

# Comparative Evaluation of 0.2% Glyceryl Trinitrate vs. 2% Diltiazem Ointment in Treatment of Chronic Anal Fissure Treatment - A Randomized Trial

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## Abstract

**Introduction:** The initial management of chronic anal fissures nowadays is increasingly becoming medical since surgical procedures may be complicated by prolonged healing of wounds, higher incidence of incontinence of flatus/ mucous, anaesthesia requirement and higher cost. Medical treatment can be carried out on an outpatient basis and is cost-effective.

**Aim and study design:** We conducted a prospective randomised trial to comparatively evaluate the topical efficacy and complications of 0.2% GTN vs. 2% Diltiazem ointment in patients with chronic anal fissure.

**Methods:** A total of fifty patients were randomly assigned to two groups of 25 patients each, all of whom were treated with topical medication twice daily for a period of six weeks: group A was treated with 0.2% glyceryl trinitrate and group B with 2% diltiazem. None of the patients in either group received analgesics in any form during the course of treatment and follow-up. Cases of acute anal fissure, pregnancy, Crohn's disease, HIV, tuberculosis, fistula in ano or anal cancer, known allergy to drugs, heart disease, hypertension and patients who refused consent were excluded.

**Observation:** The mean age of patients in both groups ( $34.6 \pm 12.8$  vs.  $30.6 \pm 9.5$  years) was comparable. Group A (GTN) comprised 19 males and 6 females and Group B (Diltiazem) 17 males and 8 females ( $p > .05$ ). The mean duration of symptoms for both groups was  $16.64 \pm 12.3$  vs.  $16.08 \pm 11.9$  weeks, and the mean pain score of patients before treatment was  $8.64 \pm 0.95$  vs.  $8.44 \pm 1.19$  weeks, which was comparable. Perceptible pain relief as compared to pre-treatment levels was recorded for both groups after six weeks of therapy ( $p = .905$ ). Complete healing was observed in 72% patients in group A vs. 80% in group B at the end of six weeks ( $p$  value 0.508). Headache was reported in 36% patients in group A and 8% in group B; this difference was statistically significant ( $p$  value 0.041). The incidence of recurrence in both groups was comparable at 3-month follow-up ( $p$  value 0.756).

**Conclusion:** Both 0.2% GTN and 2% Diltiazem ointment are equally effective in chronic anal fissure treatment in terms of symptomatic pain relief, healing and recurrence, but headache is a troublesome side effect in patients treated with glyceryl trinitrate ointment. When considering medical management of chronic anal fissure, 2% Diltiazem ointment may be preferable as first-line treatment.

**Key words:** *Chronic anal fissure; glyceryl trinitrate; diltiazem ointment*

## Introduction

Anal fissure (also known as fissure in ano) is a painful linear tear situated in the distal anal canal extending from

just below the dentate line to the anal verge [1]. It affects all age groups but is particularly seen in young and healthy adults with an equal incidence across both sexes. An anal fissure characteristically presents with pain (as the area is supplied by highly sensitive spinal nerves), bright red bleeding per rectum, mucous discharge and constipation. Anal fissures occur predominantly in the midline with 90% being located posteriorly and 10% anteriorly.

A fissure is said to be chronic if it is present for more than six weeks and fails to resolve. Digital rectal examination typically reveals a fissure with induration of the ulcer margins, fibrosis in the ulcer base, with or without exposure of horizontal fibres of internal anal sphincter and development of sentinel and tag.

There is evidence that anal fissure is associated with spasm of internal anal sphincter [2] (except in postpartum patients [3]) and a reduction in blood flow with delayed or

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non-healing of the ulcer [4]. The aim of the treatment is to improve the blood supply of the ischaemic area to facilitate healing, if necessary by reducing resting and pressure. Both anal dilatation and sphincterotomy are associated with asymmetry of the anal canal and irreversible damage to the anal sphincter. Since mainly young individuals are affected by anal fissure, there is increasing concern over the long-term results and faecal incontinence after surgical procedures.

Medical management of fissure in ano was introduced in 1993 and involves using an agent that produces relaxation of internal sphincter which is known as "chemical sphincterotomy". A variety of agents like botulinum toxin, isosorbide dinitrate, glyceryl trinitrate, calcium channel blockers such as nifedipine or diltiazem have been used to date, all of which focus on breaking the cycle of pain, spasm and ischaemia, thought to be responsible for development of fissure in ano. When applied locally to the anal canal twice or thrice daily for 6 to 8 weeks, glyceryl trinitrate (0.2% cream) produces sufficient relaxation of the sphincter to allow the fissure to heal in up to two-thirds of patients [5]. In addition, being a vasodilator, glyceryl trinitrate improves blood flow to the area and this aids healing. Unfortunately, adverse effects, such as orthostatic hypotension, syncopal attacks, tachyphylaxis and moderate to severe headaches, limit the utility of GTN ointment.

Later, cytoplasmic calcium also proved to be an important agent for smooth muscle contraction. In 1999, Carapeti *et al.* [6] used a calcium channel blocker, namely Diltiazem, and found that when applied locally 2% Diltiazem gel produced reduction in mean resting pressure. In addition, and unlike topical nitrates for treatment of anal fissures, it produced potentially low side-effects such as headache. The need for lateral sphincterotomy can be avoided in up to 70% of cases.

Although the debate concerning optimum first-line therapy for chronic anal fissure continues, treatment is becoming increasingly medical. Surgical techniques like anal dilatation or open or closed sphincterotomy for treating anal fissure permanently lower resting anal pressure and result in healing of the ulcer in the majority of patients, but these surgical procedures may be complicated by non-healing wounds and a higher incidence of incontinence of flatus or mucus. Medical treatment avoids all the complications related to surgical procedures and it can be carried out on an outpatient basis. It is cost-effective, does not require hospitalisation and does not incur loss of man hours. The present study was thus planned to comparatively evaluate the topical efficacy and complications of 0.2% GTN and 2% Diltiazem ointment in the management of chronic anal fissure.

## Aims and objectives

To evaluate and prospectively compare the efficacy of

topical 0.2% glyceryl trinitrate (GTN) ointment and 2% Diltiazem ointment in patients with chronic anal fissure in terms of improvement in signs and symptoms, the time taken for healing, side effects of treatment and recurrence, if any.

## Material and methods

A total of 50 patients presenting with chronic anal fissure were included in the present study. All patients were divided into two groups by computer-generated randomization.

**Group A:** Included 25 patients treated with 0.2% GTN ointment along with other conservative methods like sitz bath and stool softeners.

**Group B:** Included 25 patients treated with 2% diltiazem ointment along with other conservative methods like sitz bath and stool softeners.

The patients in both groups were instructed to apply the topical medication twice daily for a period of six weeks. None of the patients in either group received analgesics in any form during the course of treatment and follow-up.

### Inclusion criteria

- Patients willing to give written informed consent.
- All cases of single anal fissure either anterior or posterior, of more than six weeks duration.
- Anal fissures with associated features of chronicity like sentinel pile or hypertrophied papillae or exposure of horizontal fibres of the internal sphincter.

### Exclusion Criteria

- Acute anal fissure either single or multiple of <6 weeks duration without any secondary changes.
- Fissure in pregnant women.
- Known cases of Crohn's disease, HIV, tuberculosis, fistula in ano or anal cancer presenting with anal fissure.
- Patients receiving nitrates or calcium channel blockers for medical conditions like heart disease and hypertension.
- Patients with a history of chronic headache.

The intensity of pain was assessed before and during the course of treatment using the visual analogue score. This visual analogue scale is a 10 cm line on which 0 represents no pain and 10 the most severe pain. Group A patients were prescribed a single brand of 0.2% glyceryl trinitrate ointment (nitrogesic ointment) while group B patients were treated with a single brand 2% Diltiazem ointment (Diltiact ointment).

Ointment was to be applied by finger tip to the anus twice daily, once in the morning after passing stool and then again at night before going to bed. The amount of ointment recommended for each application was the size of a pea or tip of index finger (0.5 gm). The patients were

encouraged to follow a high-fibre diet and use a warm sitz bath before applying the ointment. The patients under study were initially followed twice a week during the first week to assess and record the relief of pain according to the VAS, and thereafter at 3- and 6-week follow-up to assess for fissure healing. During the course of treatment, the time taken for complete healing of the fissure (in the form of symptoms like anal pain and bleeding and the absence of fissure on examination) was noted. On complete healing of the fissure, the patients were asked to stop the application of ointment and continue with the high-fibre diet. The healed fissures were then subsequently followed up at three months for recurrence. Side effects of treatment, particularly headache, postural hypotension, palpitations and dizziness, were noted at each visit of the patient. At every follow-up, the perianal region around the fissure was also examined for excoriation because of local application of the ointment.

Patients not showing any improvement at six weeks were offered the opportunity of undergoing surgical intervention because of failed medical management of the disease.

### Statistical analysis

At the end of the study, the data was collected and analysed. The qualitative data was presented in the form of a numbered percentage. Chi-square test was used as a test of significance for qualitative data. Student's t-test was used as a test of significance for quantitative data. A p value of <0.05 was considered for significance.

### Observations

The mean age between the two groups was comparable: for group A it was  $34.6 \pm 12.8$  years (range between 18 to 65 years) and for group B it was  $30.6 \pm 9.5$  years (range between 20 to 53 years). Group A comprised 19 males and 6 females and group B 17 males and 8 females. Sex distribution was found to be comparable.

The mean duration of symptoms in group A was  $16.64 \pm 12.3$  weeks and in group B it was  $16.08 \pm 11.9$  weeks.

Patients in both groups complained of pain during defaecation. The mean pain score of patients before treatment in group A was  $8.64 \pm 0.95$  and in group B it was  $8.44 \pm 1.19$ . The mean pain score between the two groups was found to be comparable (Table 1).

Twenty-one out of 25 patients (84%) had bleeding per rectum in group A and 20/25 (80%) in group B. Sixteen out of 25 patients (64%) had constipation in group A as opposed to 19/25 (76%) patients in group B. Ten out of 25 patients (40%) had pruritus ani in group A and 9/25 (36%) in group B.

The number of patients in group A with the fissure located in the posterior midline was 22 (88%) and 3 patients

(12%) had the fissure in the anterior midline whereas in group B, 19 (76%) had the fissure in the posterior midline and 6 (24%) had an anterior midline fissure in ano. In group A, 14/25 (50%) patients had anal tags as opposed to 18/25 (72%) in group B.

### Pain relief after treatment (Table 1)

In group A (patients treated with 0.2% nitroglycerine ointment), the mean pain score at the first follow-up (at 72 hours) was  $8.40 \pm 1.19$  on the VAS. The mean pain score at follow-up at weeks 1, 3 and 6 was  $7.56 \pm 1.60$ ,  $3.00 \pm 2.25$  and  $1.64 \pm 2.43$ , respectively, while in group B (patients treated with 2% Diltiazem ointment) the mean pain score at follow-up at weeks 1, 3 and 6 was  $7.80 \pm 1.38$ ,  $6.28 \pm 1.40$ ,  $3.32 \pm 1.99$  and  $1.56 \pm 2.27$ , respectively. Patients in both groups experienced perceptible pain relief as compared to pretreatment levels after six weeks of therapy with a p value 0.905 as shown in the table below.

### Healing

None of the patients in either group achieved complete healing at the end of the first week. However, at the end of week 3, eight patients in group A and six in group B had completely healed fissures. At the end of six weeks, complete healing was observed in 18/25 (72%) patients in group A and in 20/25 (80%) patients in group B (p value 0.508).

### Side effects of the treatment

Apart from headache which was reported in 9/25 (36%) patients in group A, no other side effects were experienced in this group, whereas in group B, 2/25 (8%) patients reported headache and one patient developed anal excoriation. None of the patients in either group had to cease medication due to side effects. This difference was statistically significant (p value 0.041).

### Recurrence

Two out of 18 (11.1%) patients in group A had a recurrence whereas 3/20 (15%) patients in group B had a recur-

**Table 1.** Pain relief after treatment.

Mean pain score	Group A	Group B	p value
Before treatment	$8.64 \pm 0.95$	$8.44 \pm 1.19$	
After 72 hours	$8.40 \pm 1.19$	$7.80 \pm 1.38$	
At the end of week 1	$7.56 \pm 1.60$	$6.28 \pm 1.40$	
At the end of week 3	$3.00 \pm 2.25$	$3.32 \pm 1.99$	
At the end of week 6	$1.64 \pm 2.42$	$1.56 \pm 2.27$	0.905 (p>0.05)

**Table 2.** Comparison of previous studies with present study with respect to fissure healing.

Author	Year	N	Duration	GTN group	DTZ group	p value
Kocher HM [7]	2001	60	8 weeks	86%	77%	0.21
Shrivastava et al [9]	2004	90	6 weeks	57%	63%	0.303
Jawaid et al [11]	2009	80	8 weeks	82%	77%	0.576
Rithin et al [12]	2012	200	6 weeks	68%	72%	<0.0001
Present study	2014	50	6 weeks	72%	80%	0.508

rence of the fissure at the same site at 3-month follow-up (p value 0.756).

### Discussion (Tables 2-4)

The aim of the treatment is to improve the blood supply of the ischaemic area to facilitate healing and breaking the cycle of pain, spasm and ischaemia which is thought to be responsible for development of fissure in ano.

The mean pain score after initiating treatment decreased from 8.64 to 1.64 (after application of GTN ointment) and from 8.44 to 1.56 in the case of DTZ ointment at the end of six weeks. Therefore, both 0.2% GTN ointment and 2% DTZ ointment were found to be equally effective with respect to the degree of pain relief (p value 0.905). This result was consistent with the study undertaken by Kocher HM [7] in 60 patients of chronic anal fissure which showed no significant difference (p value >0.24) between groups treated by DTZ ointment and GTN ointment in reduction of mean pain score at eight weeks. In a randomized prospective double-blind placebo controlled trial of GTN ointment, Lund and Scholefield [8] found marked pain relief after using GTN ointment in comparison to placebo. However, the results of the present study were at variance with a study conducted by Shrivastava et al. [9] of 90 chronic anal fissure patients that found DTZ ointment to be associated with a higher degree of pain relief in comparison to GTN ointment (p value 0.015).

Complete healing was observed in 18/25 patients (72%) in group A and 20/25 patients (80%) in group B at the end of six weeks of treatment (p value >0.05). Similar findings

were observed by Kocher HM [7], Lund and Scholefield [8] and Knight et al. [10]. In another study, Shrivastava et al. [9] found that 63% patients healed with DTZ ointment while 57.3% of patients healed with GTN ointment at six weeks of treatment (p value 0.303). Likewise, Jwaid M et al. [11] in a study of eight patients with symptomatic chronic anal fissure reported healing in 31/40 patients treated with DTZ ointment and 33/40 patients treated with GTN ointment after eight weeks of treatment and concluded that there was no significant difference between the two groups (p value 0.576). However, the results of the present study were at variance with the findings of a recent study conducted by Rithin Suvarna et al. [12] involving 200 patients with chronic anal fissure that found a statistically significant difference (p value <0.0001) between the two groups treated with DTZ and GTN ointment. Complete healing was achieved in 71.87% patients in the DTZ group while 68.23% patients in the GTN group achieved complete healing by the end of six weeks of treatment.

As concerns the side effects, 9/25 patients treated with 0.2% GTN reported headache as the main side effect whereas only 2/25 patients experienced headache in the DTZ group, and the difference was significant (p value <0.05). Only one patient in the DTZ group had perianal itching and excoriation but none of the patients in either group had to stop the medication due to side effects. However, Carapeti et al. [13] reported headache in 72% of the 70 patients with chronic anal fissure treated by GTN ointment which also led to discontinuation of treatment by many patients. Kocher HM [7] in a study of 60 patients reported more headaches with GTN (17/29 patients) than with DTZ (8/31 patients).

**Table 3.** Comparison of previous studies with present study with respect to headache as a side effect of the treatment

Author	Year	N	Duration	GTN group	DTZ group	p value
Kocher HM [7]	2001	60	8 weeks	59%	26%	0.01
Shrivastava et al [9]	2004	90	6 weeks	66%	-	<0.05
Jawaid et al [11]	2009	80	8 weeks	68%	23%	<0.0001
Rithin et al [12]	2012	200	6 weeks	67%	05%	<0.0001
Present study	2014	50	6 weeks	36%	08%	0.041

**Table 4.** Comparison of previous studies with present study with respect to recurrence.

Author	Year	N	Duration	GTN group	DTZ group	p value
Kocher HM [7]	2001	60	8 weeks	08%	-	0.157
Shrivastava et al [9]	2004	90	6 weeks	32%	13%	0.303
Rithin et al [12]	2012	200	6 weeks	20%	10%	0.142
Present study	2014	50	6 weeks	11%	15%	0.756

The difference was statistically significant (p value 0.01) and in line with the present study. Likewise, Shrivastva et al. [9] reported 20 out of 30 (66%) patients using GTN ointment with headache as a major side effect whereas those in DTZ group did not complain of any side effects. These results were significant (p value <0.05) and were in agreement with the results of the present study. Similarly, Jawaid M et al. [11] reported fewer cases of side effects overall with DTZ (13/40) as compared against GTN ointment (29/40). In particular, headache occurred more commonly with GTN (27/40) than with DTZ ointment (9/40) with p value <0.0001. A recent study by Rithin Suvarna et al. [12] observed that 67% of patients in GTN group suffered from headache compared to only 5.20% in DTZ group (p value <0.0001).

In the present study recurrence rate at 3-month follow-up were 11% and 15% in patients using GTN and DTZ ointment respectively (p value 0.756). These results are in keeping with the study conducted by Shrivastva et al. [9] who found a recurrence rate of 12.5% in patients using DTZ ointment and 32% in patients using GTN ointment. In a study conducted by Carapeti et al. [13] in 70 patients, 67% of fissures healed in the GTN group and 32% healed in the control group. Out of all healed fissures, 33% experienced a recurrence with GTN ointment as compared to 43% in the control group. Kocher HM [7] observed that only two patients had a recurrence at 12-week follow-up out of 25 patients with healed fissures in the GTN group whereas out of 24 patients with healed fissures in the DTZ group, none of the patients experienced recurrence. A study by Rithin Suvarna et al. [12] involving 200 patients with chronic anal fissure also reported that 6 out of 62 patients had a recurrence in the DTZ group whereas 9 out of 46 patients reported recurrence at the end of one-year follow-up. The difference was statistically insignificant.

## Conclusions

Although surgical techniques like anal dilatation and open or closed sphincterotomy may be a one-time solution with good symptomatic relief, surgical treatment may be complicated by non-healing wounds and permanent incontinence of flatus or faeces. The treatment of chronic anal fissure nowadays is becoming increasingly medical since it

can be carried out on an outpatient basis, it is cost-effective and, moreover, incurs no loss of man hours. The results of the present study demonstrate that both 0.2% glyceryl trinitrate ointment and 2% diltiazem ointment are equally effective in terms of symptomatic pain relief, healing and recurrence in the treatment of chronic anal fissure. However, headache may be a troublesome side effect in patients treated with glyceryl trinitrate ointment. Therefore, when considering medical management for treating chronic anal fissure, 2% diltiazem ointment may be preferable as first-line treatment.

## Ethical Approval

The Authors declare that the study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964.

Also informed consent was obtained from the patients prior to treatment.

## Conflicts of interest

The authors declare that there is no conflict of interest.

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