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ORIGINAL CONTRIBUTIONS

Treatment of Benign Anal Disease with Topical Nitroglycerin

Stephen R. Gorfine, M.D.

From The Mount Sinai School of Medicine, New York, New York

PURPOSE: Fissure-in-ano and acutely thrombosed external hemorrhoids are common, benign anal conditions, usually characterized by severe anal pain. Internal anal sphincter hypertonia appears to play a role in the etiology of this pain. Nitric oxide has recently been identified as the "novel biologic messenger" that mediates the anorectal inhibitory reflex in humans. This report documents a therapeutic role for nitroglycerin, a nitric oxide donor, in the treatment of acutely thrombosed external hemorrhoids and anal fissure. METHODS: Five patients with thrombosed external hemorrhoids and fifteen patients with anal fissure or ulcer were identified. A treatment regimen that included 0.5 percent nitroglycerin ointment applied topically to the anus was instituted. After one week of therapy, all patients were re-examined and questioned regarding pain relief and side effects of treatment. Fissure patients were followed for eight weeks or until healing occurred. RESULTS: All patients reported dramatic relief of anal pain following application of nitroglycerin. Pain relief lasted from two to six hours. Complete healing of fissures occurred within two weeks in ten patients and within one month in two patients. One patient, whose fissure had not healed completely within two weeks requested surgical sphincterotomy. Two patients remained with persistent anal ulcers despite two months of therapy. Both, however, were pain-free. Side effects were limited to transient headache in 7 of 20 patients. CONCLUSION: Topically applied nitroglycerin ointment appears to have a therapeutic role in the treatment of thrombosed external hemorrhoids and anal fissure. [Key words: Hemorrhoid; Anal fissure; Anal sphincter; Nitric oxide; Nitroglycerin]

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Fissure-in-ano is a common anal disorder, which manifests as a linear ulcer typically occurring in the posterior midline anoderm, distal to the dentate line. A fissure that has developed signs of chronicity (associated "sentinel pile," hypertrophied papilla, visible internal sphincter fibers at the base of the wound) is called a chronic anal fissure or anal ulcer.

Acute thrombosis of an external hemorrhoid (TEH) is also a common anal condition, usually characterized by a tender perianal mass. The thrombus forms within the lumen of the external hemorrhoidal vessels.[1] External hemorrhoidal thrombosis may be associated with an episode of constipation,[2] but often there is no history of antecedent straining or exertion.[3]

Both anal fissure and TEH are notable for associated pain that is disproportionately severe given the typical size of these lesions. The reason for this is unknown. However, physical examination of patients suffering from TEH and anal fissure often shows internal anal sphincter hypertonia or spasm. It, therefore, seems possible that an abnormal pressure response of the internal anal sphincter (IAS) plays a role in the pain of these lesions. This hypothesis seems plausible in light of evidence that hypertonia of the IAS plays an etiologic role in the development of hemorrhoidal disease and anal fissure.[4-10]

Work by Shafik[7] demonstrated increased electromyographic activity in the IAS associated with TEH. In this study, relief of pain by warm sitz bath was associated with relaxation of the IAS. Similarly, sphincterotomy reduces anal canal pressure, relieving pain and promoting healing in the setting of anal fissure.[6]

Recent evidence suggests that the IAS is innervated by nitric oxide-releasing nerves.[11-15] Stimulation of

Address reprint requests to Dr. Gorfine: 25 East 69th Street, New York, New York 10021.

these nerves releases the chemical mediator, nitric oxide (NO), which causes the IAS to relax. Exogenous NO will cause a similar response.[16] Organic nitrates, such as nitroglycerin, are degraded by cellular metabolism, liberating NO.[16] Nitroglycerin (NTG) applied topically to the anus has been shown to cause a lowering of IAS pressure in normal human subjects.[17, 18] It, therefore, seemed likely that NTG applied topically to the anus would relieve pain associated with thrombosed external hemorrhoids and anal fissure and possibly promote healing of anal fissures.

MATERIALS AND METHODS

TEH Group

Five patients (3 women and 2 men; ages 23–51 years) were recruited to participate in a trial of topical NTG treatment for acutely thrombosed external hemorrhoids. Duration of symptoms ranged from two to four days. Anorectal examination of all patients revealed typically thrombosed external hemorrhoids in one (three patients) or two (two patients) anal quadrants. None of these patients had evidence of internal hemorrhoidal thrombosis, fissure, abscess, or fistula. All of these patients had used one or more topical preparations (Anusol®, Anusol HC®, Parke-Davis, Morris Plains, NJ; Preparation H®, Whitehall, Madison, NJ; ProctoCream-HC®, Reed & Carnrick, Jersey City, NJ) without symptomatic relief.

Fissure Group

Fifteen patients (10 women and 5 men; ages 23–61 years) were recruited to participate in a trial of topical NTG treatment for anal fissure or ulcer. Duration of symptoms ranged from two days to two years. Three patients had posterior midline anal ulcers, 11 had acute, posterior midline anal fissures, and 1 had an acute, anterior midline anal fissure. Two patients had a history of Crohn's ileitis. None of these patients had a history of recent anal surgery.

After obtaining informed consent from each participant, a program of therapy was begun. Treatment consisted of psyllium seed (12 gm daily) and sitz baths as needed. Approximately 500 to 1,000 mg of 0.5 percent NTG ointment was applied with the finger to the external anus and distal anal canal four or more times daily and after bowel movements. All patients were interviewed and examined one week after initiating therapy. Fissure patients were re-examined three weeks after initiating therapy and every one to two weeks thereafter until either the fissure had healed or eight weeks of therapy had passed.

RESULTS

TEH Group

All patients reported total or near total relief of anal pain within two to three minutes of NTG application. NTG was especially useful in relieving the pain that typically occurred following defecation. Each application of NTG relieved pain from four to six hours in all patients. All patients reported the need for fewer sitz baths. NTG was used for an average of three (range, 2–6) days. Resolution of the thrombus appeared to follow the usual time course. Side effects were limited to transient headache in two patients (40 percent).

Fissure Group

All patients reported dramatic relief of anal pain within three to four minutes of NTG application. Pain was relieved promptly after application of NTG, and the effect was sustained from two to six hours. Most patients reported that NTG was especially useful in relieving the pain that occurred following defecation. Fourteen patients applied the ointment every four to six hours while awake. One patient required application every two to three hours to achieve satisfactory pain control.

Of the 12 patients with superficial anal fissures, 10 (83 percent) were healed within two weeks. This group included the two patients with Crohn's disease. Two patients who had discontinued NTG treatment after complete healing at two weeks had recurrences of their fissures. Both responded to another two weeks of therapy with no further recurrence of symptoms. The remaining two patients with anal fissures healed after four weeks of continuous treatment.

One patient with a posterior anal ulcer was improved but not completely healed after two weeks of therapy. She requested sphincterotomy, which resulted in complete healing within another month. Two patients with posterior anal ulcers were improved but not completely healed after two months of therapy. Sphincterotomy was refused in both cases. Side effects were limited to mild, transient headache in five patients (33 percent).

DISCUSSION

This initial report describes the first clinical application of nitric oxide in the treatment of benign anal

diseases. Theoretic rationale behind this intervention is irresistible. Clear and convincing data indicate that endogenously secreted neuronal NO mediates relaxation of the human internal anal sphincter.[15] Exogenous nitric oxide, such as that produced by cellular metabolism of organic nitrates, will also produce IAS relaxation in normal humans.[17, 18]

Patients in this study experienced dramatic pain relief after the first dose of topically applied NTG. Others have shown that reduction of IAS pressure by sphincterotomy, sphincter stretch, and paralysis by botulinum toxin relieves fissure-associated anal pain.[6, 19] Similarly, Shafik[7] noted decreased IAS pressure and electromyographic activity associated with pain relief following hot sitz baths in patients with TEH. It seems highly probable that the pain relief experienced by patients in this study was caused by NO-mediated relaxation of the IAS.

Nitroglycerin ointment applied topically to the anus was well tolerated by most patients in this study. Seven of 20 subjects (35 percent) experienced headaches after topical anal application of NTG ointment. Headaches were generally self-limited and abated after about 15 minutes.

Nitroglycerin has been used as an antianginal agent since 1879, and its side effects are well known. Adverse reactions to nitroglycerin are related to its activity as a vasodilator and are proportional to dosage.[20] Headache is the most common complication of nitrate therapy of coronary artery disease. Other potential side effects of NTG therapy such as hypotension, syncope, rebound hypertension, crescendo angina, and allergic dermatitis were not observed in this small sample. It is possible that the relatively small NTG dosages used in this study did not produce clinically significant systemic levels and hence few extra-anal effects were noted.

It seems likely that pain associated with anal fissure and thrombosis of external hemorrhoids is caused at least in part by hypertonicity of the IAS. This study suggests that NTG therapy is superior to traditional modalities[21, 22] for relief of pain in the setting of TEH and relief of pain and time to healing in the setting of anal fissure.[23, 24] The reported pain relief by this group of patients was impressive in its degree, consistency, and proximity to NTG therapy. Controlled, randomized, prospective trials are clearly warranted.

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Invited Editorial

To the Editor—The association of internal sphincter hypertonicity with thrombosis of external hemorrhoids is a new concept, which, if substantiated, may help direct therapy toward more rapid relief of the associated pain. Dr. Gorfine presented an admittedly small series of patients in whom symptomatic relief was so dramatic and sustained as to justify publication. He chose for his study group patients with whose pain is self-limited and for whom other traditional measures (sitz baths, psyllium seed) were simultaneously prescribed. The results, further, are based on patient interviews rather than any objective data, such as anorectal manometry or even physical examination. However, the results are provocative. I wonder about the following points. First, why was a group with anal fissure rather than thrombosis of external hemorrhoids not chosen for such a pilot project? The association of internal sphincter spasm and fissures is better known, and the effect should be even more dramatic. Second, how is nitroglycerine paste absorbed (through the skin or the anoderm)? Third, can a similar effect be obtained by sublingual use of the drug? And last, how much of the reported benefit can be attributed to the placebo effect? It does seem, from the data presented, that a controlled, randomized, and prospective study is warranted, but this should be possible with relative ease, minimal expense, and rapid patient accrual. It is hoped that results of such a study can be reported in these pages in the very near future.

Richard P. Billingham, M.D.
Seattle, Washington

The Author Replies

To the Editor—Dr. Billingham's skepticism is appropriate, given the small number of patients and dramatic results reported in this preliminary study. However, nitroglycerin therapy for anal fissure and acute hemorrhoidal disease is based on sound experimental evidence. A recent report documents significantly increased IAS pressure in patients with fissures and hemorrhoids compared with normal controls.[1] Certainly in the setting of anal fissure and most probably in the setting of acutely thrombosed external hemorrhoids, pain is in some way related to increased intra-anal pressure. The theory that fissure pain is caused by relative anodermal ischemia[2] is particularly attractive in light of the results obtained with NTG therapy.

In those patients with TEH and fissure, pain relief is manifest within five minutes of the initial dose of NTG. This result has been confirmed by in-office application of the first dose. Pre-NTG application of white petrolatum (placebo) has not produced the same degree of pain relief in either TEH or fissure patients. Manometric data confirm that pain relief is temporally associated with a decline in anal pressure (Fig. 1). That TEH and anal fissures are usually self-limited problems is not relevant to pain relief in the acute situation.

Transcutaneous nitroglycerin therapy for angina pectoris has been used since the 1950s. Absorption of NTG through intact, normal skin occurs by passive diffusion through the stratum corneum.[3] When used

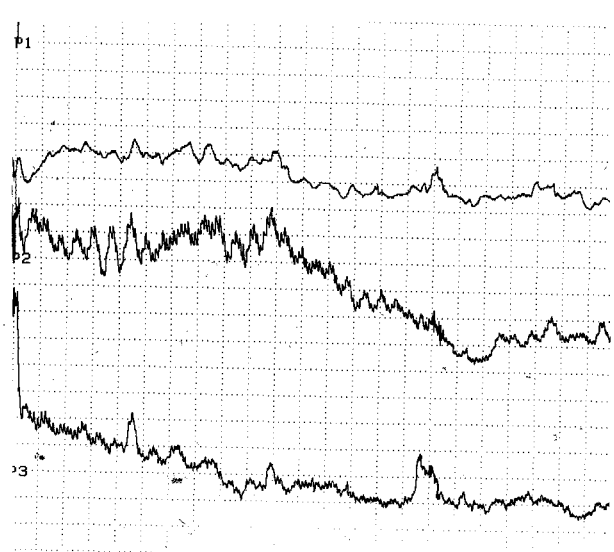

Figure 1. Manometric data confirm that pain relief is temporally associated with a decline in anal pressure.

as a two percent ointment for treatment of angina pectoris, the amount of NTG available for absorption usually exceeded skin permeability, and plasma levels of 0.1 μg/liter to 1 μg/liter were measured. Systematic studies involving skin site of NTG application and resultant plasma levels have not been performed. In view of the fact that perianal and intra-anal application of NTG results in headache in some patients, it seems safe to assume that the mechanism underlying cutaneous absorption also applies to the perianal skin and anoderm.

As of this writing, 43 patients with fissure/ulcer and 27 patients with TEH have been treated with nitroglycerin. Among the fissure/ulcer patients, 41 (93 percent) reported pain relief within five minutes of application. Physical examination showed complete healing of the fissure or ulcer in four weeks or less in 30 patients (70 percent). Of the TEH patients, 25 (92 percent) reported symptomatic relief with the initial dose. Resolution of the thrombus followed the usual three-week to four-week time course. Interestingly, I have treated two fissure patients who were taking oral nitrates (isosorbide dinitrate) for relief of angina. Neither noted any diminution of symptoms associated with their nitrate use, and both responded symptomatically to topical anal NTG.

I hope to further support the conclusion that NTG effectively relieves pain in the setting of TEH and anal fissure and promotes healing in the setting of fissure/ulcer with the results of a randomized, double-blind study currently in the final stages of planning.

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Stephen R. Gorfine, M.D.
New York, New York