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A randomized trial of glyceryl trinitrate ointment and nitroglycerin patch in healing of anal fissures

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Abstract Mean maximum anal resting pressure is directly related to the activity of the smooth muscles of the internal and external sphincters and has been found to be increased in the patients of anal fissure. It has been shown that blood flow at the posterior midline of anoderm is inversely related to the mean maximum anal resting pressure, and topical application of glyceryl trinitrate (GTN) ointments is a very successful treatment. This randomized study was designed to evaluate the relative value of a nitroglycerin patch applied at a distance from the fissure site in healing anal fissure compared to GTN ointment and compared to surgical treatment. Forty-two consecutive patients with chronic anal fissure of more than 4 months' duration were randomized into two equally sized groups: those in group A received 0.2% GTN ointment while those in group B received a 10-mg

nitroglycerin patch for 8 weeks. Patients were also asked to rate their pain intensity on a scale of 0–10. Five patients were excluded for various reasons; results were analyzed for the remaining 37 patients (group A, $n=18$; group B, $n=19$). A control group C consisted of 12 patients who underwent surgical treatment. Fissures healed completely in 12 of 18 (66.7%) patients in group A, 12 of 19 (63.2%) in group B and 11/12 (91.7%) in group C. The healing rates in groups A and B did not differ significantly ($P=0.7$), nor was there a difference between these and surgical group C ($P=0.13$). The local application of GTN ointment and the nitroglycerin patch are both effective, economical, and alternative treatment options for most patients with anal fissures.

Keywords Anal fissure · Glyceryl trinitrate · Nitroglycerin

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Introduction

Anal fissure is a common problem and is associated with severe pain and rectal bleeding. It is a longitudinal or elliptical ulcer in the anoderm, extending below the dentate line to the anal verge. One of the many suggested causes of anal fissure is mean maximum anal resting pressure (MMARP), which is directly related to the activity of the smooth muscles of the internal and external sphincters [1]. MMARP has been found to be increased in patients with anal fissure [1]. Another cause may be ischemia of the anal lining due to increased MMARP,

causing pain and ulceration; it also thwarts efforts to heal of the fissure [2]. Doppler studies [3] have shown that blood supply to the posterior commissure is relatively poor, and this is the site at which 90% of fissures occur. It has also been shown that blood flow at the posterior midline of anoderm is inversely related to MMARP: the higher the pressure, the lower the blood flow [3].

MMARP is decreased by the lateral sphincterotomy, which is the most commonly performed operation for anal fissures [4], but this entails has a high incidence of fecal incontinence [5, 6, 7]. Recently it has been shown that nitric oxide is one of the most important inhibitory

neurotransmitters in the internal sphincter [8, 9]. Many studies have shown that the topical application of glyceryl trinitrate (GTN) can cause relaxation of the internal anal sphincter and thus help in healing of the fissures [10, 11]. GTN is thought to provide nitric oxide to the sphincter and thus mediate its effects [10].

The present study compared topical application of GTN ointment for healing anal fissure to treatment using a nitroglycerin patch applied at the distance from the fissure site and to surgical treatment.

Materials and methods

Forty-two consecutive patients with chronic anal fissure of more than 4 months' duration were included in this study conducted over a period of 1 year. Excluded were patients already on nitrate treatment due to cardiac problems, pregnant women, patients with migraine, and those with inflammatory bowel disease. After selection and initial evaluation patients were randomized to either of two equally sized groups. Patients in group A (aged 47.7 ± 8.2 years) received GTN ointment while those in group B (aged 48.4 ± 6.0 years) were treated by nitroglycerin patch. GTN ointment was prepared by pharmacist using yellow paraffin to attain the 0.2% GTN concentration. A control group C comprised 12 patients (aged 45.6 ± 7.9 years) undergoing surgical sphincterectomy. The mean duration of the anal fissure before entering this study was 11.4 ± 4.8 weeks in group-A (range 5–20), 11.6 ± 5.6 weeks in group B (range 5–24), and 10.4 ± 3.2 weeks in group C (range 6–15). Four patients (two each groups A and B) did not complete the follow-up and were excluded; a further patient from group A was excluded for violating the study protocol. The results were thus analyzed for the remaining 37 patients (18 in group A, 19 in group B).

Patients were shown how to apply the ointment correctly. They were advised to take 0.5 ml the ointment (a pea-sized quantity) and apply it manually over the skin of anal verge circumferentially around the anal opening three times daily for 8 weeks. Caution was advised not to apply it intra-anally. The nitroglycerin patch of 10 mg/24 h was applied below umbilicus at the flanks of abdomen and changed daily. It was advised that the patch should be kept applied for all 24 h of the day. Patients were also given a daily diary card for rating the severity of pain on a scale of 0–10 (0=no pain, 10=maximum pain). Patients were followed up for clinical examination fortnightly. If at the end of 8 weeks the fissure had not healed, but there was clinical improvement, the treatment was continued for a further 6 weeks before the case was considered as a treatment failure. All patients in whom treatment failed were offered surgical treatment. Those who could not tolerate the ointment treatment were also offered surgical treatment and were considered as treatment failure in the analysis. During the period of study all patients were advised to take a high-fiber diet of 20 g/day and senna tablets (Senocot) twice daily with a full glass of water or lactulose 15 ml \times h.s. All patients were also advised to drink ample amounts of water.

The groups were compared in terms of means \pm SD; statistical significance was set at the level of $P < 0.05$ and power 0.9. For a difference of 10% in the outcome of the two groups the required sample size would be 21 in each group.

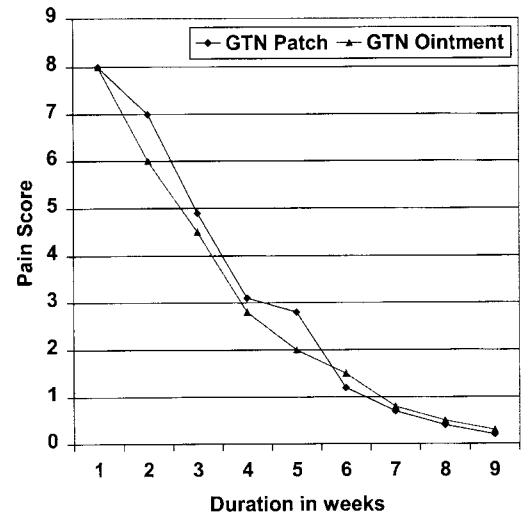


Fig. 1 Plot of mean pain score over time

Results

Fissures healed completely in 67% of patients in group A (12/18) and in 63% of those in group B (12/19; $P=0.7$, Fisher's exact test). Fissures healed in 92% of patients (11/12) in group C (91.7%); the difference to groups A and B was also not statistically significant ($P=0.13$; Pearson's χ^2). The mean healing time was 7.75 ± 4.2 weeks (range 3–19) in group A and 8.7 ± 4.0 weeks (range 5–20) in group B; 95% (CI -4.5 to 2.6; $P=0.56$, t test). A 50% reduction in the mean pain score was observed at 3 weeks; this is plotted in Fig. 1. Side effects included headaches in 72% of patients in group A and 63% in group B, but these were of mild intensity and tolerable; there was no instance of treatment being discontinued for this reason. Two patients (6%) reported transient loss of flatus control, which improved when therapy was completed. No fecal incontinence was reported.

Discussion

Our findings confirm the nitroglycerin patch to be as effective in treating chronic anal fissures as GTN ointment. The patch offers better compliance and acceptability. Various studies have shown healing rates of about 70% by GTN ointments [12, 13]. Healing is thought to be due to the sustained reduction in MMARP by GTN ointment [8, 9, 10, 13, 14]. The majority of studies have also shown that GTN ointments increase anal blood flow [12, 15, 16], but according one study found no significant increase in anal blood flow, although it did achieved healing in 65% of cases [13]. Reduction in the pain score was also significant in our patients, as shown in Fig. 1, with a reduction of 50% after 2 weeks.

Side effects were limited to mild headache, reported by 25 of our 35 patients, and flatus incontinence, reported by two. Flatus incontinence with GTN is temporary and improves when treatment is discontinued while that with surgical lateral sphincterotomy is permanent. The incidence of flatus incontinence after surgical sphincterotomy is reported as 2.4–36.0% in various studies [5, 6, 17, 18]. No fecal incontinence was seen in our study, whereas the incidence with surgical sphincterotomy is very high, with various studies reporting incontinence to solid feces to occur in 0.03–4.9% after surgical sphincterotomy [5, 6, 17, 18]. Such levels of incontinence are not seen during GTN ointment treatment. Other treatment options such as internal sphincter injections of botulinum toxin are also under trial and have shown promising results, with rates of healing anal fissures up to 96% [19] and a significant decrease in MMRP [20]. In our series no significant difference was seen in patients undergoing

surgical management and those treated with nitroglycerin ointment or patch. GTN ointment treatment has a high recurrence rate; in our series 25% of patients had suffered a relapse, but none was reported at 22 months' follow-up [21].

For the patients who wish to avoid surgery and for those unfit for surgery, GTN ointment will be preferred mode of treatment. Even in otherwise fit patients it can be tried before deciding on surgery. Some clinicians are of the opinion that it will soon become the treatment of choice in chronic anal fissures, and that surgical division of the sphincter could thus be avoided in the majority of patients [22, 23, 24]. In conclusion, local applications of GTN ointment and nitroglycerin patch are both effective, economical, and alternative treatment option for patients with anal fissures. They have no permanent side effects and are well tolerated.

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