

Treatment of Chronic Anal Fissure in Adults Using 0.2% Glyceryltrinitrate Versus 0.5% Nifedipine Ointments: A Prospective Randomized Controlled Trial in Two Centers

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Abstract

Objective: To compare the efficacy of the local application of 0.5% nifedipine ointment vs. 0.2% glyceryltrinitrate ointment (GTN) in the healing of chronic anal fissure (CAF).

Methods: Two hundred patients with symptomatic chronic anal fissures in two medical centers Alexandria Main University Hospital (Group A) and Aseer Central Hospital (Group B), each included one hundred patient, were randomly assigned to 0.2% glyceryltrinitrate ointment (groups A1/B1; n=50), and 0.5% nifedipine ointment (groups A2/B2; n=50). All patients in the four groups received stool softeners and fiber supplements and were assessed every two weeks till 12 weeks as regards healing, headache, and patients' compliance to treatment. Patients who showed complete healing at 12 weeks were further followed-up for 12 months to detect recurrence.

Results: Patients in the four groups were comparable as regards demographic data (sex and age) as well as clinical picture. Headache was the encountered in patients receiving GTN in high percentage (43.75% for group A1 and 60.68% for group B1) which was significantly higher than that experienced by patients who received nifedipine (17.02% for group B1 and 14.89% for group B2), which led to poor compliance towards GTN, compared with nifedipine. Nifedipine showed better, yet non-significant, healing rates compared with GTN. Recurrence was comparable among the four groups.

Conclusions: 0.5% nifedipine ointment showed better results than 0.2% glyceryl trinitrate ointment (GTN) in treating CAF as regards healing, headache and patient compliance to treatment with equal results as regards recurrence after complete cure in twelve months follow-up period.

Key Words: Anal fissure – Nifedipine – Glyceryl trinitrate – Compliance.

Introduction

ANAL fissure is a linear ulcer in the squamous epithelium of the anal canal located just distal to

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the dentate line. Although it is a very common disease, the exact incidence rate is not known. The most consistent finding on physical examination is spasm of the anal canal due to hypertonia of the internal anal sphincter. It has been postulated that this may either be due to or be the result of ischemia [1].

Over the years, many surgical treatment options have been offered, of which operative lateral sphincterotomy, either open or closed, remains the standard of treatment [2] and offers the highest cure rate of 85%, with only 5% persistence and 10% recurrence rates [3]. However, this was on the expense of occurrence of variable degrees of anal incontinence in some patients, which may be related to the method of sphincterotomy [1,3,4].

The use of topical agents to cause chemical sphincterotomy gained a rapid success because of its reversible nature. The most commonly used agent is glyceryl trinitrate [1-5], that works as a nitrogen donor increasing nitric oxide, which in turn, induces a dose-dependent relaxation of the internal anal sphincter [5]. Early studies reported up to 80% healing rates but these were small and nonrandomized studies. Later meta analysis of larger randomized controlled studies showed a healing rate about 48.9%, and still an early recurrence rate of almost 50% of healed cases [5,6]. Furthermore, it was associated with a troublesome severe headache in up to 27% of patients [4,6].

This led to trials on another group of agents, i.e., calcium channel blockers to produce chemical sphincterotomy [1-6]. Many agents in this group have been tried, the most common of which was

diltiazem which led to similar healing rates as for glyceryl trinitrate and still with the annoying side effect of headache, although at a lower incidence rate [6].

Nifedipine is a calcium channel-blocking agent that has been used for chemical sphincterotomy with promising results and fewer reported side effects [4,5] but results need to be further evaluated.

This study aimed to evaluate the use of topical 0.5% nifedipine ointment versus 0.2% glyceryl trinitrate ointment in treatment of chronic anal fissures (CAF) as regard healing, recurrence, complications and compliance of the patient.

Patients and Methods

This study was carried out in 2 different medical centers: Alexandria Main University Hospital, Alexandria, Egypt (group A), and Aseer Central Hospital, Abha, Kingdom of Saudi Arabia (group B) during the period from January 2010 till February 2011. Sample size was calculated (37 patient each group) with G-power program 3.1.3 [2010] as alpha error 0.05 beta error (power 80) and assuming effect size 0.5.

As we noticed withdrawal of patients from similar researches due the headache associated with topical treatment of anal fissure, we decided to increase the initial number in each group to be 50 patients. So, 100 patients were included in this study in each center. Using the closed envelope technique (by an investigator with no involvement in our clinical trial), patients were randomly assigned into two groups; Groups A1 and B1 (50 patients each) subjected to 0.2% glyceryl trinitrate ointment four times daily (QID) for 12 weeks and groups A2 and B2 (50 patients each) subjected to 0.5% nifedipine ointment four times (QID) daily for 12 weeks.

Inclusion criteria:

Adult patients (aged 18-60 years) with chronic anal fissure defined as anal fissure that has been symptomatic for at least 8 weeks without improvement on diet modifications or stool softeners. Clinical assessment should confirm 2 or more of the following present:

- Perianal pain.
- Visible fibers of the internal anal sphincter at the base of the fissure.
- Visible sentinel tag.

Exclusion criteria:

The following patients were excluded from this study:

- Patients with previous anal surgery including sphincterotomy.
- Anal fissures caused by special diseases e.g. inflammatory bowel diseases.
- Patients with considerable cardiovascular conditions.
- Patients with associated anal pathology rather than CAF.
- Patients who were lost in follow-up or who were non-compliant due to intolerance to treatment.

All patients were subjected to thorough history taking and clinical examination. Informed consent was taken from all patients according to regulations of the Research Ethical Committee. The patients were instructed to wear gloves during application to prevent systemic absorption and to apply ointment to an area of about 1cm circumferentially around the anus. Patients were prescribed 15cc lactulose syrup once daily to be used concomitantly.

Patients were followed-up every 2 weeks for 3 months or until healing of the fissure and for 12 months for the recurrence after complete healing. During each follow-up visit, the patients were evaluated regarding the following:

- a- Anal examination to determine healing of the fissure.
- b- Recording of any adverse effect related to medication given.

Outcomes:

• *Primary endpoints:*

◦ Healing of the fissure (complete disappearance of the ulcer in the anoderm) within 12 weeks of beginning of treatment detected by anal examination by the surgeon in outpatient clinic visits. Patients who did not show complete healing at 12 weeks were offered an alternative method of treatment.

◦ Recurrence: Healed patients were followed up after healing for 12 months using phone calls to report any clinical symptom, who were examined during a follow-up clinic visit to confirm the recurrence.

• *Secondary endpoints:*

◦ Headache associated with treatment to be reported to the doctor in outpatient clinic every two weeks for 12 weeks.

° Patients' compliance to treatment to be reported to the doctor in outpatient clinic every two weeks for 12 weeks.

° Patients who did not show any improvement of symptoms with the given medication or those who did not tolerate the treatment due to side effects of a given medication were reported and also offered an alternative treatment.

Statistical analysis:

Frequency, percentage, arithmetic mean and standard deviation were applied. Unpaired Student "t" and χ^2 tests were used as tests of significance at 5% level.

Results

Patients in the four groups were comparable as regard sex and age, as well as clinical picture (Table 1). Some patients did not show up in follow-up visits and were excluded from the study. Flow charts for distribution of patients in groups A and B are shown in Figs. (1,2).

Headache was encountered in patients receiving GTN in high percentage (43.75% for group A1 and 60.68% for group B1) which was significantly higher than that experienced by patients who received nifedipine (17.02% for group B1 and 14.89% for group B2). Headache was the cause of intolerability for many patients toward topical medications for chemical sphincterotomy, specifically toward GTN. These patients were excluded from the study and were offered alternative options for treatment. Healing after 12 weeks was better in patients receiving Nifedipine (85.71% for group A2 and 84.09% for group B2) compared with patients who received GTN (63.15% and 64.28% for groups A1 and B1, respectively) but this difference was not statistically significant. Patients from the four groups showed comparable results as regards recurrence after 12 months. Results of the four groups as regard headache, healing and recurrence are shown in Table (2).

Table (1): Clinical data of the patients in the four groups.

	Group A		Group B		P value
	Group A1 (receiving GTN)	Group A2 (receiving Nifedipine)	Group B1 (receiving GTN)	Group B2 (receiving Nifedipine)	
Sex (Female/Male)	26/24	23/27	27/23	24/26	0.865
Age (mean±SD)	35.1±10.99	33.7±12.33	33.9±10.25	36.2±12	0.671
Location (posterior/anterior)	46/4	47/3	47/3	48/2	0.871
Duration of symptoms months (mean±SD)	7.45±4.59	8.21±4.62	8.32±5.06	7.52±4.47	0.705

*Significant (p<0.05).

Table (2): Comparison between the four groups as regards healing, headache and recurrence.

	Group A		Group B		P value
	Group A1 (receiving GTN)	Group A2 (receiving Nifedipine)	Group B1 (receiving GTN)	Group B2 (receiving Nifedipine)	
Headache	21/48 (43.75%)	8/47 (17.02%)	28/46 (60.68%)	7/47 (14.89%)	<0.001*
Withdrawal from the study	10/48 (20.83%)	5/47 (10.63%)	18/46 (39.13)	3/47 (6.38%)	<0.001*
Healing (12 weeks)	24/38 (63.15%)	36/42 (85.71%)	18/28 (64.28%)	37/44 (84.09%)	0.057
Recurrence (up to 12 months)	5/24 (20.83%)	11/36 (30.55%)	6/18 (33.33%)	8/37 (21.62%)	0.819

*Significant (p<0.05).

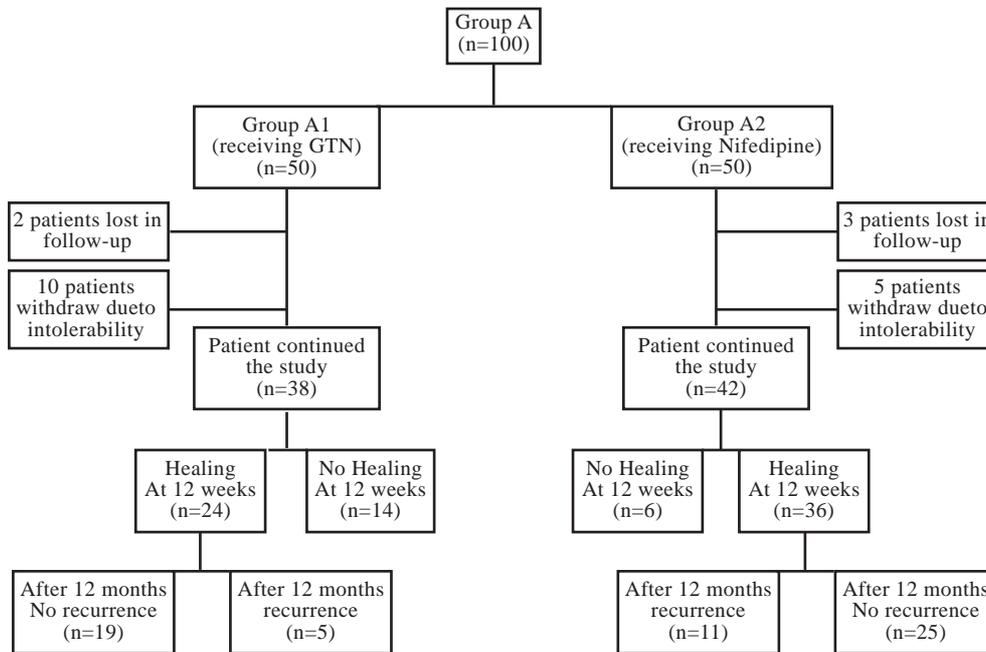


Fig. (1): Flow chart showing distribution of Group A patients.

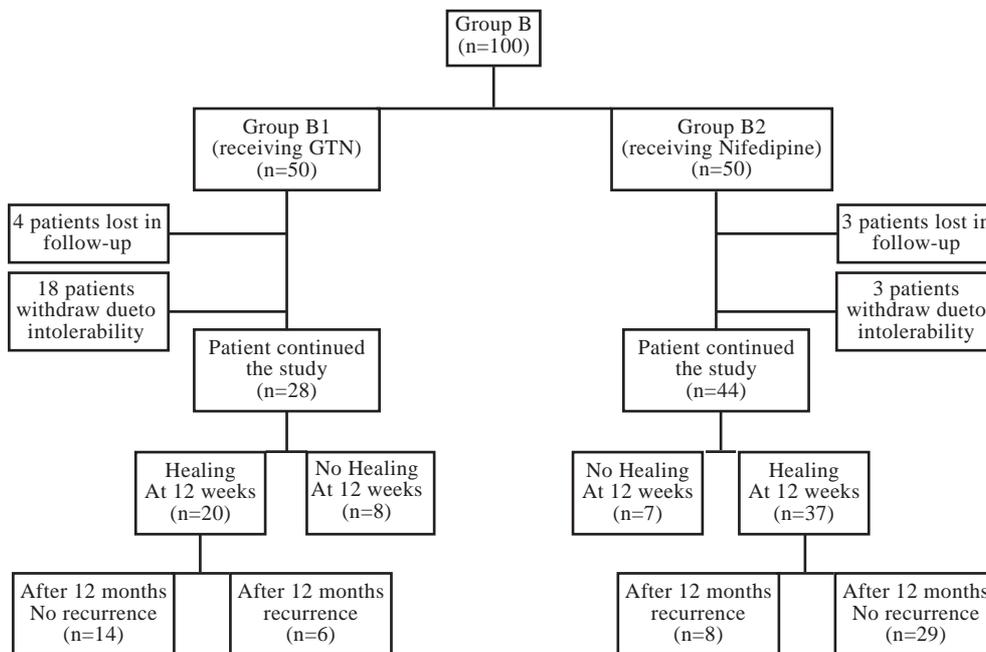


Fig. (2): Flow chart showing distribution of Group B patients.

Discussion

There is a variety of acceptable treatment options for anal fissures. Acute fissures tend to cure with simple conservative measures. However, CAF usually needs other types of treatment as chemical sphincterotomy or surgery [7,8]. Despite surgery has proved superior to chemical sphincterotomy [9], non-surgical therapy for CAF has many advan-

tages, especially with increasing evidence of impaired continence after sphincterotomy, which is more common than previously thought [10,11]. In addition, non-surgical treatments are with low risk, repeatable, reversible and could be used in patients who refuse surgery.

Authors show differences in defining CAF. In this study, we used subjective data in the form of

pain for at least two months, and morphological features in the form of skin tag and fibrosis of the internal sphincter as basis for diagnosing chronic anal fissure.

Sound understanding of the pathogenesis of CAF and the role of hypertonicity of internal sphincter, was the guide to use nitrates in the treatment of CAF, which may be beneficial for breaking the vicious circle of pain, fissure and more pain. However, it was associated with high incidence rates of headache, which markedly reduces the tolerability of the drug. Lack of good compliance to the drug resulted in a wrongfully perceived lack of effect of it, and was an important factor of failure in patients who were not compliant with the treatment protocol [12].

Topical calcium channel blockers have shown to lower anal resting pressure by relaxing the internal anal sphincter [13]. Calcium and its entry through the L-type calcium channels are important for the maintenance of the internal anal sphincter tone. As opposed to glyceryl trinitrate, which reduces the resting anal tone by releasing nitric oxide, nifedipine (a calcium channel antagonist) reduces the tone and spontaneous activity of the sphincter by decreasing the intracellular calcium availability [14].

In this study, we chose headache among the different complications of chemical sphincterotomy to be reported. We believe it is the most important side effect, as is it has the great influence on patients' compliance to treatment with subsequent effect on the final outcome of treatment. Patients who were treated by GTN showed a high incidence of headache (43.75% and 60.68% for groups A1 and B1, respectively). This was significantly higher than the headache associated with nifedipine application (17% and 14.89% for groups A2 and B2, respectively). This headache was the cause of patients' intolerability and withdrawal from the study which was significantly higher in groups using GTN (20.83% for A1 and 39.13% for B1) compared with groups using nifedipine (10.63% for A2 and 6.38% for B2).

Similar results with high incidence of headache and patients' withdrawal for patients treated with GTN were found in different studies in the literature [15-18]. What was interesting in our results is the significant difference between group A1 and B1 regarding patients' non-compliance due to intolerability of GTN (20.83% vs. 39.13% withdrawal percentages, respectively). Withdrawal from group

B1 was exceeding our expectations and even what was written in the literature. This raises the question about the difference in compliance according to demographic characteristics and factors affecting this compliance.

Patients receiving nifedipine showed significant improvement in healing after 12 weeks of treatment, compared with GTN (84% for A2, 84.09% for B2 compared with 63.15% for A1 and 71.14% for B1). The incidence of healing after GTN application showed great variability [15,16,19]. Other studies showed worse results after GTN treatment [17,20]. Previous studies showed better healing results of nifedipine in treating CAF than ours [21,22].

Bernal et al. [23] have pointed out that the dissimilar clinical results reported by different authors could be due to differences in the preparation formulas. In many countries including Egypt and Saudi Arabia, there are no commercial standard products for topical GTN or Nifedipine for treatment of anal fissure. Subjectivity of clinical assessment could be a contributing factor and different views on what are good results of treatment. We considered that successful treatment is complete cure. This is the most objective and standard criteria and a good measurement of results [24]. For others, success is the disappearance of anal pain and/or fissure or simply relief from pain and patient satisfaction [25].

Recurrence after complete healing was monitored for up to 12 months after cure. Recurrence rates in all groups were comparable (20.83% for A1, 30.55% for A2, 30% for B1, and 21.6% for B2) and similar to other studies [16,17]. This high recurrence rate after complete healing usually raises the question: "Does chemical sphincterotomy delay surgical sphincterotomy for CAF?" We think the choice for the treatment option should be after discussion with the patient with good explanation of all alternatives and expected results of each option.

Limitations:

Patients and doctors were not blinded in this study, and the non-existence of commercially standardized products of topical GTN and Nifedipine are considered the main limitations of this study.

Conclusions:

Topical 0.5% Nifedipine application for treatment of CAF yields better results, compared with 0.2% GTN, as regard patients' compliance to treatment, incidence of healing and with significant less associated headache. Both drugs still have a

high incidence of recurrence. Finally, compliance of the patients differs with their characteristics and this should be considered as an important factor that may influence the results.

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