

Headache With Local Application Of Glyceryl Trinitrate And Diltiazem In Chronic Anal Fissure: A Randomized Controlled Trial

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Citation

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Abstract

Objectives: To compare the frequency and severity of headache after topical application of 0.2%-glyceryl trinitrate (GTN) versus 2%-diltiazem ointment in the treatment of chronic anal fissures.

Methodology: This clinical trial was carried out in the outpatient department of all surgical units of the Civil Hospital Karachi from 21st August 2009 to 20th February 2010. Eighty patients of chronic anal fissure were randomly assigned to receive topical 0.2%-GTN (group A) and 2%-diltiazem ointments (group B). Forty patients were included in each group. Frequency and severity of headache were then determined with one week of follow-up. The SPSS version 11 was used for the data analysis.

Results: There were 65 (81.3%) males and 15 (18.7%) females with a mean (+SD) age of 38.79 (+14.86) years. There was a statistically significant difference in headache (30% in the GTN versus 7.5% in the diltiazem group; $p=0.02$). In two (5%) patients of the GTN group, the treatment had to be abandoned due to severe headache. However, none of the participants of the diltiazem group experienced severe pain.

Conclusion: Headache is common with the use of topical GTN ointment as compared to topical diltiazem. It is sometimes severe enough to compel the patient to discontinue treatment.

INTRODUCTION

Anal fissure is a split in the skin of the distal anal canal.¹ The classical symptoms of anal fissure are anal pain during or after defecation accompanied by the passage of bright red blood per anus.² Chronicity of fissures relates to duration of greater than 6 weeks, associated pathology may include a sentinel pile.¹

Anal fissure is one of the most common benign anorectal problems³ and is associated primarily to hypertonia and spasm of internal anal sphincter.⁴ The principle of treating anal fissures is to reduce internal sphincteric hypertonia, to improve anal mucosal blood flow and to promote healing of fissure. For a long time, it has only been amenable to anal dilatation and lateral sphincterotomy⁵; however, surgery is associated with the side effect of fecal incontinence.⁶ With the advancement in pharmacotherapy, chemical sphincterotomy is considered as an alternative modality of managing chronic anal fissure. It includes topical application of glyceryl trinitrate (GTN), diltiazem, nifedipine, and botulinum toxin⁷; among them, GTN and diltiazem are commonly used in Pakistan.^{8,9} Danish et al.¹⁰ showed that GTN-associated headache

sometimes became so severe and intractable that the treatment was abandoned. Despite this fact, it is still widely used for the treatment of chronic anal fissures. Calcium-channel blockers have been the focus of considerable recent work on chemical sphincterotomy for chronic fissure treatment. Numerous recent studies including randomized controlled trials proved that topical 2-percent diltiazem appears to be well tolerated and the preferred first-line method of chemical sphincterotomy for chronic anal fissures.⁸ Therefore, this study aims to compare the frequency and severity of headache in patients using topical 0.2% GTN versus patients using 2% diltiazem to emphasize the need of changing GTN in order to avoid normal daily routine interruption with the use of this drug.

PATIENTS AND METHOD

This clinical trial was carried out in the surgical units of the Civil Hospital Karachi from 21st August 2009 to 20th Feb 2010. A total of 80 patients with chronic anal fissure in the outpatient department of the Civil Hospital Karachi were included in this study. Informed consent was taken from each patient. Patients with anal fissure secondary to other

diseases like inflammatory bowel disease, malignancy and sexually transmitted disease, previous treatment with local ointment or surgery, cardiac patients and those who had history of migraine or headache were excluded from the study.

Patients were randomly allocated to group A (0.2% GTN) and group B (2% diltiazem) by using the random allocation software version 1.0.0. Each group contained 40 patients. In group A, patients were advised to apply a pea size (approximately 250-500 mg) quantity of 0.2% GTN ointment by fingertip to the anus (anal verge) twice daily for one week. In group B, patients were also advised to apply a pea size (approximately 250-500 mg) quantity of 2% diltiazem ointment by fingertip to the anus twice daily for one week. All patients were counseled about the headache associated with the usage of these topical ointments. Patients were categorized into the mild headache group (grade 0) if they had no headache or mild headache (i.e. not hampered their normal daily routine and no analgesics required) and moderate headache group (grade 1) if their normal daily routine became disrupted. These patients were advised to take two tablets of paracetamol 500mg thrice daily for two days. Patients were classified into the severe headache group (grade 2), if despite using paracetamol 500mg, the headache was not improved and treatment was abandoned by the patient. These patients were advised to come in the ward the next day after discontinuation of therapy. All patients were followed in the outpatient department after one week of treatment for assessment of headache.

RESULTS

A total of 80 patients were included in the study with a mean age (\pm SD) of 38.79 (\pm 14.86) years (range from 17 to 78 years). Sixty-five (81.3%) patients in this study were male, out of which 31 (47.7%) were in group A and 34 (52.3%) were in group B. Overall, 15 (18.8%) patients experienced headache at one week of follow-up.

In the 0.2%-GTN group, mild headache or no headache was observed in 28 (70%) and moderate headache was noticed in 10 (25%) patients. In 2 (5%) cases, the headache was so severe that treatment was discontinued by the patient.

In the 2%-diltiazem group, mild or no headache was observed in 37 (92.5%) patients and moderate headache in 3 (7.5%) patients. None of the patients encountered severe headache with diltiazem.

Overall, 12 (30%) patients of the 0.2%-GTN group experienced headache, whereas the complaint of headache was encountered only in 3 (7.5%) patients of the 2%-

diltiazem group ($p=0.02$). (Figure 1, Table 1)

Figure 1

Severity of headache in both groups of chronic anal fissure at one week of therapy

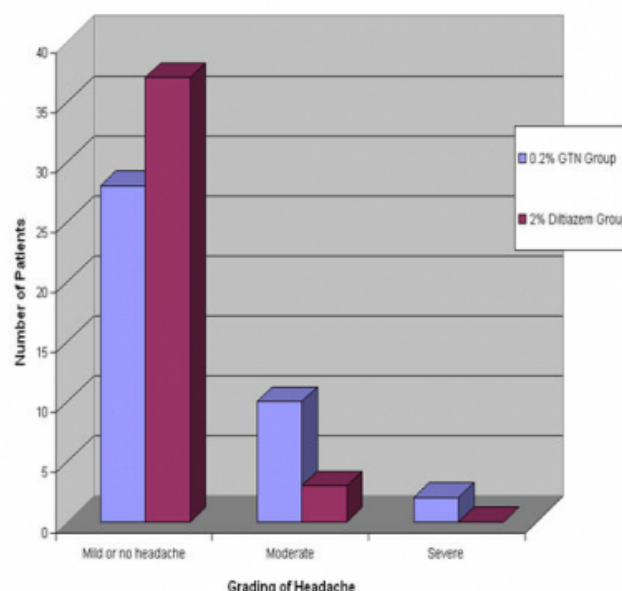


Table 1

Final outcome at week 1 of therapy in patients with chronic anal fissure

Outcome	Group A (0.2% GTN)		Group B (2% Diltiazem)	
	(n = 40)	%	(n = 40)	%
No headache	28	70	37	92.5
Headache	12	30	03	7.5

Chi2 test applied between the groups; $p = 0.02$, $df = 1$; GTN - Glyceryl trinitrate

DISCUSSION

GTN ointment showed a statistically significant difference to topical diltiazem in terms of headache (30% in the GTN versus 7.5% in the diltiazem group, $p=0.02$). Furthermore, participants of the GTN group had more severe headache as compared to the diltiazem group and some even became non-compliant to the treatment.

Anal fissure is one of the common painful perianal conditions.¹¹ With the passage of time, chronicity of the disease process occurs and pain becomes worse.¹² In this study of 80 patients, the maximum number of patients with chronic anal fissure was between 31 and 40 years of age, the youngest subject being 17 years and the oldest 78 years.

Mean age was 38.79 years. Hashmi and Siddiqui¹³ encountered an average age of 30 years in their series. There is a wide variation in sex incidence in different studies. Young adults of both genders are equally affected, as previously mentioned by Bhardwaj and Parker in their review article.¹ Out of 246 patients of chronic anal fissure, Liratzopoulos et al.¹⁴ encountered 120 (48.8%) males and 126 (51.2%) females in their clinical study. In this study, the male-to-female ratio found was 4:1.

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. Glyceryl trinitrate remains the standard chemical sphincterotomy against which other newer treatments are compared. Controlled trials have shown varied results of healing with topical GTN¹⁵⁻¹⁶; however, headache is common with nitrates, which may limit their application and reduce patient compliance.^{15,17} This study has shown less significant headache with diltiazem as compared to GTN, a finding also reported by other studies.^{8-10,13}

Calcium-channel blockers have been a focus of considerable recent work on pharmacological fissure therapy. Carapeti et al. found that oral diltiazem (60 mg twice daily) reduced anal pressure by 17%.¹⁸ They also performed a dose-ranging trial using diltiazem gel and found that a concentration of 2% produced a maximal effect of 28% reduction in the resting anal tone. Topical diltiazem is associated with fewer side effects, probably because of minimal systemic absorption.

Jawaid and associates⁸ prospectively randomized patients with chronic anal fissure to treatment by 0.2% GTN and 2% diltiazem. Forty patients were randomized into the 0.2%-GTN group and 40 patients received 2%-diltiazem ointment. Headache was observed in 22.5% of participants receiving diltiazem in contrast to 67.5% of those in whom GTN was used as a pharmacological modality. They concluded that diltiazem caused fewer side effects, particularly headache, than glyceryl-trinitrate ointment. Shrivastava and colleagues¹⁹ randomly divided patients of chronic anal fissure into three groups. Group I was treated with 2%-diltiazem ointment, Group II was treated with 0.2%-glyceryl-trinitrate (GTN) ointment, and Group III was kept as the control group. They favor the usage of diltiazem ointment as it was associated with better patient outcome and compliance.

In this study, the number of patients with headache reported

was significantly lower in the diltiazem group (7.5%) as compared to the GTN group (30%). Umer et al.⁹ encountered a frequency of headache of 40% in patients using GTN ointment as opposed to 6% in those whose primary treatment modality was diltiazem ointment, which is nearly comparable to the results of this study.

Limitation: The sample size of study is small and long-term follow-up is required.

CONCLUSION

Topical 2%-diltiazem ointment is a safe alternative in patients with chronic anal fissure as it is associated with lower frequency of headache than 0.2%-GTN ointment. Furthermore, the severity of headache with the use of GTN ointment was so marked that treatment was abandoned. Therefore, 2% diltiazem should be the first line therapy in treatment of chronic anal fissure when considering chemical sphincterotomy.

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