Medical Treatment of Chronic Anal Fissure. Where do we stand on Reversible Chemical Sphincterotomy?

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Abstract

Anal fissure is a common problem which can evolve to chronicity. Chronic anal fissure is thought to be an ischemic ulceration related to sphincter hypertonia. Lateral internal sphincterotomy, the most common treatment for chronic anal fissure, may cause permanent injury to anal sphincter leading to fecal incontinence. To avoid such side effect were developed medications producing a temporary or reversible sphincterotomy reducing the sphincter pressure only until the fissure has healed: nitrates, calcium channel antagonists and botulinum toxin. Authors aimed to summarize the state of research on such treatments (efficacy, side effects, recurrence risk) and to clarify the role of these different medical options in the current treatment of chronic anal fissure. (Acta gastroenterol. belg., 2004, 67, 265-271).

Key words: fissure in ano, nitrates, nitroglycerin, isosorbide dinitrate, calcium channel blockers, nifedipine, diltiazem, botulinum toxin.

Introduction

Anal fissure is the second proctological affection after hemorrhoidal disease and the first cause of pain in proctology. Diagnosis of idiopathic anal fissure is easy, based on classical clinical triad: longitudinal or elliptical ulcer at the distal anal canal, nearly always commisural and more often posterior; spasm of the internal anal sphincter (IAS); characteristic painful syndrome (pain activated by defecation, followed by a transient inconstant attenuation of a few minutes and a more intense secondary recrudescence lasting eventually hours).

Two stages, acute and chronic, of anal fissure are described. Acute anal fissures have the appearance of a superficial tear in the anoderm. Cicatrisation occurs in up to 45-87% spontaneously or by medical conservative treatment (stool softeners, bran supplementation, warm sitz baths and topical anaesthetic solutions) (1-4). Chronic anal fissures are characterised by thickening of skin margins and visualisation IAS fibers at its base. There are frequently accompanied by a sentinel skin tag at the distal fissure margin and a hypertrophied anal papilla just proximal to the fissure within the anal canal. They tend to be refractory to conservative treatment (1).

Physiopathology of anal fissure is multifactorial. Usually it is thought to be induced by a trauma (passage of a large/hard stool or diarrhea) but such an initial factor is not always found. Its posterior commissure location is explained by less anatomical resistance and hypoperfusion of this zone (5). Hypertonia of the internal anal sphincter is frequently found in chronic fissure patients (6) and it has been recognised to play a major role in persistence of fissure by an ischemic mechanism. Indeed anodermal perfusion depends on arterioles that must cross the IAS and there is an inverse correlation between posterior midline anodermal blood flow and resting anal pressure (7). Increase in anodermal blood flow has been reported by procedures that normalise anal resting pressure such as sphincterotomy (8).

The following model resume these different theories. (Fig. 1) (9). Anal fissure is initially caused by a trauma. In case of normal anal resting tonus, it heals spontaneously or by medical treatment. In case of anal resting hypertonia, which can be caused by stress or pain, fissure persist and become a chronic ischemic ulceration.

Discovery of ischemic nature of anal fissure, in close relation to resting hypertonia, explain efficacy of classical treatment of chronic anal fissure -surgical treatment- which mostly consist on lateral internal sphincterotomy (LIS). Fissure healing under surgery occurs in more than 95% of patients (10-11). However it can also induce faecal incontinence in up to 30% of patients (10-12). Drugs capable of inducing a reversible relaxing effect on the IAS have thus been proposed: nitrates, calcium channel antagonists and botulinum toxin (13-14). This article is focused to results of this reversible chemical sphincterotomy.

Nitrates

Topical nitrates – mainly glyceryltrinitrate (GTN) but also isosorbide dinitrate (ISDN) – were the first specific pharmacological therapy applied topically for chronic anal fissure. Exogenous nitrates release in vivo nitric oxide which is the most principal nonadrenergic non-cholinergic neurotransmitter mediating relaxation of IAS. In 1994, Loder et al. showed a significant decrease in resting anal pressure after anal application of GTN ointment (15). First open studies reported 86-88% healing rate in chronic anal fissure (16-17). In contrast, more recent randomised studies showed extremely various and often lower healing rates. Results of principal
randomised trials with topical application of nitrates in chronic anal fissure are resumed in table 1 (18-34). Healing rate varied from 30% for worse results to 83-86% in best ones with a mean of 50-60%. If considering only randomised versus placebo studies, two important parameters must be noted. Healing rate has been evaluated to 36-70% in treatment groups but was also very different in placebo groups (8-52%) (19,22-24,31-32). These differences could be explained by various definition used for chronicity of anal fissure : symptom duration varying from 6 weeks to four months in some studies (19,21,24,26,30-34), need of sentinel skin tag or hypertrophied anal papillae presence (24,25,27,34), exposed IAS fibers (18,24-25,27,30,34), fibrotic fissure basis or sides (19,22,24-25,30). If acute fissures are integrated as chronic ones in these studies, proportion of fissures which heal spontaneously increases such as healing rate does both in treatment and placebo groups. This is likely to cause a reduction in differential healing rate between active and placebo arms leading to under powering of the trial. These differences could also be explained by non standardised nitrates preparations, by non clearly defined associated conservatives treatments (warm sitz bath, high-fiber diet, analgesics) and by different treatment duration (4 weeks for Altomare et al. (24) and 8 weeks for Scholefield et al. (32)). Although no healing difference was sometimes noted, more rapid pain relief was sometimes mentioned in nitrate groups comparing to placebo (23).

Five studies have compared GTN application to LIS (18,25-27,30) (table 1). LIS was always more efficacious than GTN but, save Richard et al. (25), more than 50% of patients healed under topical therapy. These patients won’t consequently be submitted to potential incontinence risk of LIS (6.5% reversible minor anal incontinence for Evans et al. (27) and 3% flatus incontinence for Libertiny et al. (30)).

No incontinence trouble has been reported with topical nitrates but this treatment induced orthostatic hypotension, anal burning and especially headaches. Headaches were present in about 65%, dose-dependent, more often transitory but sometimes severe (20.5% (25)), leading to treatment discontinuation in 10% patients. Headaches constituted a major compliance problem. Another compliance brake was necessity to frequent application of topical nitrates (2 or 3 times a day for 4 to 8 weeks). To avoid this difficulty, Zuberi et al. tested 10 mg GTN patch (26). Healing rate were comparable to topical application (63% GTN patch vs.

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<th>Authors</th>
<th>Treatment</th>
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<th>Healing Rate (%)</th>
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<tbody>
<tr>
<td>Oettle et al. (18)</td>
<td>GTN 1.5 mg tid vs. LIS</td>
<td>24</td>
<td>83</td>
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<tr>
<td>Lund et al. (19)</td>
<td>0.2% GTN vs. Placebo</td>
<td>80</td>
<td>68</td>
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<td>Bacher et al. (20)</td>
<td>0.2% GTN vs. Lidocaïne</td>
<td>13</td>
<td>63</td>
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<tr>
<td>Brisinda et al. (21)</td>
<td>0.2% GTN vs. BT 20 U</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>Carapeti et al. (22)</td>
<td>0.2% to 0.6% GTN vs. Placebo</td>
<td>70</td>
<td>65 to 70</td>
</tr>
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<td>Kennedy et al. (23)</td>
<td>0.2% GTN vs. Placebo</td>
<td>43</td>
<td>46</td>
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<tr>
<td>Altomare et al. (24)</td>
<td>0.2% GTN vs. Placebo</td>
<td>119</td>
<td>49</td>
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<tr>
<td>Richard et al. (25)</td>
<td>0.25% GTN vs. LIS</td>
<td>82</td>
<td>30</td>
</tr>
<tr>
<td>Zuberi et al. (26)</td>
<td>0.2% GTN vs GTN 10 mg patch vs. LIS</td>
<td>49</td>
<td>67</td>
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<tr>
<td>Evans et al. (27)</td>
<td>0.2% GTN vs. LIS</td>
<td>65</td>
<td>61</td>
</tr>
<tr>
<td>Were et al. (28)</td>
<td>1% ISDN vs. Placebo</td>
<td>37</td>
<td>85</td>
</tr>
<tr>
<td>Kocher et al. (29)</td>
<td>0.2% GTN vs. 2% Diltiazem</td>
<td>60</td>
<td>86</td>
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<tr>
<td>Libertiny et al. (30)</td>
<td>0.2% GTN vs. LIS</td>
<td>70</td>
<td>54</td>
</tr>
<tr>
<td>Bailey et al. (31)</td>
<td>0.1 to 0.4% GTN vs. Placebo</td>
<td>304</td>
<td>50</td>
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<tr>
<td>Scholefield et al. (32)</td>
<td>0.1 to 0.4% GTN vs. Placebo</td>
<td>200</td>
<td>36 to 57</td>
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<tr>
<td>Bielecki et al. (33)</td>
<td>0.5% GTN vs. 2% Diltiazem</td>
<td>43</td>
<td>86</td>
</tr>
<tr>
<td>Ezri et al. (34)</td>
<td>0.2% GTN vs. 0.2% Nifedipine</td>
<td>52</td>
<td>58</td>
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(GTN, glyceryl trinitrate ; LIS, lateral internal sphincterotomy ; BT, botulinum toxin ; ISDN, isosorbide dinitrate).
Calcium Channel Antagonists

Because calcium is important for smooth muscle contraction, calcium channel antagonists have also been evaluated for anal fissure treatment. Nifedipine and diltiazem have been used topically or orally in this indication. Manometric studies established reduction of anal pressure on nifedipine or diltiazem therapy (41-43). In acute anal fissure, Antropoli et al. showed, in a cohort of 283 patients, superiority of topical 0.2% nifedipine ointment on association 1% lidocaine / 1% hydrocortisone (95% vs. 50% healing rate respectively) (44). Main trials on calcium channel antagonists in treatment of chronic anal fissure are shown on table 2 (29,33-34,42-43,45-50). Cook et al. observed healing in nine of 15 patients (60%) after 8 week of therapy with oral nifedipine (2 × 20 mg) (42). Two randomised studies on topical nifedipine showed good results with respectively 89% and 95% healing rate (34,45). Oral nifedipine seemed to be less efficacious (42). Studies on topical diltiazem ointment are more numerous: five open (43,46,48-50) and 3 randomised (29,33,47) studies (one vs. oral diltiazem and 2 vs. GTN ointment). Elevated healing rate were confirmed in most studies with topical diltiazem. DasGupta et al., Jonas et al. and Griffin et al. reported less efficacy with respectively 48%, 49% and 47% healing rate (48-50). But, in these open trials, studied populations were partially (48) or totally (49-50) patients who failed to heal on GTN ointment. Randomised trials on topical diltiazem showed 65 to 86% healing rate, roughly as effective as GTN treatment (29,33,47). Oral diltiazem seemed less efficacious than topical application (38% vs. 65% healing rate) (47). Major advantage of calcium channel antagonists on nitrates is best tolerance. In topical use, side effects mainly consisted on local hyperhemia (2 to 10%) (29,46,48). Headaches were less frequent, from 5 to 26%, even in randomised studies compared to GTN ointment (29,33). In oral use, tolerance was poorer with rash, headaches, nausea or vomiting (46). Recurrence rate is still not really known (4 to 17% at 6 months follow-up (46-47)) because long term studies are lacking. Until now there are no comparative studies with placebo or surgery. Despite these promising results, however, no commercially or commonly accepted magistral preparation with calcium channel antagonists are available in our country.

### Botulinum Toxin

Locally injected botulinum toxin (BT) has been used as an alternative approach to sphincter relaxation in the treatment of anal fissure. BT is a neurotoxin which prevents acetylcholine release from presynaptic nerve terminals and inhibits neuromuscular transmission in striated muscles. It leads to smooth muscle relaxation by a reversible action by new nerve terminals regrowth in a not clearly yet known mechanism. Interest of BT is cost-effective first-line treatment strategy for the management of anal fissure (40).
been chosen by two research teams exclusively in open studies (53-57). No clear manometric measures were systematically done but decrease in resting pressure was described, explained either by direct action on EAS or by diffusion in IAS. These open studies showed healing rate of 78-85% with 5-20 U Botox° (53-54,57) or 20-40 U Dysport° (55) injection. On the other hand, in IAS injection, manometric measures showed significant decrease of resting anal pressure by 18-30% with minor or no modification of squeeze pressures (21, 58-65).

Open studies reported healing rate of 67-100% with 10-20 U Botox° (61). Healing occurred in significantly less time in BT group (1 vs. 15 days in LIS group). A first-line topical nitrate treatment followed by BT injection on either side of the fissure vs. saline in 60% healing rate respectively and showed less side effects in BT group (0% vs. 20% – headaches – in GTN group) (21). In this study there was no anal incontinence nor fissure recurrence at 15 months. Combined therapy by BT and topical nitrates (DNI) was not more efficacious even though healing was more rapid (67). Compared to LIS, healing was less frequent in BT group (96% in LIS group vs. 74% at 2 months and 87% at 8 months with 16% second injection in BT group) (68). However there were no side effects in BT group while reported side effects were < 1% haemorrhoid prolapse or self-limited subcutaneous injection; < 3% anal haematoma, haemorrhoidal thrombosis, flu-like syndrome or transient faeces incontinence, 3 to 16% transient flatus incontinence (54-55,62,64,67,68,71). Recurrence rate is usually estimated to 0 to 12% depending on duration follow-up (21,54-56,60-61,63-64,68). Miguez et al. recently reported higher recurrence rate of 41.5% at 42 months (72). Risk factors for recurrence were anterior location of fissure, longer duration of the disease, need for re-injection, high dose to achieve healing and lower decrease of maximum squeeze pressure. Main problem of BT use is cost. Botox° is available on 100-

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<tr>
<td>Maria et al. (61)</td>
<td>BT 20 U vs. placebo</td>
<td>45</td>
<td>73% (100%*) 13%</td>
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<tr>
<td>Brisinda et al. (21)</td>
<td>BT 20 U vs. topical 0.2% GTN</td>
<td>50</td>
<td>96% 60%</td>
</tr>
<tr>
<td>Maria et al. (63)</td>
<td>BT 20 U ant vs. BT 20 U post</td>
<td>50</td>
<td>60% (80%<em>) 80% (100%</em>)</td>
</tr>
<tr>
<td>Lysy et al. (67)</td>
<td>BT 20 U vs. BT 20 U / 2.5 mg ISDN</td>
<td>30</td>
<td>73% 66%</td>
</tr>
<tr>
<td>Brisinda et al. (64)</td>
<td>BT 20 U vs. BT 30 U</td>
<td>150</td>
<td>89% (100%<em>) 96% (100%</em>)</td>
</tr>
<tr>
<td>Colak et al. (65)</td>
<td>BT 50 U vs. topical Lidocaine</td>
<td>62</td>
<td>71% 22%</td>
</tr>
<tr>
<td>Mentes et al. (68)</td>
<td>BT 0.3 U/kg vs. LIS</td>
<td>111</td>
<td>74% (87%*) 96%</td>
</tr>
<tr>
<td>Siproudhis et al. (69)</td>
<td>BT 100 U vs. placebo</td>
<td>44</td>
<td>23% 50%</td>
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</table>

(BT, botulinum toxin ; GTN, glyceryl trinitrate ; ant, anterior midline injection ; post, posterior midline injection ; ISDN, isosorbide diminate ; LIS, lateral internal sphincterotomy ; *= with second injection).

Complications of BT treatment are not very frequent. Reported side effects were < 1% haemorrhoid prolapse or self-limited subcutaneous injection; < 3% anal haematoma, haemorrhoidal thrombosis, flu-like syndrome or transient faeces incontinence, 3 to 16% transient flatus incontinence (54-55,62,64,67,68,71). Recurrence rate is usually estimated to 0 to 12% depending on duration follow-up (21,54-56,60-61,63-64,68). Miguez et al. recently reported higher recurrence rate of 41.5% at 42 months (72). Risk factors for recurrence were anterior location of fissure, longer duration of the disease, need for re-injection, high dose to achieve healing and lower decrease of maximum squeeze pressure. Main problem of BT use is cost. Botox° is available on 100-
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unit vial at a cost of nearly 220 € and Dysport° on 500-unit vial at a cost of nearly 250 €, that is to say a patient-cost of about 40-42 €, on a 80 U-Dysport or 20 U-Botox basis, if you find 5-6 patients to treat the same day!

Conclusion

There is no proven optimal treatment for anal fissure (73). Different options with their merits and disadvantages must be examined with patient. Proposed algorithm fissure treatment is shown in fig. 2. In practice, topical treatment can always be tried. Ideal topical therapy could be calcium channel antagonist but, in the absence of adequate ointment formula, topical treatment is at present based on nitrates. In case of failure, choice between BT injection and surgery exists with a preference to BT injection in case of sphincter risk factors. A first-line BT injection therapy could also be discussed. It is limited by price and current availability of BT.

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