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

C. Van Kemseke, J. Belaiche

Department of Hepato-Gastroenterology, Centre Hospitalier Universitaire de Liège, Liège, Belgium.

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 summary 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 commissural 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 noncholinergic 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

Reprints are to be sent to : Dr. C. Van Kemseke, Department of Hepato-Gastroenterology, Centre Hospitalier Universitaire de Liège, Domaine Universitaire du Sart Tilman B35, 4000 Liège, Belgium.

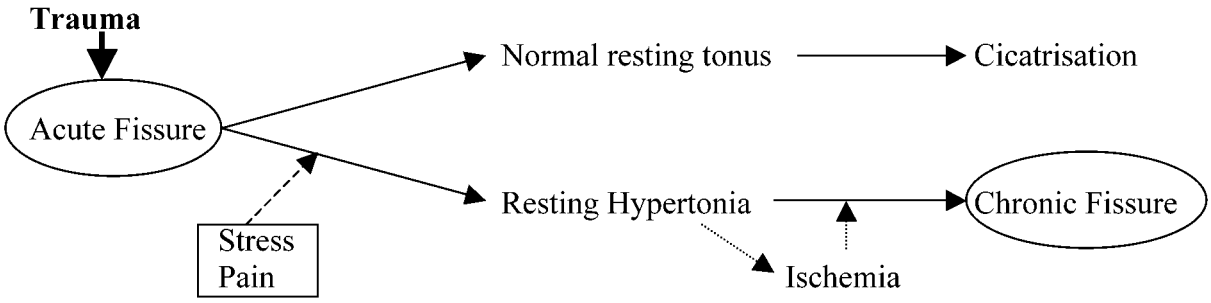

Fig. 1. — Physiopathology of Anal Fissure (according de Parades and Parisot)

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.

Table 1. — **Main Randomised Trials in Treatment of Chronic Anal Fissure using Topical Nitrates**

Authors	Treatment	n	Healing Rate (%)
Oettle *et al.* (18)	GTN 1.5 mg tid **vs. LIS**	24	83 **100**
Lund *et al.* (19)	0.2% GTN *vs. Placebo*	80	68 *8*
Bacher *et al.* (20)	0.2% GTN vs. Lidocaine	13	63 20
Brisinda *et al.* (21)	0.2% GTN vs. BT 20 U	50	60 96
Carapeti *et al.* (22)	0.2% to 0.6% GTN *vs. Placebo*	70	65 to 70 *32*
Kennedy *et al.* (23)	0.2% GTN *vs. Placebo*	43	46 *16*
Altomare *et al.* (24)	0.2% GTN *vs. Placebo*	119	49 *52*
Richard *et al.* (25)	0.25% GTN **vs. LIS**	82	30 **90**
Zuberi *et al.* (26)	0.2% GTN vs GTN 10 mg patch **vs. LIS**	49	67 63 **92**
Evans *et al.* (27)	0.2% GTN vs. LIS	65	61 97
Werre *et al.* (28)	1% ISDN *vs. Placebo*	37	85 *35*
Kocher *et al.* (29)	0.2% GTN vs. 2% Diltiazem	60	86 77
Libertiny *et al.* (30)	0.2% GTN **vs. LIS**	70	54 **100**
Bailey *et al.* (31)	0.1 to 0.4% GTN *vs. Placebo*	304	50 *50*
Scholefield *et al.* (32)	0.1 to 0.4% GTN *vs. Placebo*	200	36 to 57 *24*
Bielecki *et al.* (33)	0.5% GTN vs. 2% Diltiazem	43	86 86
Ezri *et al.* (34)	0.2% GTN vs. 0.2% Nifedipine	52	58 89

(GTN, glyceryl trinitrate ; LIS, lateral internal sphincterotomy ; BT, botulinum toxin ; ISDN, isosorbide dinitrate).

Table 2. — **Main Trials in Treatment of Chronic Anal Fissure with Calcium Channel Antagonists**

Author	Treatment	n	Healing Rate
Cook *et al.* (42)	Nifedipine 20 mg po bid	15	60%
Perrotti *et al.* (45)	Top 0.3% Nifedipine / 1.5% Lid vs. top 1.5% Lid/1% HC	110	95% 17%
Ezri *et al.* (34)	Top 0.2% Nifedipine vs. top 0.2% GTN	52	89% 58%
Carapeti *et al.* (43)	Top 2% Diltiazem	30	67%
Knight *et al.* (46)	Top 2% Diltiazem	71	75%
Jonas *et al.* (47)*	Top 2% Diltiazem vs. Diltiazem 60 mg po bid	50	68% 38%
DasGupta *et al.* (48)	Top 2% Diltiazem	23	48%
Kocher *et al.* (29)*	Top 2% Diltiazem vs. top 0.2% GTN	60	77% 86%
Jonas *et al.* (49)	Top 2% Diltiazem	39	49%
Griffin *et al.* (50)	Top 2% Diltiazem	47	47%
Bielecki *et al.* (33)*	Top 2% Diltiazem vs. top 0.5% GTN	33	86% 86%

(po, by mouth ; bid, twice daily ; Top, topical ; Lid, lidocaine ; HC, hydrocortisone ; GTN, glyceryl trinitrate ; *randomised trial).

67% topical GTN) with similar headache side effects. Other important problems were tachyphylaxis which reduced treatment efficacy (35) and, above all recurrence risk. Recurrence rate varied from 16 to 46% depending on studies and follow-up duration (24,26-27,32,36-39). Some studies were especially designed to fissure recurrence in GTN healed patients. Lund *et al.* (36) showed 27% fissure recurrence rate at 28 months while Lysy *et al.* (37), Jonas *et al.* (38) and Libertiny *et al.* (30) showed 21% at 11 months, 27% at 6 months and 16% at 24 months respectively. In these studies 0 to 8.6% of GTN-healed patients were at last treated by LIS for fissure recurrence, all others being treated again by GTN ointment with success or spontaneously healed. Recurrence of fissure after healing has been associated with the presence of a sentinel pile (38,39). At last Christie *et al.* calculated that a nitroglycerin ointment is a cost-effective first-line treatment strategy for the management of anal fissure (40).

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% lidocaïne / 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 $\times$ 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 not clearly yet known mechanism. Interest of BT is reversible action by new nerve terminals regrowth in a few months, thus preserving sphincter from definitive lesions. BT is commercially available on two forms : Botox° (Allergan) and Dysport° (Ipsen Pharma). These two forms are not dose equivalent : one labelled unit of Botox° is thought to be equivalent to 3-4 labelled units of Dysport (51-52). Most studies were made with Botox°. All later BT dose in the text will be in Botox° unit in absence of contrary mention. Two different techniques have been described with injection location either in external anal sphincter (EAS) or in IAS. Jost and Schimrigk first reported the use of BT injection in EAS for anal fissure in 1993 (53). This injection location has

Table 3. — **Main Randomised Trials in Treatment of Chronic Anal Fissure using Botulinum Toxin Injection. All injections were made in the IAS (internal anal sphincter). All botulinum toxin injections were made with Botox° except one (BT) with Dysport°**

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

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

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 10-40 U BT injection (58,60,62,66). Main randomised trials of BT injection in IAS for treatment of chronic anal fissures are shown in table 3 (21,61,63-65,67-69). These studies confirmed healing rate of 71-96% save Siproudhis *et al.* whose injection in IAS was unilateral in contrast to others (bilateral injection). Maria *et al.* conducted a double-blind, placebo-controlled trial of BT injection on either side of the fissure vs. saline in 30 chronic anal fissure patients (61). Healing occurred in 73% of treated patients at 2 months (vs. 13% in control group). The 4 unhealed patients in the BT arm underwent second injection (rescue therapy) and all healed within 2 months. Other authors have latest confirmed that rescue therapy after failure at 2 months was safe and efficacious either with the same dose (61,68) or with a slightly higher dose (25 U instead of 20 U (63) ; 50 U instead of 50 U (64)). Another trial by Maria *et al.* investigated the influence of the site of injection on healing rate (63). In this randomised, double-blind study, authors injected, in the IAS, a total of 20 U BT either on each side of the posterior midline or on each side of the anterior midline. Anterior midline injection seemed more efficacious with a healing rate of 100% with 12% retreated patients in contrast with 80% healing rate with 25% retreated patients in posterior midline injection. This could be explained by marked fibrosis at the base of the fissure reducing IAS compliance and BT diffusion. Optimal dose to use is difficult to determinate because studies were made with different dosages. Minguez *et al.* studied three doses : 10, 15 and 21 U with healing rate of 83%, 81% and 95% and necessity of two injections in 52%, 30% and 37% of patients respectively (62). Brisinda investigated two doses : 20 and 30 U with 100% healing rate in both groups and a second injection in 11% and 4% of patients respectively (64). However in 30 U group, 3% of patients experienced transitory gas anal incontinence. 20 U injection could consequently be optimal dose even though injections were not identically realised in these two studies. Brisinda *et al.* injected on each side of the anterior midline of IAS while Minguez *et al.* injected “through the intersphincteric groove in the direction of the internal sphincter” on each side of anal canal (10-unit group), with a third aliquot injected into the IAS immediately below the fissure in 15-unit and 21-unit groups.

BT has been compared both to nitrate therapy and to surgical treatment. Brisinda *et al.* demonstrated superior efficacy of BT injection on topical nitrates (96% vs. 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 16% transitory anal incontinence was noted in LIS group. Full return to daily activities took also significantly less time in BT group (1 vs. 15 days in LIS group). A first-line topical nitrate treatment followed by BT injection in case of failure could allow to avoid surgery in 80 to 85% patients (70).

Complications of BT treatment are not very frequent. Reported side effects were < 1% haemorrhoid prolapse or self-limited subcutaneous infection ; < 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). Minguez *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 reinjection, high dose to achieve healing and lower decrease of maximum squeeze pressure. Main problem of BT use is cost. Botox° is available on 100-

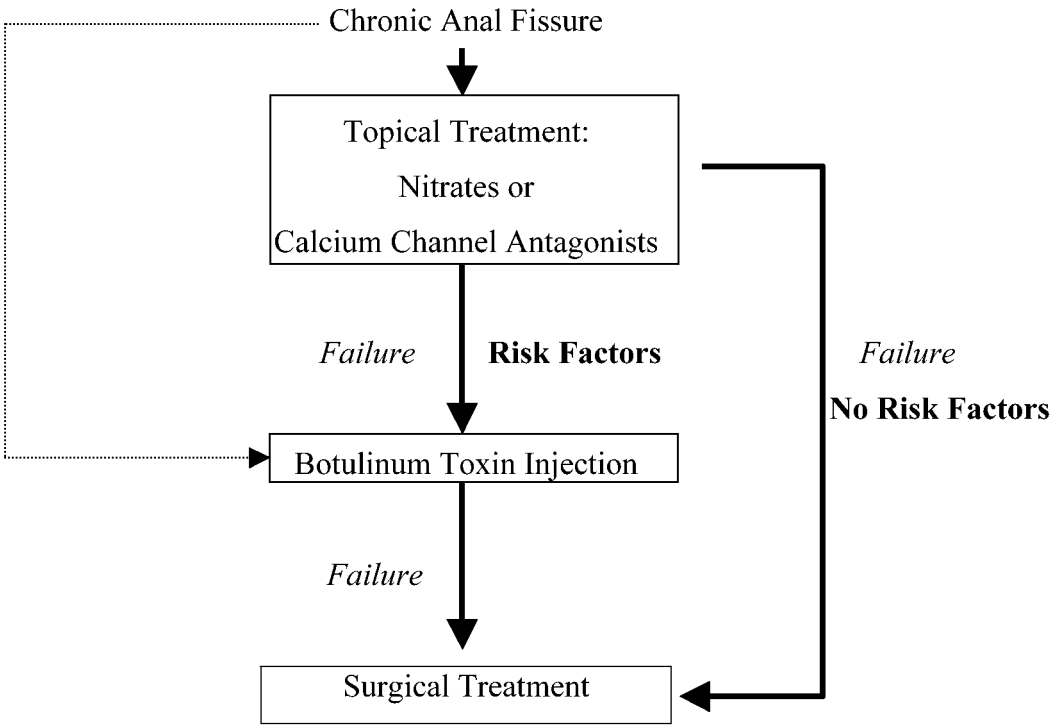

Fig 2. — Proposed algorithm chronic anal fissure treatment

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.

References

1. LOCK M.R., THOMSON J.P.S. Fissure-in-ano : the initial management and prognosis. *Br. J. Surg.*, 1977, **65** : 355-358.
2. SHUB H., SALVATI E., RUBIN R. Conservative treatment of fissure : an unselected, retrospective and continuous study. *Dis. Colon Rectum*, 1978, **21** : 582-583.
3. HANANEL N., GORDON P.H. Re-examination of clinical manifestations and response to therapy of fissure-in-ano. *Dis. Colon Rectum*, 1997, **40** : 229-233.
4. JENSEN S.L. Treatment of first episodes of acute anal fissure : prospective randomised study of lignocaine ointment versus hydrocortisone ointment or warm sitz baths plus bran. *Br. Med. J.*, 1986, **292** : 1167-1169.
5. KLOSTERHALFEN B., VOGEL P., RIXEN H., MITTERMAYER C. Topography of the inferior rectal artery : a possible cause of chronic, primary anal fissure. *Dis. Colon Rectum*, 1989, **32** : 43-52.
6. FAROUK R., DUTHIE G.S., MACGREGOR A.B., BARTOLO D.C. Sustained internal sphincter hypertonia in patients with chronic anal fissure. *Dis. Colon Rectum*, 1994, **37** : 424-429.
7. SCHOUTEN W.R., BRIEL J.W., AUWERDA J.J. Relationship between anal pressure and anodermal blood flow. The vascular pathogenesis of anal fissures. *Dis. Colon Rectum*, 1994, **37** : 664-669.
8. SCHOUTEN W.R., BRIEL J.W., AUWERDA J.J.A., DE GRAFF E.J.R. Why do anal fissures heal after lateral internal sphincterotomy ? *Dis. Colon Rectum*, 1995, **37** : 9.
9. DE PARADES V., PARISOT C. La fissure anale à l'épreuve de l'evidence based medicine : définition et concepts pathogéniques. Le Courrier de Colo-Proctologie, 2000, **I** : 5-7.
10. NELSON R.L. Meta-analysis of operative techniques for fissure-in-ano. *Dis. Colon Rectum*, 1999, **42** : 1424-1428.
11. NYAM D.C., PEMBERTON J.H. Long-terms results of lateral internal sphincterotomy for chronic anal fissure with particular reference to incidence of fecal incontinence. *Dis. Colon Rectum*, 1999, **42** : 1306-1310.
12. GARCIA-AGUILAR J., BELMONTE C., WONG W.D., LOWRY A.C., MADOFF R.D. Open vs closed sphincterotomy for chronic anal fissure : long-term results. *Dis. Colon Rectum*, 1996, **39** : 440-3.
13. MADOFF R., FLESHMAN J. AGA technical review on the diagnosis and care of patients with anal fissure. *Gastroenterology*, 2003, **124** : 235-245.
14. UTZIG M.J., KROESEN A.J., BUHR H.J. Concept in pathogenesis and treatment of chronic anal fissure. A review of litterature. *Am. J. Gastroenterol.*, 2003, **98** : 968-974.
15. LODER P.B., KAMM M.A., NICHOLLS R.J., PHILLIPS R.K. 'Reversible chemical sphincterotomy' by local application of glyceryl trinitrate. *Br. J. Surg.*, 1994, **81** :1386-1389.
16. LUND J.N., ARMITAGE N.C., SCHOLEFIELD J.H. Use of glyceryl trinitrate ointment in the treatment of anal fissure. *Br. J. Surg.*, 1996, **83** : 776-777.
17. SCHOUTEN W.R., BRIEL J.W., BOERMA M.O., AUWERDA J.J., WILMS E.B., GRAATSMA B.H. Pathophysiological aspects and clinical outcome of intra-anal application of isosorbide dinitrate in patients with chronic anal fissure. *Gut*, 1996, **39** : 465-469.
18. OETTLE G.J. Glyceryl trinitrate vs. sphincterotomy for treatment of chronic fissure-in-ano. A randomised controlled trial. *Dis. Colon Rectum*, 1997, **40** : 1318-1320.

19. LUND J, SCHOLEFIELD J. A randomised, prospective, double-blind, placebo-controlled trial of glyceryl trinitrate oinment in treatment of anal fissure. *Lancet*, 1997, **349** : 11-14.
20. BACHER H., MISCHINGER H.-J, WERKGARTNER G, CERWENKA H., EL-SHABRAWI A., PFEIFER J., SCHWEIGER W. Local nitroglycerin for treatment of anal fissures : an alternative to lateral sphincterotomy ? *Dis. Colon Rectum*, 1997, **40** : 840-845.
21. BRISINDA G., MARIA G., BENTIVOGLIO A.R., CASSETTA E., GUI D., ALBANESE A. A comparison of botulinum toxin and topical nitroglycerin ointment for the treatment of chronic anal fissure. *N. Engl. J. Med.*, 1999, **341** : 65-69.
22. CARAPETI E.A., KAMM M.A., MC DONALD P.J., CHADWICK S.J., MELVILLE D., PHILLIPS R.K. Randomised controlled trial shows that glyceryl trinitrate heals anal fissures, higher doses are not more effective, and there is a high recurrence rate. *Gut*, 1999, **44** : 727-730.
23. KENNEDY M.L., SOWETR S., NGUYEN H., LUBOWSKI D.Z. Glyceryl trinitrate ointment for the treatment of chronic anal fissure : results of a placebo-controlled trial and long-term follow-up. *Dis. Colon Rectum*, 1999, **42** : 1000-1006.
24. ALTOMARE D.F., RINALDI M., MILITO G., ARCANA F., SPINELLI F., NARDELLI N., SCARDIGNO D., PULVIRENTI-D'URSO A., BOTTINI C., PESCATORI M., LOVERGLIO R. Glyceryl trinitrate for chronic anal fissure : healing or headache ? Results of a multicenter, randomised, placebo-controlled, double-blind trial. *Dis. Colon Rectum*, 2000, **43** : 174-179.
25. RICHARD C.S., GREGOIRE R., PLEWES E.A., SILVERMAN R., BURUL C., BUIE D., REZNICK R., ROSS T., BURNSTEIN M., O'CONNOR B., MUKRAJ D., MC LEOD R. Internal sphincterotomy is superior to topical nitroglycerin in the treatment of chronic anal fissure : results of a randomised, controlled trial of the Canadian Colorectal Surgical Trials Group. *Dis. Colon Rectum*, 2000, **43** : 1048-1057.
26. ZUBERI B. F., RAJPUT M. R., ABRO H., SHAIKH S. A. A randomised trial of glyceryl trinitrate ointment and nitroglycerin patch in healing of anal fissures. *Int. J. Colorectal. Dis.*, 2000, **15** : 243-245.
27. EVANS J., LUCK A., HEWETT P. Glyceryl trinitrate vs lateral sphincterotomy for chronic anal fissure. Prospective, randomised trial. *Dis. Colon Rectum*, 2001, **44** : 93-97.
28. WERRE A.J., PALAMBA H.W., BILGEN E.J., EGGINK W.F. Isosorbide dinitrate in the treatment of anal fissure : a randomised, prospective, double-blind, placebo-controlled trial. *Eur. J. Surg.*, 2001, **167** : 382-385.
29. KOCHER H.M., STEWARD M., LEATHER A.J.M., CULLEN P.T. Randomised clinical trial assessing the side-effects of glyceryl trinitrate and diltiazem hydrochloride in the treatment of chronic anal fissure. *Br. J. Surg.*, 2002, **89** : 413-417.
30. LIBERTINY G., KNIGHT J., FAROUK R. Randomised trial of topical 0.2% glyceryl trinitrate and lateral internal sphincterotomy for the treatment of patients with chronic anal fissure : long-term follow-up. *Eur. J. Surg.*, 2002, **168** : 418-420.
31. BAILEY H.R., BECK D., BILLINGHAM R., BINDEROW S., GOTTESMAN L., HULL T., LARACH S., MARGOLIN D., MILSOM J., POTENTI F., RAFFERTY J., RIFF D., SANDS L., SENAGORE A., STAMOS M., YEE L., YOUNG-FADOK T., GIBBONS R. A study to determine the nitroglycerin ointment dose and dosing interval that best promote the healing of chronic anal fissures. *Dis. Colon Rectum*, 2002, **45** : 1192-1199.
32. SCHOLEFIELD J.H., BOCK J.U., MARLA B., RICHTER H.J., ATHANASIADIS S., PRÖLS M., HEROLD A. A dose finding study with 0.1%, 0.2% and 0.4% glyceryl trinitrate ointment in patients with chronic anal fissures. *Gut*, 2003, **52** : 264-269.
33. BIELECKI K., KOLODZIEJCZAK M. A prospective randomised trial of diltiazem and glyceryltrinitrate ointment in the treatment of chronic anal fissure. *Colorectal Disease*, 2003, **5** : 256-257.
34. EZRI T., SUSMALLIAN S. Topical nifedipine vs. topical glyceryl trinitrate for treatment of chronic anal fissure. *Dis. Colon Rectum*, 2003, **46** : 805-808.
35. WATSON S., KAMM M., NICHOLLS R., PHILIPS K. Topical glyceryl trinitrate in the treatment of chronic anal fissure. *Br. J. Surg.*, 1996, **83** : 771-775.
36. LUND J., SCHOLEFIELD J. Follow-up of patients with chronic anal fissure treated with topical glyceryl trinitrate. *Lancet*, 1998, 352 : 1681.
37. LYSY J., ISRAELIT-YATZKAN Y., SESTIERE-ITTAH M., KERET D., GOLDIN E. Treatment of chronic anal fissure with isosorbide dinitrate. Long term results and dose determination. *Dis. Colon Rectum*, 1998, **41** : 1406-1410.
38. JONAS M., LUND J., SCHOELFIELD J. Topical 0.2% glyceryl trinitrate ointment for anal fissures : long-term efficacy in routine clinical pratice. *Colorectal Disease*, 2002, **4** : 317-320.
39. PITT J., WILLIAMS S., DAWSON P. Reasons for failure of glyceryl trinitrate treatment of chronic fissure-in-ano. *Dis. Colon Rectum*, 2001, **44** : 864-867.
40. CHRISTIE A., GUEST J.F. Modelling the economic impact of managing a chronic anal fissure with a proprietary formulation of nitroglycerin (Rectogesic) compared to lateral internal sphincterotomy in the United Kingdom. *Int. J. Colorectal. Dis.*, 2002, **17** : 259-267.
41. CHRYSOS E., XYNOS E., TZOVARAS G., ZORAS O.J., TSIAOUSSIS J., VASSILAKIS S.J. Effect of nifedipine on rectoanal motility. *Dis. Colon Rectum*, 1996, **39** : 212-216.
42. COOK T.A., HUMPHREYS M.M., MC MORTENSEN N.J. Oral nifedipine reduces resting anal pressure and heals chronic anal fissure. *Br. J. Surg.*, 1999, **86** : 1269-1273.
43. CARAPETI E. A., KAMM M. A., PHILLIPS R. K. Topical diltiazem and bethanechol decrease anal sphincter pressure and heal anal fissures without side effects. *Dis. Colon Rectum*, 2000, **43** : 1359-1362.
44. ANTROPOLI C., PERROTTI P., RUBINO M., MATINO A., DE STEFANO G., MIGLIORE G., ANTROPOLI M., PIAZZA P. Nifedipine for local use in conservative treatment of anal fissures : preliminary results of a multicenter study. *Dis. Colon Rectum*, 1999, **42** : 1011-1015.
45. PERROTTI P., BOVE A., ANTROPOLI C., MOLINO D., ANTROPOLI M., BALZANO A., DE STEFANO G., ATTENA F. Topical nifedipine with lidocaine ointment vs active control for treatment of chronic anal fissure. *Dis. Colon Rectum*, 2002, **45** : 1468-1475.
46. KNIGHT J.S., BIRKS M., FAROUK R. Topical diltiazem ointment in the treatment of chronic anal fissure. *Br. J. Surg.*, 2001, **88** : 553-556.
47. JONAS M., NEAL K.R., ABERCROMBIE J.F., SCHOLEFIELD J.H. A randomised trial of oral vs topical diltiazem for chronic anal fissures. *Dis. Colon Rectum*, 2001, **44** : 1074-1078.
48. DAS GUPTA R., FRANKLIN I., PITT J., DAWSON P.M. Successful treatment of chronic anal fissure with diltiazem gel. *Colorectal Disease*, 2002, **4** : 20-22.
49. JONAS M., SPEAKE W., SCHOLEFIELD J. Diltiazem heals glyceryl trinitrate-resistant chronic anal fissures. A prospective study. *Dis. Colon Rectum*, 2002, **45** : 1091-1095.
50. GRIFFIN N., ACHESON A.G., JONAS M., SCHOLEFIELD J.H. The role of diltiazem in the treatment of chronic anal fissures that have failed glyceryl trinitrate therapy. *Colorectal Disease*, 2002, **4** : 430-435.
51. SAMPAIO C., FERREIRA J.J., SIMOES F. *et al.* Dysbot : a single-blind randomised parallel study to determine whether any differences can be detected in the efficacy and tolerability of two formulations of botulinum toxin type A- Dysport and Botox- assuming a ratio of 4 :1. *Mov. Disord.*, 1997, **12** : 1013-1018.
52. ODERGREN T., HJALTASON H., KAAKKOLA S. *et al.* A double blind, randomised, parallel group study to investigate the dose equivalence of Dysport and Botox in the treatment of cervical dystonia. *J. Neurol. Neurosurg. Psychiatry*, 1998, **64** : 6-12.
53. JOST W.H., SCHIMRIGK K. Use of botulinum toxin in anal fissure (letter). *Dis. Colon Rectum*, 1993, **36** : 974.
54. JOST W.H. One hundred cases of anal fissure treated with botulinum toxin : early and long-term results. *Dis. Colon Rectum*, 1997, **40** : 1029-1032.
55. JOST W.H., SCHRANK B. Chronic anal fissures treated with botulinum toxin injections : a dose-finding study with Dysport. *Colorectal Dis.*, 1999, **1** : 26-28.
56. MADALINSKI M., JAGIELLO K., LABON M., ADRICH Z., KRYSZEWSKI A. Botulinum toxin injection into only one point in the external anal sphincter : a modification of the treatment for chronic anal fissure. *Endoscopy*, 1999, **31** : S63
57. MADALINSKI M., SLAWEK J., DUZYNSKI W., ZBYTEK B., JAGIELLO K., ADRICH Z., KRYSZEWSKI A. Side effects of botulinum toxin injections for benign anal disorders. *Eur. J. Gastroenterol. Hepatol.*, 2002, **14** : 853-856.
58. GUI D., CASSETTA E., ANASTASIO G., BENTIVOGLIO A.M., MARIA G., ALBANESE A. Botulinum toxin for chronic anal fissure. *Lancet*, 1994, **344** : 1127-1128.
59. MASON P.F., WATKINS M.J., HALL H.S., HALL A.W. The management of chronic fissure-in-ano with botulinum toxin. *JR Coll. Surg. Edinb.*, 1996, **41** : 235-238.
60. MARIA G., BRISINDA G., BENTIVOGLIO A.R., CASSETTA E., GUI D., ALBANESE A. Botulinum toxin injections in the internal anal sphincter for the treatment of chronic anal fissure : long-term results after two different dosage regimens. *Ann. Surg.*, 1998, **228** : 664-669.
61. MARIA G., CASSETTA E., GUI D., BRISINDA G., BENTIVOGLIO A.R., ALBANESE A. A comparison of botulinum toxin and saline for the treatment of chronic anal fissure. *N. Engl. J. Med.*, 1998, **338** : 217-220.
62. MINGUEZ M., MELO F., ESPI A., GARCIA-GRANERO E., MORA F., LLEDO S., BENAGES A. Therapeutic effects of different doses of botulinum toxin in chronic anal fissure. *Dis. Colon Rectum*, 1999, **42** : 1016-1021.

63. MARIA G., BRISINDA G., BENTIVOGLIO A.R., CASSETTA E., GUI D., ALBANESE A. Influence of botulinum toxin site of injections on healing rate in patients with chronic anal fissure. *Am. J. Surg.*, 2000, **179** : 46-50.
64. BRISINDA G., MARIA G., SGANGA G., BENTIVOGLIO A.R., ALBANESE A., CASTAGNETO M. Effectiveness of higher doses of botulinum toxin to induce healing in patients with chronic anal fissures. *Surgery*, 2002, **131** : 179-184.
65. COLAK T., IPEK T., KANIK A., AYDIN S. A randomised trial of botulinum toxin vs lidocain pomade for chronic anal fissure. *Acta Gastroenterol. Belg.*, 2002, **65** : 187-190.
66. FERNANDEZ LOPEZ F., CONDE FREIRE R., RIOS RIOS A., GARCIA IGLESIAS J., CAINZOS FERNANDEZ M., POTEL LESQUEREUX J. Botulinum toxin for the treatment of anal fissure. *Dig. Surg.*, 1999, **16** : 515-518.
67. LYSY J., ISRAELIT-YATZKAN Y., SESTIERY-ITTAH M., WEKSLER-ZANGEN S., KERET D., GOLDIN E. Topical nitrates potentiate the effect of botulinum toxin in the treatment of patients with refractory anal fissure. *Gut*, 2001, **48** : 221-224.
68. MENTES B.B., IRKORUCU O., AKIN M., LEVENTOGLU S., TATLICIOGLU E. Comparison of botulinum toxin injection and lateral internal sphincterotomy for the treatment of chronic anal fissure. *Dis. Colon Rectum*, 2003, **46** : 232-237.
69. SIPROUDHIS L., SEBILLE V., PIGOT F., HEMERY P., JUGUET F., BELLISSANT E. Lack of efficacy of botulinum toxin in chronic anal fissure. *Aliment Pharmacol. Ther.*, 2003, **18** : 515-524.
70. LINDSEY I., JONES O., CUNNINGHAM C., GEORGE B., MORTENSEN N. Botulinum toxin as second-line therapy for chronic anal fissure failing 0.2 percent glyceryl trinitrate. *Dis. Colon Rectum*, 2003, **46** : 361-366.
71. MADALINSKI M., SLAWEK J., DUZYNSKI W., ZBYTEK B., JAGIELLO K., ADRICH Z., KRYSZEWSKI A. Side effects of botulinum toxin injection for begnin anal disorders. *Eur. J. Gastroenterol. Hepatol.*, 2002, **1** : 853-856.
72. MINGUEZ M., HERREBOS B., ESPI A., GARCIA-GRANERO E., SANCHIZ V., MORA F., LLEDO S., BENAGES A. Long-term follow-up (42 months) of chronic anal fissure after healing with botulinum toxin. *Gastroenterology*, 2002, **123** : 112-117.
73. American Gastroenterological Association. American Gastroenterological Association medical position statement : diagnosis and care of patients with anal fissure. *Gastroenterology*, 2003, **124** : 233-234.