard surgical intervention for this condition. Moreover, emerging therapies, such as PRP, ADRC, and PTNS, are showing promising results, which are gaining attention as potential alternatives in the management of chronic AF.

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Marta Domínguez Muñoz, Andrea Balla, Juan C. Gómez-Rosado, Salvador Morales-Conde have made substantial contributions to the conception or the design of the manuscript, to acquisition, analysis and interpretation of the data. All authors have participated in drafting the manuscript and revised it critically. All authors read and approved the final version of the manuscript.

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