

Topical Diltiazem Hydrochloride and Glyceryl Trinitrate in the Treatment of Chronic Anal Fissure

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ABSTRACT

Objective: To compare the symptomatic relief, healing and side-effects of topical diltiazem (DTZ) and glyceryl trinitrate in the treatment of chronic anal fissure.

Study Design: Randomized controlled trial.

Place and Duration of Study: The Surgical Outpatient Department of Civil Hospital, Karachi, from March 2006 to February 2007.

Methodology: Patients with chronic anal fissure were included in the study and randomized to two groups. One group was administered topical 2% diltiazem hydrochloride and other was given 0.2% glyceryl trinitrate (GTN), perianally twice daily for 8 weeks. Patients with anal fissure due to other diseases like inflammatory bowel disease, malignancy, sexually transmitted diseases, previous treatment with local ointment or surgery; patients who required anal surgery for any concurrent disease like hemorrhoids, pregnant women and patients with significant cardiovascular conditions were excluded. There were four follow-up sessions during the course of treatment. Healing and side-effects were recorded. Analysis was done by SPSS version 10 on intention-to-treat basis. Chi-square was used where appropriate.

Results: Eighty patients with symptomatic chronic anal fissure were included in the study and equally divided into two groups. After 8 weeks of treatment healing occurred in 31 of 40 patients treated with diltiazem and 33 of 40 patients treated with GTN ($p = 0.576$). There were less side-effects with DTZ ($n=13$) than with GTN ($n=29$, $p < 0.001$). In particular, headache occurred more commonly with GTN ($n=27$) than with DTZ ($n=9$, $p < 0.0001$).

Conclusion: Diltiazem hydrochloride and glyceryl trinitrate were equally effective in healing chronic anal fissure. Diltiazem caused fewer side-effects particularly headache than glyceryl trinitrate ointment. Diltiazem may be the first-line treatment for chemical sphincterotomy for the chronic anal fissure.

Key words: Anal fissure. Diltiazem. Glyceryl trinitrate. Chemical sphincterotomy.

INTRODUCTION

An anal fissure is a linear tear in the anal canal distal to the dentate line. An acute anal fissure usually heals spontaneously or with the use of simple measures like high fibre diet with adequate water intake.¹ Chronic anal fissure is associated with persistent hypertonia and spasm of the internal anal sphincter.² Surgical division of the internal anal sphincter is the traditional treatment of chronic anal fissures, but this causes significant short and long-term morbidity with incontinence rates of up to 30%.³

The ischemic nature of chronic anal fissure is due to high resting anal pressure.⁴ This theory is now widely accepted as the cause for the chronicity of these fissures. Various medical therapies have now been introduced to reduce the resting anal pressure and improve the blood supply to the affected anoderm and

thus enhance healing. Chemical sphincterotomy is attempted using a variety of agents. The agents used have been glyceryl trinitrate (GTN), botulinum toxin, nifedipine, diltiazem hydrochloride (DTZ) and bethanechol.⁵⁻⁸ Topical glyceryl trinitrate (GTN) lowers the anal sphincter pressure and heals anal fissures, but a majority of patients experience headache.⁹ The internal anal sphincter has a calcium dependent mechanism to maintain tone. It is, therefore, possible to lower anal sphincter pressure using calcium channel blocker i.e. diltiazem with fewer side-effects.¹⁰⁻¹⁴ The objective of this study was to compare the perianal application of diltiazem with GTN ointment in the treatment of chronic anal fissure.

METHODOLOGY

This study was conducted in the Surgical Outpatient Department of Civil Hospital, Karachi, from March 2006 to February 2007. Approval was obtained from the Ethical Review Board of the Dow University of Health Sciences. Consecutive adult patients with symptomatic chronic anal fissures were enrolled in the study using non-probability purposive sampling. All patients had a pretreatment evaluation that included history, general physical examination, clinical inspection of the fissure

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and proctoscopy. Chronic anal fissure was defined as anal symptoms lasting for more than 8-12 weeks, with horizontal muscle fibres showing at the fissure base and/or the presence of a sentinel tag. Patients with anal fissure secondary to other diseases like inflammatory bowel disease, malignancy, sexually transmitted diseases, previous treatment with local ointment or surgery; patients who needed anal surgery for any concurrent disease like hemorrhoids, pregnant women and patients with significant cardiovascular conditions were excluded from the study.

Eligible patients were randomly assigned to one of the two treatment groups according to a computer generated list using Random Allocation Software, Version 1.0. Patients were advised to apply a pea size (approx. 250-500 mg) quantity of 2% diltiazem or 0.2% GTN ointment by fingertip to the anal verge twice daily for 8 weeks. They were allowed to withdraw from the trial at any time, without stating any reason. Patients were followed for 8 weeks on a two weekly basis and those who did not respond were offered lateral internal sphincterotomy.

Pain, healing and side-effects were rerecorded. The severity of pain was assessed using visual analogue scale ranged from 1 (absence of pain) to 10 (unendurable pain).

Statistical analyses were carried out by SPSS version 10, on intention-to-treat basis. Side-effects (headache, gastrointestinal effects, perianal itching, vertigo, flatus incontinence) were analyzed by chi-square test while postoperative pain was analyzed by un-paired t-test. Any differences were accepted as statistically significant at the $p < 0.05$ level.

RESULTS

Eighty patients with chronic anal fissure were included in the study. Forty patients were randomly assigned to receive 2% diltiazem cream and 40 patients 0.2% GTN ointment. Demographic profile, duration and nature of symptoms are shown in Table I. The fissure was posterior in 73 (90.1%) of the patients and anterior in 6 (7.4%) while both anterior and posterior in 2 (2.4%) of patients.

Table I: Patients demographic and symptoms profile.

	DTZ (n = 40)	GTN (n = 40)
Age mean (range) years	37.3 (20-51)	40.1 (21-50)
Gender (Male : Female)	26:14	23:17
Median symptoms duration (weeks)	24	20
Pain	40	40
Constipation	35	37
Bleeding	34	31
Anal pruritis	29	25
Discharge	15	17

DTZ = 2% diltiazem hydrochloride; GTN = 0.2% glyceryltrinitrate.

Seven patients withdrew due to side-effects or did not attend the follow-up. Thirty-eight patients completed treatment in the DTZ group while 35 patients in the GTN group. At 8 weeks, 32 (78.0%) patients in the DTZ group were healed compared with 33 (82.5%) patients in the GTN group ($p = 0.775$). Thirteen of the 40 patients in the DTZ group experienced side-effects, compared with 29 of 40 patients in GTN group. Headache occurred in 9 patients of the DTZ group, compared with 27 patients of the GTN group ($p = < 0.001$). The side-effects are shown in Table II along with their statistical significance. There was less pain in both groups during the treatment period, with no significant differences between the groups at any time during the course of treatment (Figure 1).

Table II: Side-effects during the treatment period.

Side effects	DTZ (n=40)	GTN (n=40)	p-value
Headaches	9 (22.5%)	27 (67.5%)	< 0.001
Gastrointestinal effects*	7 (17.5%)	11 (27.5%)	0.284
Perianal itching	4 (10.0%)	3 (7.5%)	0.692
Vertigo	1 (2.5%)	5 (12.5%)	0.09
Incontinence (flatus)	0 (0%)	1 (2.5%)	0.314
Total	13	29	-

*Gastrointestinal side effects mean abdominal pain, nausea, vomiting and diarrhea.

Note: Many patients experienced more than one side-effect during the treatment.

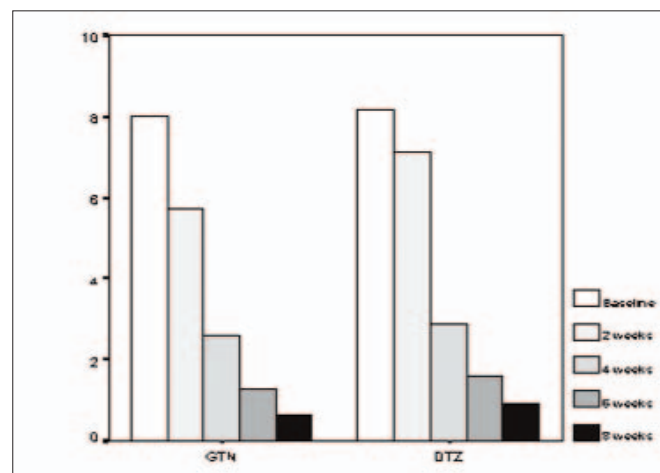


Figure 1: Reduction in Visual Analogue Scale (VAS; 0-10mm) scores during the treatment period. Values are mean. No significant difference between two groups at any point. (Student t-test: $p \geq 0.15$).

DISCUSSION

The treatment of chronic anal fissure has shifted in the recent years from surgical to medical modalities because of disability and the risk of incontinence associated with surgery. Chemical sphincterotomy can be done using a variety of agents. A first line use of medical therapy cures most chronic anal fissures economically and conveniently.¹⁵ Glyceryl trinitrate remains the standard chemical sphincterotomy against which other newer treatments are compared. Controlled clinical trials have shown varied results of healing (45-80%) with topical GTN.^{9,16,17} However, side-effects such

as headaches and dizziness are common with nitrates, which may limit their application and reduce patient compliance.^{9,16}

The lower number of female (38.75%) patients in this study and other local studies may be due to the conservative attitude of females in the local set up especially for perianal diseases.¹² This study has shown same rates of healing for both topical GTN and DTZ with no significant difference between them. Side-effects are less significant with diltiazem, a finding also reported by other studies.¹⁰⁻¹⁴

Calcium channel blockers have been a focus of considerable recent work on pharmacological fissure therapy. Cook *et al.* administered oral nifedipine to healthy volunteers and to chronic anal fissure patients.¹⁸ Maximum resting anal pressure decreased by a third in both groups. Carapeti *et al.* found that oral diltiazem (60 mg twice daily) reduced anal pressure by 17%.² He also performed a dose ranging trial using diltiazem gel and found that 2% concentration produced a maximal effect of 28% reduction in the resting anal tone. The effect lasted 3-5 hours after a single application. Topical diltiazem is associated with fewer side-effects, probably because of minimal systemic absorption.¹⁹ Studies also showed that topical diltiazem is an effective and safe treatment for chronic anal fissure in patients who have failed topical 0.2% GTN and need for sphincterotomy can be avoided in upto 70% of cases.^{20,21} Recently the effect of nitric oxide donors and calcium channel blockers was compared *in vitro* on isolated strips of sheep internal anal sphincter.²² It was found that the combined effect of GTN and DTZ was greater than the effect of either agent alone.

Headache is a major problem for patients with anal fissure treated by GTN ointment. Headaches were not reported in some initial studies using DTZ,² but neither were they reported in the initial case series using nitrates,^{23,24} and only became apparent in later trials.⁸ Nevertheless, the number of headaches reported in this study were significantly fewer than with the GTN group. In the present study, one patient developed flatus incontinence with the use of GTN ointment but it was reversible after cessation of treatment.

While it will be necessary to determine the outcome after a long period, the study has proved the superiority of diltiazem over glyceryl trinitrate in the short-term. Surgery can be used for failures of pharmacological treatment or fissures that recur frequently after cessation of local treatment.

CONCLUSION

Topical 2% diltiazem appeared to be well tolerated and equally efficacious proving to be the preferred first-line method of chemical sphincterotomy for chronic anal fissures. Long-term follow-up is needed to assess the risk of fissure recurrence after initial healing with diltiazem.

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