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CHRONIC ANAL FISSURE; A RANDOMISED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL OF 0.5% GLYCERYL TRINITRATE OINTMENT

*DR. SAQIB ZEESHAN
Ireland

DR. JEHAN ZEB CHUGHTAI
Ireland

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***Correspondence Address:**

Dr. Saqib Zeeshan (saqibzeeshan23@hotmail.com)
5 Castle Avenue Kilminchy, Portlaois County Laois, Ireland

ABSTRACT... Topical application of glyceryl trinitrate (GTN) ointment heals anal fissures, providing an alternative to the traditional first line treatment of surgical sphincterotomy. **Setting:** Tathlith General Hospital Saudi Arabia. **Period:** January 2001 – April 2003. **Objective:** To determine the effectiveness and safety of topical 0.5% glyceryl trinitrate (GTN) in the management of chronic anal fissure. **Patients & methods:** Individual Patients were randomized to receive 0.5%GTN paste or placebo three times per day for six weeks in addition to oral senna and/or lactulose. Patients took laxatives alone for further 6 weeks. Patients were followed every week for six weeks and then fortnightly for another six weeks to assess pain scores and were given advice. **Results:** Fifty patients were recruited in this study and 44 patients completed the trial (23 in the GTN group and 21 in the placebo group), patients who could not complete the study were excluded. At 6 weeks, 74% of patients had no pain in the GTN group as compared to the 29% in the placebo group. In 26% of cases treatment was unsuccessful. At three month follow up there was no early recurrence. The prevalence of headaches was 65% in GTN group (reported by 15 patients) and 24% in placebo group (reported by 5 patients). Mean pain scores were lower in the GTN group as compared to the placebo group. **Conclusions:** The use of 0.5% GTN induces healing of chronic anal fissures and may be used as a first line of treatment in patients with chronic anal fissure. Successful treatment may come at the expense of a high incidence of headaches.

Key words: Chronic anal fissure glyceryl trinitrate (GTN) ointment Pain.

INTRODUCTION

Chronic anal fissure is a common ailment characterized by pain on defecation and rectal bleeding¹. Fissures are often precipitated by an episode of constipation, followed by passage of a hard stool resulting in a perianal tear^{2,3}. On examination a split in the skin of the distal anal canal is seen; most anal fissures occur in the posterior midline^{3,4}.

Unlike acute anal fissures, chronic fissures-in-ano do not usually respond to dietary advice alone⁵. The aim of treatment is to alleviate sphincter hypertonia and improve blood flow to the ulcerated area⁶. Lateral internal anal sphincterotomy has replaced anal stretching (Lord's dilatation) as the mainstay of treatment due to concerns over adverse effects on continence⁷. Lateral sphincterotomy permanently lowers resting anal pressure and in doing so aids the healing of anal fissures^{6,7}. It may,

however, be associated with temporary or permanent alterations in continence in up to 35% of patients^{6,7}.

Recent work has suggested that anal sphincter spasm and subsequent ischaemia are important factors in the development and persistence of an anal fissure^{6,7,12}. The maximum resting anal pressure (MRP), which relates mainly to internal anal sphincter smooth muscle activity, is raised¹². This contributes to the pain and localised ischaemia of the traumatised anal lining, perpetuating ulceration and preventing healing. Patients with anal fissure tend to have a high anal maximum resting pressure (MRP) which if reduced leads to fissure healing and increased blood flow to the fissure ulcer. Anal dilatation and lateral internal sphincterotomy lower the MRP and heal the fissure in most cases but with the complication of minor incontinence in up to 30 per cent of cases¹⁰.

Nitric oxide has recently been identified as the neurotransmitter mediating relaxation of the internal anal sphincter. GTN is metabolised to nitric oxide and leads to sphincter muscle relaxation and reduction in the maximum anal resting pressure¹¹. This results in an improvement in pecten perfusion which aids in healing and eliminates the risk of permanent anal incontinence associated with surgery.

Existing data concerns mainly the efficacy of 0.2% GTN paste. Little is known about the use of higher doses. We present the results of using 0.5% GTN paste as first line treatment of chronic anal fissures.

PATIENTS AND METHODS

Forty-four consecutive patients with chronic anal fissure were included in this study. A positive diagnosis of anal fissure was made in the presence of: (1) a visible anal fissure; and (2) painful defaecation with or without rectal bleeding on defaecation.

Chronicity was determined by a history longer than 3

months, the presence of a sentinel tag or fibrosis at the base of the ulcer on examination. Patients were excluded if there was a history of recurrent fissure, already on nitrates for other conditions or severe headaches.

At presentation, a pain score (0-10) was established as well as a symptom score (0-4) with one point each for pain, bleeding, discharge and itching.

Patients were assigned to receive thrice daily perianal 0.5% GTN or placebo paste for six weeks in a double blind manner by a senior pharmacist using a code. The code was kept secret in the pharmacy. The GTN ointments were made in the hospital pharmacy using the commercially available GTN to a concentration of 0.5% in paraffin. Both 0.5% GTN and placebo bottles looked identical.

Patients were instructed to apply the trial ointment by measuring out the appropriate amount 'pea size' approx 0.1 gm and then applying this to the peri and intraanal region three times per day. All patients received senna and lactulose for 12 weeks. All medication was dispensed directly from the hospital pharmacy with written instructions.

All patients were reviewed 3 weekly for 3 months and then at 6 months to assess pain and symptom score and to assess fissure healing, compliance. Patients who did not respond to treatment or who were unable to comply with the treatment were offered lateral anal sphincterotomy.

Primary outcome

Primary outcome to this study was the time to painless defaecation in 3 weeks.

Statistical Analysis Cochran Mantel Haenszel statistic is used to test the hypothesis that the Group (row) mean scores are same by Statistical Analysis Software (SAS). P-value less than or equal to 0.05 consider significant.

Table-I. Patients characteristics

	No. Of pts.	Median age (range) (year)	Sex	Median duration of symptoms (range) (year)	Site of fissure	
					Anterior	Posterior
0.5% GTN	23	36 (22-54)	16M	5 (3-7)	2	14
			07F		1	06
Placebo	21	35 (21-78)	13M	5 (3-8)	1	12
			08F		1	07

RESULTS

At the time of presentation 33 (75%) out of the total 44 patients had two or more of the documented symptoms. At 3 weeks 15 (65%) patients were symptom free in the GTN group and only 04 in the Placebo group. At 3 months follow up 17 (74%) patients were symptom free in the GTN group and 07 (38%) in the placebo group.

The mean age of the patients was 36 years range (22-56) in the GTN group and 35 years range (21-78) in the placebo group. The mean duration of history of the fissure was 5 months range (3-7) in GTN group and (3-8) in placebo group.

The mean pain score at presentation was 7 range (3-9) in both the groups.

The mean pain score at 3 weeks follow up was 3 range (2-5) in the GTN group and 6 range (3-7) in the placebo group with 15 (65%) patients in the GTN group and 04 (28%) patients in the placebo group experienced no pain at 3 weeks, and 17 (74%) in GTN group and 08 (38%) in the placebo group were pain free at 3 months follow up.

Mean score for Pain and Visible fissure in both groups are statistically significant as p-values 0.05, 0.04 respectively.

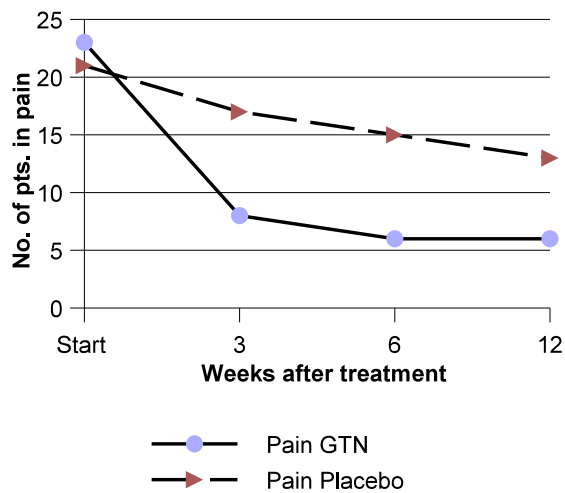
Overall, at 12 weeks following treatment with 0.5% GTN paste, 17/23(74%) patients had a clinically healed fissure (Table-II). Six of these patients continued to experience pain and were offered a lateral internal sphincterectomy. In the placebo group 13 patients (62%) had visible fissure and pain at 12 weeks follow up and were offered 0.5% GTN ointment or lateral internal sphincterectomy.

In six (26%) patients, treatment with 0.5% GTN paste was unsuccessful, and these patients were offered lateral internal sphincterectomy. 15 (65%) patients in the GTN group developed head aches of varying intensity as compared to 2 (10%) patients developing headaches in the placebo group. At 6-month follow-up, out the 17 patients successfully treated with 0.5% GTN ointment 16 remained symptom free one patient developed recurrence of the disease.

Table-II. Symptoms and signs at outpatient review

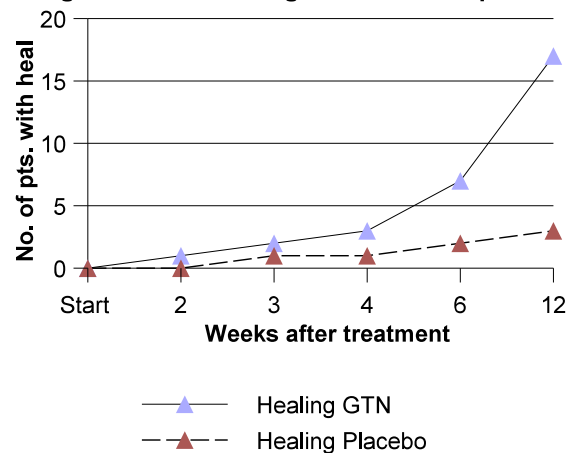
Symptom	Group	Start of trial (%)	3 weeks (%)	6weeks (%)	12weeks (%)	p-value
Pain	GTN	23/23 (100%)	08/23 (34%)	06/23 (26%)	06/23 (26%)	0.05
	Placebo	21/21 (100%)	17/21 (81%)	15/21 (71%)	13/21 (62%)	
Bleeding	GTN	18/23 (78%)	01/23 (4%)	01/23 (4%)	01/23 (4%)	0.68
	Placebo	17/21 (85%)	02/21 (9%)	01/21 (5%)	00/21 (0%)	
Constipation	GTN	18/23 (78%)	01/23 (4%)	0/23 (0%)	0/23 (0%)	1.00
	Placebo	18/21 (86%)	01/21 (5%)	0/21 (0%)	0/21 (0%)	
Visible fissure	GTN	23/23 (100%)	21/23 (91%)	16/23 (69%)	6/23 (26%)	0.04
	Placebo	21/21 (100%)	20/21 (95%)	19/21 (90%)	18/21 (85%)	

Fig-1. Pain control after GTN treatment and placebo



effective for over two thirds of patients^{4,7,9,12}. Our current study provides further evidence that topical GTN paste is an effective alternative to surgery in treating chronic fissures-in-ano.

Fig-2. Fissure healing with GTN and placebo



DISCUSSION

Unlike acute anal fissures, chronic fissures-in-ano do not usually respond to dietary advice alone. Treatment of anal fissures using topical GTN has been shown to be

Most data available is on the use 0.2% GTN^{3,8,11}. Only one small uncontrolled study has previously assessed the use of topical 0.5% GTN ointment in the treatment of anal fissures, this study¹², however, included patients with Crohn's disease and thrombosed external piles; indeed only 12 patients in this series had primary fissures-in-ano. Relief of pain was shown to be rapid and complete but no physical examination was performed to assess fissure healing and follow-up was to 8 weeks only. Curiously, headaches were reported in only 7 of the 20 patients in Gorfine's (1995)¹² study despite use of the 0.5% GTN paste 4 times a day. More recently, a randomized controlled trial showed that after eight weeks of treatment the healing rate in the placebo group was 37.5% compared with 46.9% for 0.1%, 40.4% for 0.2%, and 54.1% for 0.4% GTN⁹. Our series is unique in the use of 0.5% GTN paste. It shows that up to 75% of patients with chronic anal fissures can be successfully treated using topical 0.5% GTN paste as a primary measure. The effect of treatment appears to be almost immediate with symptomatic improvement evident at 3 weeks from the commencement of treatment. The rapid symptomatic improvement with 0.5% GTN compares favourably with the use of 0.2% GTN. Whilst there is little difference in the overall outcome of treatment there does appear to be a better outcome with the use of higher doses (75% with 0.5% vs. 64% with 0.2%). This benefit, however, occurs at the expense of more headaches and a lower compliance rate. Indeed, as in the use of GTN for angina, headaches are a significant side effect of treatment. The use of 0.5% GTN is associated with a 65% incidence of headaches. This compares with a headache incidence of 58%, when using 0.2% GTN ointment.

Of note is the minimal difference in the findings at 6 and 12-week follow-up. Symptom scores were nearly identical with partially healed ulcers at 6 weeks completing the healing process within 12 weeks. It would appear that compliant that responds to treatment do so within 6 weeks or probably not at all. This suggests that failure to

respond to topical GTN at 6 weeks is an indication for an alternative therapeutic approach.

Early recurrence does not appear to be a significant problem.

CONCLUSION

Patients with chronic fissure in ano, can greatly benefit from 0.5% GTN ointment, which is non-invasive and effective. It should be considered as first line of treatment, especially in patients who do not want surgery or are unfit for surgery. Healing of the chronic anal fissure using the 0.5% GTN ointment comes at a cost of some side effects mainly head aches which is more sever as compared to the use of 0.2%GTN ointment and it usually disappear once the treatment is stopped. Fissures, resistant to conservative measures or in patients who cannot tolerate the side effects lateral internal sphincterotomy can be performed. Moreover, topical treatment proved to be significantly cost-effective.

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