Clinical Efficacy of O.2% Glyceryl Trinitrate Ointment for Anal Fissures

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Objective To validate the clinical efficacy of 0.2% glyceryl trinitrate ointment, a nitric oxide donor, in the management of anal fissures. **Patients and methods:** A prospective clinical study conducted on consecutive patients with anal fissures presented to the surgical clinic of Jinnah Hospital and Allama Iqbal Medical College Complex Lahore. These patients were treated with topical 0.2% glyceryl trinitrate paste in soft white paraffin three times a day. Patients were examined at regular intervals to evaluate the fissure status, adverse reactions, symptomatic control and recurrence. All subjects were followed-up until they were pronounced cured or treatment terminated. **Results:** 121 patients comprised this study group. 6 cases were lost to follow-up and 109 (94.7%) of the remaining 115 subjects were cured. Of those cured, 13 (11.3%) presented with acute and 102 (88.7%) chronic fissures. There were 98 male and 17 female patients with median age of 41 years (range, 14-70 years). Complete symptomatic relief was achieved in all patients within one month of therapy. Treatment had to be terminated in 6 (5.2%) patients: 5 (4.3%) experienced intolerable adverse effects and 1 (0.8%) patient failed to respond. All these cases were successfully treated with lateral internal sphincterotomy. There was no change of continence in this series. **Conclusion:** Glyceryl trinitrate ointment produces healing of the anal fissures and adequate symptomatic relief and should be considered as the first line treatment for anal fissures.
Key words: Anal fissure, glyceryl trinitrate ointment, lateral internal sphincterotomy, nitric oxide donor.

Raised resting internal anal sphincter pressure is important in the pathogenesis of anal fissure, possibly by impairing tissue perfusion and leading to ischemic ulcer[1,2,3]. Conservative management of the anal fissures traditionally involves stool softeners, warm sitz baths and the application of topical anesthetics. Chronic fissures tend to be more resistant to conservative management characterized by frequent recurrences[4]. Surgical procedures to reduce resting anal tone for the recalcitrant fissures are effective but carry a significant risk of permanent minor impairment of continence[5,6]. Manual anal dilatation may cause irreversible, uncontrolled injury to the internal and external anal sphincters[7], with the associated incidence of fecal incontinence being 39%[8]. Lateral subcutaneous internal sphincterotomy leads to successful healing of the fissure in more than 90% patients but temporary incontinence for the flatus or feces occurs in 0 – 30% of the cases[9]. Such observations have fuelled attempts to develop non-operative measures for reducing internal sphincter spasm.

Nitric oxide has emerged as the most important neurotransmitter mediating internal sphincter relaxation.[10] Topical glyceryl trinitrate (GTN), a nitric oxide donor produces a successful chemical sphincterotomy and improves anodermal blood flow[11]. The aim of this study was to present a more pragmatic assessment of the ultimate usefulness of GTN in the treatment of acute and chronic anal fissures.

Patients & methods:

This prospective study included all patients with acute and chronic anal fissures presented to the Surgical Clinic of Jinnah Hospital and Allama Iqbal Medical College Complex Lahore over a period of one year. These patients had persistent, symptomatic anal fissures that were recalcitrant to sitz bath, fiber supplements and topical anesthetics. The chronicity of the fissure was established by the presence of a sentinel pile, hypertrophied papillae or exposed internal sphincter fibers at the base of the anal fissure[12]. Patients with inflammatory bowel disease, HIV infection and those with cardiac disease using oral or sublingual nitrates were excluded from this study. Informed consent was obtained from all the patients after an explanation of the nature of the disease, treatment method and the possible unwanted effects. Patients were instructed to apply small amounts of especially prepared 0.2% GTN paste in soft white paraffin, to the anoderm with finger tips three times per day[13].

Patients were evaluated at two-week intervals and at each visit the symptoms control, adverse effects and fissure status were recorded. If there was symptomatic relief or the fissure healing was in progress, the treatment was continued for a total duration of eight weeks. Afterwards, the patients were given the option to resume the treatment in case of recurrence or abandon this therapy and consider surgical intervention. Two follow up visits, at two-month interval, were arranged after the completion of the initial therapy. Treatment was considered successful in case of complete symptomatic relief with fissure healing. The SPSS 10.0 software package (SPSS Inc., Chicago, IL) was used for data analysis.

Results:

Out of a total of 121 patients, 6 were lost to follow up, and of the remaining 115 subjects, there were 98 men and 17 women patients with a mean age of 41 years (range 14 –

70) for males and 40.2 years (range 14–67) for females (Table I). 109 (94.7%) patients were cured of anal fissures: 11 (10%) acute and 98 (90%) chronic fissures (Figure 1). 2 (1.7%) patients with acute and 3(2.6%) with chronic anal fissures presented with symptomatic relief sufficient to obviate the need for any operative treatment, despite the persistence of fissure. Complete symptomatic relief was obtained within one month of the therapy for all those patients cured of the disease. 2(1.7%) patients presented with recurrent symptoms three months after the initial treatment which was successfully treated with a second course of 0.2% GTN. No change in flatus or fecal continence was reported in this study. 5 (4.3%) subjects experienced intolerable side effects while 1 (0.8%) patient failed to respond to 0.2% GTN therapy (Table 2). All these patients were treated with lateral internal sphincterotomy with uneventful recovery.

Fig.1: Distribution and cure rates of acute and chronic anal fissures.

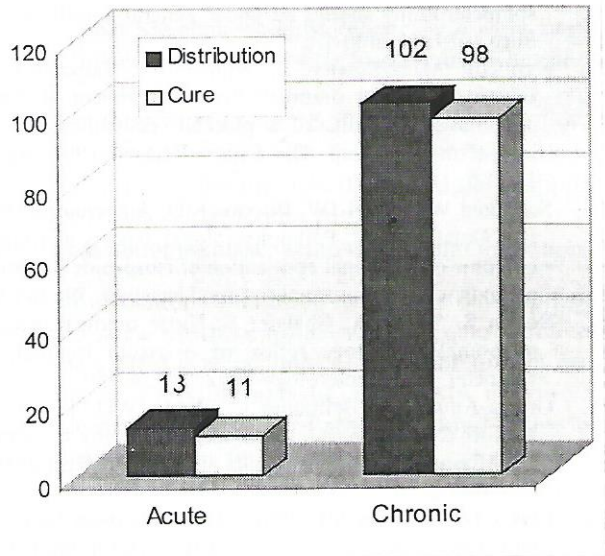

Table 1: Demographic data of patients with anal fissures

No. of patients	115
Male: Female	98:17
Median age-years(range)	41(14-70)
Median duration of symptoms (months)	6.1
Acute: Chronic fissures	3:102

Table 2: Adverse Effects of 0.2% GTN Ointment (n = 115)

Adverse Effects	No.	%
• Tolerable side effects		
o Mild headache	4	3.4
o Perianal irritation	1	0.8
• Intolerable side effects		
o Severe headache	3	2.6
o Light headedness	2	1.7

Table 3: Comparison of results with 0.2%GTN Treatment

Group (Year)	Cure Rate%
Present study (2001)	94.7
Ward et al [11] (1999)	75
Bacher et al [15] (1997)	80
Lund and Scholefield [16] (1997)	70

Discussion:

The published data is indicative of a high cure rate of 70-80 percent [11, 14, 15] with the use of 0.2% GTN along with a paucity of significant side effects (Table 3). In a recent study [16] the recurrence rate has been less than 5% and major complications were quite uncommon with the use of GTN ointment. Gorfine[17] used 0.3% GTN ointment four times a day to induce healing in 12 of 15 anal fissures within one month of treatment. Another study showed 77 % healing rate for anal fissure with a reported incidence of 35% for headaches [18]. In our series, 4.3% cases felt headache because the dose of GTN was significantly lower than the dose used in other studies (0.3%-0.5%)[10,13,16]. Similarly, tachyphylaxis (rapid development of tolerance to the effects of GTN) was not observed in this study which is explained by the volatility of the preparation when exposed to air and the short half life of GTN. The available reports [19-21] have shown a recurrence rate of 3-25% with internal sphincterotomy for anal fissures while in this study 2 (1.7%) patients had symptomatic recurrence with GTN ointment necessitating repeat therapy. Kennedy et al[22] have concluded in their placebo-controlled, randomized, double-blind trial of 43 patients that topical GTN produced a successful chemical sphincterotomy, which resulted in long-term healing of 59% of chronic anal fissures. GTN therapy provides outright benefit for those patients with the highest risk of anal incontinence, including multiparous women, and those with previous anal surgery, recurrent fissures or peri anal irradiation [10]. Cost effectiveness and complete treatment in the Outpatient Clinic, with a subsequent reduction in the hospital waiting lists are among other advantages of this treatment modality. The reported efficacy of nitric oxide donors varies widely in the literature (47-88%)[23,24], depending on the agent used, the duration of treatment, whether the fissure was acute or chronic, and how the success of therapy was measured i.e. symptomatic relief, healed fissure or manometric finding of reduced anal sphincter tone. This highlights the need for further data-based clinical trials to elucidate the correct dose, optimal dosing intervals and the best delivery method of GTN. Lateral internal sphincterotomy has been among the most gratifying surgical interventions for anal fissures [25] but the published literature has reported a 2.3% wound infection rate[26] and 0 to 34% incidence of incontinence to flatus and liquid stool [27] following this procedure. Our study did not reveal any change in the continent status, an observation which highlights the safe clinical profile of the GTN therapy.

In conclusion, GTN is a safe and effective therapeutic modality in the management of acute and chronic anal fissures which are refractory to dietary modifications, fiber supplements and sitz baths.

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