

# Evaluation of clinical effectiveness of topical 0.2% glyceryl trinitrate, topical 2% diltiazem and their combination in the treatment of chronic anal fissure

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## Abstract

**Background:** The longitudinal tear or defect in the epithelial lining of the anal canal distal to the dentate line is called anal fissure. It is of two types: acute and chronic. The break in the cycle of pain, spasm and ischemia is essential for successful treatment of anal fissure. Among multiple non-surgical treatment approaches, the appropriate approach with good patient compliance might be the use of topical agents as chemical sphincterotomy. However, the effectiveness of these agents has not been evaluated widely.

**Objectives:** To evaluate clinical effectiveness of topical 0.2% glyceryl trinitrate, topical 2% diltiazem and their combination in the treatment of chronic anal fissure.

**Methodology:** The study was prospective comparative type including total 158 patients. Initially, they were given first line therapy followed by chemical sphincterotomy agents. The study drugs were given to 84 patients (three groups - 0.2% glyceryl trinitrate, 2% diltiazem and their combination) who were not healed after initial therapy. Patients were assessed for pain using visual analogue scale and other symptoms prior to and after two and six weeks of therapy.

**Results:** Complete healing rate was higher with combination (92.86%) than individual agents. The reduction of visual analog scale score within each group and between the groups in the period between before and after treatment was found to be statistically significant. Headache and hypotension were the common side effects seen during study.

**Conclusion:** Anal fissures can be successfully managed by chemical sphincterotomy. The topical nitrates and calcium channel blockers in combination are found to be effective choice rather than individual agents.

**Key words:** Anal Fissure; Chemical Sphincterotomy; Constipation; Pain; Sitz bath

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## INTRODUCTION

Anal fissure or fissure in ano is a longitudinal tear or defect in the epithelial lining of the anal canal distal to the dentate line<sup>1</sup>. Though it is not a fatal condition,

it can significantly influence the quality of life of the affected person due to its troubling symptoms such as severe pain and bleeding per rectum. Both genders are equally affected, with a slight predilection towards females<sup>2</sup>. Anal fissure are classified into two types: acute and chronic, based on symptoms, duration and per rectal examination findings. An acute fissure is a simple laceration of less than six weeks duration whereas a chronic anal fissure is an ulceration of more than six weeks duration characterized by presence of hypertrophied anal papilla, sentinel skin tag and exposed internal sphincter muscle fibers<sup>3</sup>. Healed anal fissure is defined as complete re-epithelialization of the tear or defect in anal canal<sup>4</sup>.

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The treatment of anal fissure mainly aims at breaking the cycle of pain, spasm and ischemia. To minimize pain following anal trauma, all patients are initially managed with first line therapy in the form of stool softeners or bulk forming agents, topical 2% lignocaine gel application and warm sitz baths for two weeks<sup>5</sup>. Any patients who do not achieve symptom relief with initial treatments can be prescribed with topical calcium channel blockers (nifedipine, diltiazem), or topical nitric oxide donors (glyceryl trinitrate) or botulinum toxin injection which is regarded as chemical sphincterotomy. Surgical management is instituted only in the treatment resistant or failure cases as it may lead to fecal incontinence<sup>6</sup>.

Though there are multiple non-surgical treatment approaches for anal fissure, the appropriate approach with good patient compliance might be the use of topical agents as chemical sphincterotomy. Various studies have shown that nitrate and calcium channel blockers are found to be effective as topical application. No single drug therapy has been proven superior as they show relatively poor healing rate when compared with surgical therapy which necessitates the investigation of combination drug therapies<sup>7</sup>. However, the effectiveness of these agents has not been evaluated widely<sup>8</sup>. The aim of this study is to evaluate the clinical effectiveness of chemical sphincterotomy i.e. topical 0.2% glyceryl trinitrate, topical 2% diltiazem and their combination in treatment of chronic anal fissure.

## METHODOLOGY

This was a prospective comparative clinical study which involved 158 patients with diagnosis of anal fissure attending the surgical outpatient department (OPD) of tertiary level hospital of Central Nepal during the period from June 2018 to May 2019. Informed written consent was taken from patients before the commencement of the study after getting ethical approval from the institution.

A detailed history, general and systemic examination along with per rectal examination were done. Patient's age, gender, dietary habits, bowel habits and BMI were recorded as demographic variables. The new patients with anal fissure having symptoms more than six weeks duration who were treated with first line therapy for six weeks were included in the study. Patient with systemic diseases like diabetes mellitus, hypertension, chronic kidney or liver diseases, collagen tissue disease, malignancies, pregnancy, congestive cardiac failure, patients allergic to nitrates and diltiazem, patients with

previous perineal surgery and immunocompromised patient or patient on immune suppressive therapy were excluded from the study.

All 158 patients diagnosed as anal fissure were initially treated with stool softeners or bulk forming agents, topical 2% lignocaine gel and warm sitz baths for six weeks. Those patients with persistent symptoms for 10 minutes per session after initial therapy were randomly divided into three groups (n=84) by stratified random sampling for chemical sphincterotomy viz. 0.2% glyceryl trinitrate (GTN) group (n=28), 2% diltiazem (D) group (n=28) and their combination (GTN+D) group (n=28). All drugs were given topically twice a day for six weeks along with twice daily warm sitz bath and high fiber diet. Patients were assessed for pain and other related symptoms prior to and following two and six weeks of therapy. Pain was assessed using visual analogue scale (VAS) score ranging from 0 to 10, 0 as no pain and 10 as worst pain imaginable. Effectiveness was also measured with relief of other symptoms and side effects of drug therapy. Statistical analysis was performed using graph pad prism 8.1. Analysis of variance and Brown Forsythe test were used for the comparison between the groups. A *p* value of <0.05 was considered statistically significant.

## RESULTS

The number of patients diagnosed as anal fissure in surgical OPD during 12 months duration was 158. After treating them with first line therapy i.e. warm sitz bath, stool softeners or bulk forming agents and topical 2% lignocaine gel for six weeks, 74 (46.84%) patients were healed whereas 84 (53.16%) patients were not healed. Those 84 patients were randomly divided into three groups of twenty eight patients in each group to receive topical 0.2% glyceryl trinitrate, 2% diltiazem and their combination respectively.

The dietary habit pattern and body mass index (BMI) distribution of patients along with demographic profile are shown in table 1. The maximum number of patients in GTN group, D group and GTN+D group were 11 from 20 to 29 years age group, nine from 30 to 39 age group and eight from 20 to 29 age group respectively. The maximum number of patients from overall groups was 25 from 20 to 29 years age group. The number of male and female involved in the study were 36 and 48 respectively. The number of male in GTN, D and GTN+D group were 12, 14 and 15 respectively whereas numbers of female were 16, 14 and 13 from each group respectively.

The common symptoms presented by all patients were painful defecation (n=158), per rectal (PR) bleeding (n=151), constipation (n=136), perianal itching (n=47) and perianal discharge (n= 12). The patterns of symptoms present after initial six weeks of therapy are shown in table 2. Overall reduction rate in per rectal bleeding and pain were 90.47% and 54.76% after six weeks of therapy. The reduction rate of per rectal bleeding and pain after six weeks of topical 0.2% glyceryl trinitrate therapy were 84.61% and 39.28% whereas with topical 2% diltiazem therapy were 88.46% and 53.57% and with their combination were 96.29% and 71.42% respectively.

The pain was assessed by observing the change in VAS score prior to and after therapy. VAS score showed that pain reduced by  $\geq 50\%$  in GTN, D and GTN+D group were 57.14% (n=16), 75% (n=21) and 92.85% (n=26) respectively. The average pain score prior to/ after six weeks of treatment were found to be  $6.89 \pm 0.17 / 3.71 \pm 2.35$ ,  $6.61 \pm 0.19 / 2.57 \pm 0.32$  and

$6.11 \pm 0.18 / 0.32 \pm 0.22$  in GTN, D and GTN+D groups respectively. The reduction of VAS score within each group and between the groups in the period between before and after treatment was found to be statistically significant (Table 3).

The number of patient with partial healing i.e.  $> 50\%$  reduction in VAS or VAS 1-3 and disappearance of symptoms in GTN and D groups were 16 and 21 respectively whereas 26 patients from GTN+D group showed complete healing (VAS=0). None of the patient with GTN and D groups showed complete healing. The numbers of non-healed patients were 12, seven and two from GTN, D and GTN+D groups respectively.

Following six weeks of treatment with glyceryl trinitrate, diltiazem and their combination, the common side effects observed were headache (n=12), hypotension (n=7) and gastrointestinal upset (n=1) as shown in table 4.

**Table 1: Demographic Profile**

Drugs		GTN	D	GTN+D
Age in years (Mean $\pm$ SEM)		34.4 $\pm$ 1.42	37.4 $\pm$ 1.96	32.93 $\pm$ 1.40
Gender (Male:Female)		1.3:1	1.5:1	1.5:1
BMI	Normal	7	6	9
	Overweight	16	4	16
	Obesity	5	18	3
Dietary Habits	Non-vegetarian	21	24	25
	Vegetarian	7	4	3

**Table 2: Measurement of effectiveness**

Symptoms	After 6 wks of first line therapy (n=84)	GTN Group (n=28)			D Group (n=28)			GTN+D Group (n=28)		
		Day 0	After 2 wks	After 6 wks	Day 0	After 2 wks	After 6 wks	Day 0	After 2 wks	After 6 wks
Painful defecation	84	28	25	17	28	20	13	28	14	8
Bleeding PR	79	26	14	4	26	18	3	27	10	1
Perianal itching	0	0	0	4	0	0	3	0	0	1
Perianal discharge	5	2	2	0	2	2	0	1	1	0

**Table 3: Visual Analogue Scale Score in different drug groups**

Drugs	Before treatment	After 2 weeks	After 6 weeks	ANOVA	Brown-Forsythe Test
Glyceryl trinitrate	6.893 $\pm$ 0.1654	4.643 $\pm$ 0.2071	2.643 $\pm$ 0.4431	F = 14.34 P<0.0052	F = 0.21 P=0.8128 (ns)
Diltiazem	7.345 $\pm$ 0.1879	5.276 $\pm$ 0.2492	2.2827 $\pm$ 0.4176		
Combination	6.107 $\pm$ 0.1806	2.679 $\pm$ 0.2827	0.8214 $\pm$ 0.2245		

**Table 4: Side effect of the treatment**

Side effects	GTN Group (n=28)	D Group (n=28)	GTN+D Group (n=28)
Headache	7 (25%)	2 (17.14%)	3 (10.71%)
Hypotension	2 (7.14%)	2 (7.14%)	3 (10.71%)
Gastrointestinal upset	0	0	1 (3.57%)

## DISCUSSION

Anal fissure is one of the common benign ano-rectal problems presenting to the surgical outpatient department. Anal fissure develops in approximately 10-15% of the patients presenting with proctologic discomfort. 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. Anal fissure was found to be common in young adults (20 to 29 years age groups) which is similar to study done in India<sup>9</sup>. Our study has shown that 57.14% and 42.86% were male and female respectively. Our study showed slight male preponderance in occurrence of anal fissure which is in contrast to Shrestha SK et al and in coherence to the findings of Kuri SS et al. and Giridhar CM et al<sup>2,10,11</sup>.

Our study demonstrated that non-vegetarian diet, overweight and constipation were present in patients of anal fissure. Non-vegetarian diet has less fiber content which may predispose to constipation. Straining during defecation is common in constipation which leads to tear in the soft friable anal mucosa leading to anal fissure. Similarly, anal fissures are common in overweight population due to inadequate fiber intake, decreased physical activity and prolonged sitting, thereby leading to high basal internal sphincter tone and poor blood flow<sup>7,8</sup>.

In our study, 46.84% of the patients with anal fissure were successfully treated with first line therapy i.e. warm sitz bath, stool softeners or bulk forming agents and topical 2% lignocaine gel. The common symptoms they presented with were painful defecation (100%) followed by per rectal bleeding (95.57%), constipation (86.07%), perianal itching (29.74%) and perianal discharge (7.56%). Perianal itching was completely relieved and pain and bleeding was reduced by half after six weeks of first line therapy with warm sitz bath, stool softeners or bulk forming agents or topical lignocaine gel application<sup>12</sup>. Fissures are likely to be related to local trauma following passage of hard stool, chronic constipation and straining during bowel movements. Stool softeners helps to hydrate and soften the fecal material whereas bulk forming agents add bulks and water to stool facilitating

natural defecation. Similarly, warm sitz bath improves local hygiene, reduce inflammation and promote blood flow at the ulcer site whereas 2% lignocaine gel application helps to relieve the pain, itching and burning associated with anal fissure.

Out of 158 patients, 84 patients who remained symptomatic after first line therapy were candidates for comparative study comprising of three groups. All three groups showed partial alleviation of symptoms like pain, bleeding and constipation whereas complete alleviation of perianal discharge after six weeks of therapy. The patients receiving topical 0.2% glyceryl trinitrate showed 61.65% reduction in VAS score from day 0 (i.e. before starting treatment) to 6 weeks following treatment. Similarly, the patients receiving topical 2% diltiazem showed 68.93% decrement in VAS score whereas patient receiving topical 0.2% glyceryl trinitrate and 2% diltiazem in combination showed 86.54% reduction in VAS score from day 0 to six weeks after the treatment which is similar to the study done by Bulus H et al<sup>8</sup>. The change in VAS score before and after treatment with glyceryl trinitrate, diltiazem and their combination is found to be statistically significant ( $p=0.0052$ )<sup>13</sup>. The symptomatic relief was seen more with combination therapy rather than individual drug therapy. This might be due to synergistic effect of two commonly used agents i.e. glyceryl trinitrate and diltiazem which are already proven effective agents for chemical sphincterotomy. Persistence of anal sphincter spasm and the ischemia after tear in the epithelial lining of anal canal leads to chronic anal fissure. The aim of chronic anal fissure treatment is to remove ischemia by reducing spasm of anal sphincter. Various surgical and medical treatments have been tried for healing anal fissure. Chemical sphincterotomy have been suggested as an alternative to surgery to avoid possible complications of surgical treatment. Among these, nitrates, calcium channel blockers, and botulinum toxin are the most studied and used agents. Nitroglycerin, which is locally metabolized to nitric oxide, promotes fissure healing by decreasing anal sphincter pressure and concurrently increasing ano-dermal blood flow. Similarly, diltiazem is a calcium channel blockers which inhibits muscle contraction by preventing calcium influx into the cytoplasm via

membrane channels, thus causing relaxation of anal sphincter and increasing ano-dermal blood flow<sup>13</sup>.

Complete healing rate after six weeks of combination (GTN+D) therapy was 92.86% whereas there was no complete healing in six weeks when drugs were applied as individual therapy. Partial healing rate after individual drug application with GTN and D were 57.14% and 75% respectively. Non-healing rates were 42.86%, 25% and 7.14% for GTN, D and GTN+D groups respectively. A systematic review done by Poh A et al. showed healing rates for topical glyceryl trinitrate and diltiazem from 40.4% to 68% and 67% to 89.4% respectively<sup>7</sup>. There are various studies with topical diltiazem application among patients who are glyceryl trinitrate treatment resistance cases showing improvement in almost 50% cases. This could be due to its tolerance being higher than and mechanism of action being different from those of nitrates. Hence healing rates is higher among patients receiving combination drugs. Though first line medical therapy cures most anal fissures, chemical sphincterotomy with glyceryl trinitrate and diltiazem remains standard mode of treatment in chronic anal fissures<sup>8, 14</sup>. However, these drugs as individual therapy and in combination are not devoid of side effects such as headache, perianal itching, hypotension and gastrointestinal upset which may restrict its use by decreasing patient compliance<sup>15-17</sup>. A common

disadvantage of chemical sphincterotomy is non-permanent effect of sphincter relaxation resulting in high recurrence rate between 10 to 50% on long term follow up<sup>7</sup>.

Headache and hypotension were the main side effects occurring in almost 30% patients using topical glyceryl trinitrate application whereas almost 25% among patients using topical diltiazem brought about by its vasodilatation effect<sup>8, 9</sup>. Topical diltiazem is associated with fewer side effects, probably because of minimal systemic absorptions<sup>8</sup>. Gastrointestinal upset like nausea, vomiting and loose stool was seen in one patient with combination treatment only<sup>18, 19</sup>.

The significance of this study would have been better if it was conducted in multi-center with larger sample size, positive control group and longer duration including the follow up period and recurrence rate.

## CONCLUSION

Anal fissures are common ano-rectal problem encountered in surgical OPD. Chemical sphincterotomy is found to be effective armamentarium against chronic anal fissures. The combination of topical nitrates and calcium channel blockers seem effective option rather than individual agents though further effectiveness study is needed.

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