Local Nitroglycerin for Treatment of Anal Fissures: An Alternative to Lateral Sphincterotomy?

Heinz Bacher, M.D, Hans-Jörg Mischinger, M.D,
Georg Werkgartner, M.D, Herwig Cerwenka, M.D, Azab El-Shabrawi, M.D., Johann Pfeifer, M.D, Wolfgang Schweiger, M. D.

From the Department of Surgery, Karl-Franzens~University, Graz, Austria

PURPOSE: Nitric oxide is an important neurotransmitter mediating internal anal sphincter relaxation. Patients suffering from fissure-in-ano were treated with topical nitroglycerine. The clinical evidence for therapeutic adequacy was examined in a prospective, randomized study. METHODS: The study included 35 patients with acute and chronic anal fissures. In Group A, including 20 patients with the clinical diagnosis of acute (12 patients) and chronic (8 patients) anal fissures, treatment consisted of topical nitroglycerine. Group B, consisting of 15 patients (10 acute and 5 chronic fissures), received topical anesthetic gel during therapy. Manometry was performed before and on days 14 and 28 in the course of topical application of either 0.2 percent glyceryl trinitrate ointment or anesthetic gel (lignocaine). Anal pressures were documented by recording the maximum resting and squeeze pressures. RESULTS: In 60 percent of cases treated with topical nitroglycerine (Group A, 11 acute (91.6 percent) and 1 chronic (12.5 percent)), anal fissure healed within 14 days, in contrast to Group B in which no healing was observed. The healing rate after one month was 80 percent (11 acute (91.6 percent); 5 chronic (62.5 percent)) in Group A and was significantly superior to Group B (healing rate, 40 percent: 5 acute (50 percent); 1 chronic (20 percent)). DISCUSSION: Previously increased maximum resting pressures decreased from a mean value of 110 to 87 cm H_2O. This represents a mean reduction of 20 percent ($P = 0.0022$). We also noted a significant decrease in squeeze pressures (from 177.8 to 157.9 cm H_2O (11 percent)). However, anal pressures did not decrease significantly in the four chronic fissure patients from Group A, whose fissures only healed after 28 days. Similarly to these Group A chronic fissure patients, no significant anal pressure reduction was observed in any Group B patients. Except for mild headache (20 percent), no side effects of treatment were reported. CONCLUSIONS: Topical application of nitroglycerine represents a new, easily handled, and effective alternative in the treatment of anal fissures. All of our patients reported a dramatic reduction in acute anal pain. However, it should be noted that a lack of sphincter tone reduction is a likely reason for the great tendency of chronic anal fissures to recur. [Key words: Anal fissure; Topical glyceryl trinitrate; Clinical and manometric results]

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Address reprint requests to Dr. Bacher: Hofstatt 3, A-8042, Graz, Austria.

Glyceryl trinitrate belongs to the group of organic nitrates. Their action derives from their metabolic conversion to nitric oxide in the vascular smooth muscle cell.[1] The primary catalytic activity of this process appears to reside in the cellular plasma membrane. In addition to cellular biochemical reactions, organic nitrates also produce systemic biochemical effects by altering the body's neurohormonal status. Nitric oxide plays an important role in nonadrenergic, noncholinergic nerve-mediated relaxation of gastrointestinal smooth muscle.[2-6] Glyceryl trinitrate, a nitric oxide donor, is commonly used as a sublingual drug or as a topical gel in the treatment of angina pectoris (Nitrolingual, Nitronal Gel, Pohl-Boskamp, Hohenlockstedt, Germany).[7] Passive diffusion through normal skin leads to therapeutic plasma levels, mediating relaxation of the smooth muscle after a few minutes. This has been successfully demonstrated by induction of penile erections in cases of impotence, successful treatment of Raynaud's phenomenon and severe shoulder-hand syndrome, pretreatment for laryngoscopy and tracheal intubation, and as a healing aid for chronic skin ulcers.[8-12] Various side effects such as headache, orthostatic hypotension, cardiac arrhythmia, vomiting, nausea, and methemoglobinemia have been described with oral nitrates.[13,14] Topical application of nitroglycerine causes a lowering of internal anal sphincter pressure in normal human subjects.[15,16] Increased internal sphincter pressure is associated with the occurrence of anal fissure, an ulcer that is probably of an ischemic origin, distal to the dentate line, most often located in the posterior midline anoderm.[17] Injury to the anoderm causes a superficial acute fissure, which very often becomes chronic with sentinel pile, hypertrophied papilla, and

visible internal sphincter fibers at the wound base (Fig. 1).

PATIENTS AND METHODS

Between October 1994 and August 1995, a prospective, randomized study was performed including a total of 35 patients (16 males) who were treated on the basis of a clinical diagnosis of acute (22 patients) or chronic (13 patients) anal fissure. Criterion for an acute fissure was a benign superficial ulcer in the anal canal involving only the anal mucosa below the dentate line.[18] Reported symptoms of anal pain and bleeding during and after defecation were limited for up to four to six weeks before admission.

Commonly, the transverse fibers of the internal sphincter were not seen. A chronic fissure was defined as a benign indurated ulcer with undermined edges and a visible internal sphincter. Additionally, a characteristic edematous skin tag (sentinel pile) at its lower end and a hypertrophied anal papilla at the inner margin on the dentate line could be seen (Fig. 1). Patients had suffered from symptoms for more than a few weeks.[19,20] Criteria for healing were a full re-epithelialization of the anal canal mucosa and a nearly complete reduction of clinical symptoms. No patients in either group reported any prior anorectal surgery. Patients with additional anorectal diseases were excluded from this study. The majority (90 percent) of patients had a posterior midline fissure. We noted only four women with an acute fissure in the anterior midline position. Median history of symptoms (pains, bleeding after defecation) was six months (4 weeks to 36 months). Eight patients suffered from constipation, and three had experienced transient diarrhea (Table 1). Group A included 20 patients (9 males; mean age, 35 (range, 22-48) years) with clinical diagnoses of acute (12 patients) or chronic (8 patients) anal fissure. They received topical nitroglycerine therapy. The 15 patients in Group B (7 males; mean age, 36 (range, 20-53) years; 10 acute and 5 chronic fissures) received a topical anesthetic gel alone (Xylocaine™ 2 percent Gel, Astra Chemicals, Wedel, Holstein, Germany). Manometry and physical examination were performed before and 14 and 28 days after institution of treatment. This consisted of topical application by fingertip of either 0.2 percent glyceryl trinitrate ointment or lignocaine anesthetic gel to the anus and into the anal canal three times daily. The ointment was prepared from 2 g of Percutol™ (2 percent glyceryl trinitrate; Coma Pharma Wien, Cusi Laboratories Ltd., Haslemere, United Kingdom) and was diluted to 20 g in fatty yellow petroleum jelly. Patients were instructed to keep the paste in the refrigerator and to note any side effects such as headache or allergic skin reactions. Manometry was performed with the patients lying on the left side. Maximum resting pressures and maximum squeeze pressures were measured with a water-perfused catheter (Zinetics Medical Inc., Salt Lake City, UT), applying a continuous and a stepwise pull-through technique. Outcome assessments were classified by investigators without knowledge of the patients' treatment assignments. All results were recorded using a

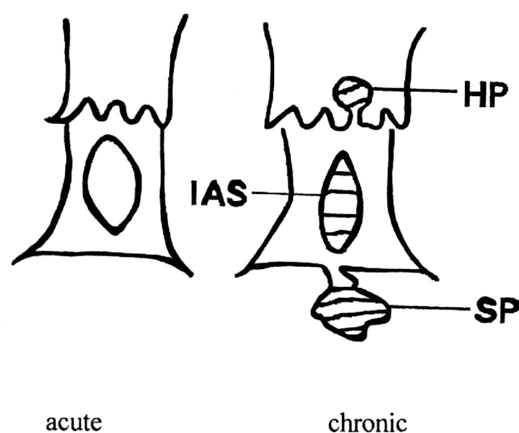

Figure 1. Clinical aspect of acute and chronic fissures. IAS = internal anal sphincter; HP = hypertrophied papilla; SP = sentinel pile.

Table 1.
Patient Characteristics

	Group A (Nitroglycerin)	Group B (Lignocaine)
No. of patients	20	15
Mean age (range)	35 (22–48)	36 (20–53)
Gender ratio (M:F)	9:11	7:8
Diagnosis, no. (%)		
Acute fissures	12 (60)	10 (66.7)
Chronic fissures	8 (40)	5 (33.3)
Location (%)		
Posterior midline	90	86.7
Anterior midline	10	13.3
Symptoms (%)		
Pain	85	86
Bleeding	75	73.3
Bowel habit (%)		
Constipation	25	20
Diarrhea	10	6.7
Length of history (wk)	24	22

computerized recording device (Polygram Software, Synectics Medical, Stockholm, Sweden). The catheter was inserted into the rectum without prior digital examination and withdrawn in 1 cm increments. The highest values were recorded as the maximum resting and squeeze pressures.

Data Analysis

Patients were randomized into two groups of equal size by computer generating a simple randomization list and replacing it by a new list until balanced groups were obtained.[21] Five cases in Group B had to be excluded because they were lost to follow-up. One male with chronic fissure underwent sphincterotomy in another hospital, three females (two chronic, one acute fissure) and one male with an acute fissure did not come to scheduled manometric follow-up examinations. Statistical analysis was performed using Wilcoxon's rank test. The groups were compared by Student's unpaired t-test. A 95 percent confidence interval was considered to be significant.

RESULTS

Sixty percent of anal fissures treated with topical nitroglycerine (Group A, 11 acute (91.6 percent) and 1 chronic (12.5 percent)) healed within 14 days. In contrast, no fissures healed in Group B during this time interval. The healing rate after one month was 80 percent in Group A (11 acute (91.6 percent); 5 chronic (62.5 percent)). This was significantly superior to a 40 percent rate in Group B (5 acute (50 percent); 1 chronic (20 percent)). In the remaining four patients (20 percent) of Group A (3 chronic, 1 acute) and nine patients (60 percent) of Group B (5 acute, 4 chronic), anal fissures did not heal within four weeks. Those patients who required surgery (lateral sphincterotomy) experienced complete healing after three to four weeks postoperatively. Furthermore, patients from Group A whose fissures had healed by day 14 showed a significant (P = 0.0022) decrease in maximum resting pressure from the levels before therapy (mean value, 110 (range, 78-156) to 87 (range, 60-120) cm H_2O). This represents a mean reduction of 20 percent after 14 days (Fig. 2). In these cases, we also noted a significant decrease in squeeze pressures from 177.8 (range, 135-268.5) to 157.9 (range, 120-240) cm H_2O (11.2 percent; P = 0.0022). However, in the four additional patients from Group A with chronic fissures that healed by day 28, there was no significant decrease in anal pressures (Fig. 3). Similarly to these Group A patients with chronic fissures, none of the Group B patients showed any significant reduction of anal pressures, with the maximum resting pressure decreasing from 98.8 (range, 80-110) to 91.2 (range, 75-100) cm H_2O (7.6 percent; P = 0.0679) and squeeze pressure from 190 (range, 160-220) to 180 (range, 160-210) cm H_2O (5.2 percent; P = 0.1088). After 28 days, the difference in mean maximum resting pressures between Groups A and B was significant (P = 0.0276; Table 2). No significant difference in mean squeeze pressures (P = 0.7898) was found. Four patients (20 percent) in Group A reported transient mild headaches. No other systemic or local symptoms were observed. In Group B, 40 percent of fissures (5 acute (50 percent); 1 chronic (20 percent)) were treated with topical anesthetic gel and healed within 28 days. Anal pressures did not decrease significantly. in all healed anal fissures, mean maximum resting pressures decreased from 105 (range, 93-122) to 102.5 (range, 82-125) cm H_2O after 14 days (2.38 percent; P = 0.4652) and further to 100 (range, 85-119) cm H_2O after 28 days (4.76 percent; P = 0.1730;

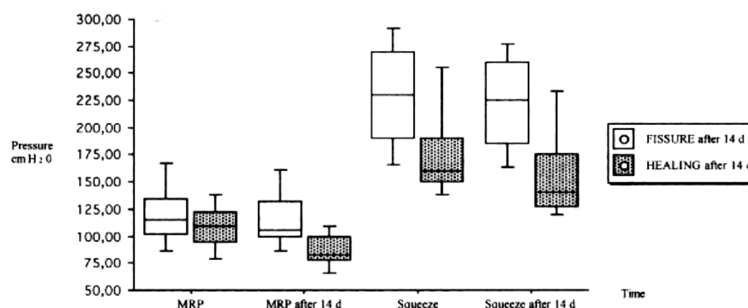

Figure 2. Maximum resting pressure (MRP) and squeeze pressure before and 14 days after topical application of 0.2 percent glyceryl trinitrate ointment (Group A). Significant decrease of pressures in healed fissures (*P* = 0.0022; Wilcoxon's test).

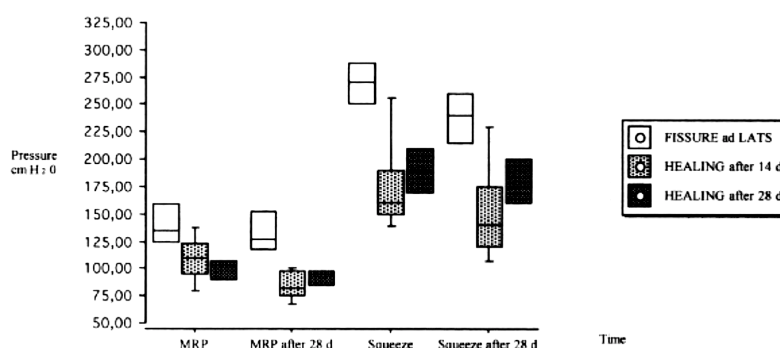

Figure 3. Maximum resting (MRP) and squeeze pressures before and 28 days after topical application of 0.2 percent glyceryl trinitrate ointment (Group A). No significant decrease of pressures in chronic fissures healed after 28 days and in nonhealing fissures (ad lateral sphincterotomy).

Table 2.
Results of Manometry

	Group A (Nitroglycerin)	Group B (Lignocaine)		
Initial median MRP (cm H_2O)	110 (78–156)	105 (93–122)		
MRP after 14 days	87 (60–120)	102.5 (82–125)	$P = 0.0822$	NS
MRP after 28 days	85.62 (60–100)	100 (85–119)	$P = 0.0276$	*
Initial median MSP (cm H_2O)	177.8 (135–268.5)	170 (142–220)		
MSP after 14 days	157.92 (120–240)	166.5 (146–200)	$P = 0.6347$	NS
MSP after 28 days	158.75 (100–230)	163.5 (140–198)	$P = 0.7898$	NS

MRP = maximum resting pressure; MSP = maximum squeezing pressure; NS = not significant.
* Significant difference in MRP pressures.

Table 2). Similarly, no significant differences in maximum squeeze pressures could be shown after 14, (2.05 percent; P = 0.5002) and 28 days (3.82 percent; $P = 0.0747$). No side effects from the therapy were reported in Group B.

DISCUSSION

Several animal studies show nitric oxide and vasoactive intestinal polypeptide to be important inhibitory neurotransmitters mediating relaxation of the internal anal sphincter.[2-6] These results have been confirmed in a recent study using human rectal circular smooth muscle. The aim of our study was to evaluate the functional influence of nitric oxide on anal sphincter mechanisms by using nitroglycerine in the therapeutic management of anal fissures. Our results demonstrate that the most effective outcome was observed in patients with an acute anal fissure treated with 0.2 percent glyceryl trinitrate ointment. In this group, we had a significant and high (91.6 percent) healing rate within two weeks. In contrast, the healing rate for chronic anal fissures was significantly reduced and prolonged. The functional influence of nitroglycerine on acute anal fissures was indirectly demonstrated by a significant continuous reduction of resting pressures during 14-day and 28-day intervals. The efficacy of nitroglycerine may result from its direct reduction of sympathetic tone, raised in response to persistent pain from the anal fissure. The healing rates we observed in acute fissures probably derive from a combination of improved vascular perfusion and a normalization of the basal sphincter tone. Other authors also reported a 27 percent reduction of mean maximum resting pressure following topical application of glyceryl trinitrate.[16] A small clinical study reported an 83 percent healing rate of superficial anal fissures.[23] These results were based on patient interviews only; nevertheless, they compare favorably with our own. In chronic fissures, we found a significantly reduced healing rate associated with elevated sphincter pressure. An attractive hypothesis explaining this circumstance is that elevated sphincter pressure may cause ischemia of the anal lining, which in turn may be responsible for the pain of anal fissures and their failure to heal.[24-27] Conversely, failure to reduce sphincter tone may be a reason for the greater tendency of chronic fissures to recur. Another factor in this tendency for recurrence may well be the po-

Table 3.
Symptomatic Pain Reduction After Topical Treatment (%)

Symptomatic Pain Reduction	Group A (Nitroglycerin)			Group B (Lignocaine)			
	I	II	III	I	II	III	
Acute fissures	11 (91.6)	—	1 (8.4)	—	5 (50)	5 (50)	*P* = 0.0289*
Chronic fissures	1 (12.5)	4 (50)	3 (37.5)	—	1 (20)	4 (80)	*P* = 0.0384*

I = immediately; II = delayed (>14 days); III = no pain reduction.
* Significant difference in symptomatic pain reduction.

tential of a functional disorder to develop an organic manifestation with time. Interestingly, the patients applying nitroglycerine (Group A) reported greater amelioration of pain than those using the local anesthetic gel (Group B; Table 3). This unexpected observation may result from the additional effect of nitroglycerine of improving vascular perfusion. In our study, we were able to demonstrate that topical nitroglycerine is an effective alternative to the usual conservative treatment[28-30] of acute anal fissures and a viable symptomatic therapy to reduce pain in chronic fissures. However, topical nitroglycerine treatment will not be able to obviate surgery in patients with chronic fissures or in those with an acute fissure and persistently elevated resting pressure.

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