

The Use of Glyceryl Tri-Nitrate Ointment in Treatment of Chronic Fissure in Ano

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Background: Chronic anal fissure is a common painful condition. It is traditionally treated by anal dilatation or by lateral sphincterotomy. However, both of these surgical treatments may cause a degree of incontinence in 35 - 45% of patients. Several recent trials have shown that glyceryl trinitrate (GTN) can reduce sphincter pressure and heal up to 70% of chronic fissures.

Objective: Assessment of the efficacy of topical 0.2% glyceryl trinitrate (GTN) ointment in the treatment of chronic anal fissure.

Design: Prospective uncontrolled clinical study.

Setting: Surgical polyclinic, Bahrain.

Method: Fifty-four patients were diagnosed as having chronic anal fissure and treated with 0.2% GTN ointment during the period from June 2002 to August 2005. They were reviewed at 1, 2, 6-8 and up to 12 weeks to assess symptoms, fissure healing, compliance, duration of symptoms free period after finishing or stopping the course of treatment.

Result: At six-eight weeks, the GTN course was completed or taken for longer duration in 34 patients (62.9%). The course was stopped before 6-8 weeks in 20 patients (37%). Pain was completely relieved in 25 /34 patients (73.5%) and partially relieved in 5/34 patients (14.7%), bleeding was absent in 32/34 patients (94%), anal tone became normal in 32/34 patients (94%), and 28/34 patients (82.4%) had either healing or healed fissures.

Twenty patients stopped GTN course before 6 weeks due to different causes, such as, side effects mainly headache (60 %), non compliance (95%), or no response at all (50%). Recurrence of symptoms in the first six months was seen in 26 patients. There was a highly significant positive relationship between duration of treatment and recurrence of symptoms. The recurrence was treated surgically in 14 patients, traditional ointments in 8 patients, and repeated GTN course in 4 patients.

Conclusion: The use of 0.2% GTN induces rapid healing of chronic anal fissures with an 82.4% healing rate in this study. Successful treatment may come at the expense of high incidence of headache although it is lower in our study due to low GTN concentration.

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An anal fissure is a linear tear in the lining of the distal anal canal below the dentate line. The majority of anal fissures are acute and relatively short-lived. If it persists more than six weeks to three months, it becomes chronic¹.

Chronic fissure in ano is a common condition affecting all age groups, but it is seen particularly in young and otherwise healthy adults, with equal incidence across the sexes. The classical symptom is anal pain during or after defecation accompanied by the passage of bright red blood per anus. On examination, the fissure may be apparent, but marked spasm of the anal sphincter often obscures the view. Secondary changes such as a sentinel skin tag, hypertrophied anal papilla or a degree of anal stenosis are often present. Fissures are usually single and in the posterior midline, but 10% of women and 1% of men have anterior fissures.

Chronic anal fissures are generally associated with raised resting anal canal pressure and subsequent ischemia, secondary to hypertonicity of the internal anal sphincter. The treatment is directed at reducing the hypertonia. In 10-30% of chronic fissures, conservative measures will eventually resolve the problem. Traditional surgical treatments, namely manual anal dilatation or sphincterotomy, effectively heal most fissures within a few weeks, but may result in permanently impaired anal continence. In 35 - 45% of patients, there is a degree of anal incontinence after such procedures²⁻⁹. This has led to the search for alternative non-surgical treatment, and various pharmacological agents have shown to lower resting anal pressure and heal fissures without anal incontinence.

Recognition of Nitrous Oxide (NO) as the non-adrenergic, non-cholinergic neurotransmitter mediating relaxation of the internal sphincter has initiated the widespread use of organic nitrates in the treatment of chronic anal fissure. These agents are metabolised at a cellular level to release NO which, in turn, mediates relaxation of the internal sphincter via the guanylyl cyclase pathway by increasing cGMP levels within the smooth muscle cells³.

Topical Preparations of 0.2% GTN ointment is probably the most widely used first line treatment in the UK with successful results, but many patients experience troublesome headaches. Most studies reported satisfactory healing in the majority of cases^{2, 10}.

The aim of the study is to evaluate the effectiveness of using 0.2% GTN ointment in the treatment of chronic anal fissure patients.

METHOD

The study was performed from June 2003 until August 2005. The follow up period for all patients ranged between 4 months and 28 months.

Fifty-four patients with chronic anal fissures were included in the study. Chronicity was determined by history of more than 3 months, had tried traditional conservative treatment (such as ointments, suppositories and laxatives) for long time, presence on examination of skin tag, and or previous surgical intervention such as anal dilatation. Oral informed consent was taken from these patients.

Pregnant and lactating patients were excluded from this study. All patients above forty years of age had barium enema or colonoscopy during their course of treatment.

All patients were evaluated regarding pain, bleeding, anal tone and fissure healing.

Pain and bleeding were evaluated by asking the patient. Anal tone and fissure healing were evaluated by clinical examination done by the senior author. Patients who had severe recurrence (i.e similar to the presenting symptoms) were treated with anal dilatation or lateral sphincterotomy.

The concentration of the glyceryl trinitrate ointment was 0.2%. The dilution was prepared in the pharmacy to reach the 0.2% concentration using soft white paraffin. It was prescribed three times / day for 6-8 weeks. Thirty-four patients completed the 6-8 weeks course. Few of them had extended their course to 12 weeks, which is acceptable if needed. All patients received fiber laxatives with the treatment.

RESULT

The results were analyzed using the SPSS system. Fifty-four patients took the GTN 0.2% ointment. Fifty-three patients (98.1%) were females. Age ranged between 19-80 years, and 25 patients (46.3%) were between 30-49 years of age.

At presentation all patients (54) complained of pain (100%), 42/54 patients (77.8%) had bleeding, and external anal skin tag. Chronic constipation was present in 46/54 patients (85.2%). Spastic colon was present in 9/54 patients (16.7%). One patient had Crohn's disease. On examination, all patients (100%) had fissure, 52 patients (96.3%) had anal spasm, and 43/54 patients (79.6%) had skin tag. Fifty-three patients out of fifty-four (98.1%) had a history of conservative treatment, and 8/54 patients (14.8 %) had surgical treatment (Table 1).

Table 1: Clinical information available before GTN treatment

	Count	%
Pain	54	100.0%
Bleeding	42	77.8%
Skin tag	42	77.8%
Chronic constipation	46	85.2%
Spastic colon	9	16.7%
Presence of fissure	54	100.0%
Anal spasm	52	96.3%
Presence of skin tag	43	79.6%
Pre-GTN medical treatment	53	98.1%
Pre- GTN surgical treatment	8	14.8%

Thirty-four patients finished the course (6-8 weeks), or took it for a longer duration. Pain and bleeding showed improvement during the 6-8 weeks treatment with GTN. Pain was absent in 25/34 patients (73.5%), and was reduced in 5/34 patients (14.7%). Therefore, 30/34 patients (88%) showed good response to GTN treatment (Table 2).

Table 2: History of Pain

	Absent		reduced		same	
	Count	%	Count	%	Count	%
1 st week	6	11.1%	39	72.2%	9	16.7%
2 nd week	21	38.9%	23	42.6%	10	18.5%
6-8th week (34/54 patients)	25	73.5%	5	14.7%	4	11.7%

Bleeding stopped in 32/34 patients (94%), and reduced significantly in 2/34 patients (5.8%). Good response was seen in 34 patients (100%). (Table 3) Anal tone became normal in 32/34 patients (94%) and was spastic in 2/34 patients (5.8%) at the end of the treatment course (Table 4). Fissures were either healed or showed signs of healing in 28/34 patients (82.4%) (Table 5).

Table 3: History of Bleeding

	Absent		Reduced		same	
	Count	%	Count	%	Count	%
1 st week	37	68.5%	10	18.5%	7	13.0%
2 nd week	41	75.9%	7	13.0%	6	11.1%

6-8 th weeks (34/54 patients)	32	94%	2	5.8%	0	0%
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Table 4: Anal Tone

	Normal		spastic	
	Count	%	Count	%
1 st week	18	33.3%	36	66.7%
2 nd week	39	72.2%	15	27.8%
6-8 th week (34/54 patients)	32	94%	2	5.8%

Table 5: Fissure Healing

	Not healed		Healing	
	Count	%	Count	%
1 st week	26	48.1%	28	51.9%
2 nd week	17	31.5%	37	68.5%
6-8th week (34/54 patients)	6	17.6%	28	82.4%

The duration of treatment ranged between 1 week and 28 weeks. Twenty patients (37%) did not finish the 6-8 weeks. Twenty-four patients (44.4%) took treatment for 6-8 weeks. Ten patients (18.5%) took the treatment more than 8 weeks, up to 28 weeks.

Twenty patients who stopped the GTN course had headache in 12/20 patients (60%), noncompliance to the dosage, frequency or the drug finished before the end of the course in 19/20 (95%). Ten patients out of twenty (50%) claimed to have no response to GTN course.

Twenty-six patients (48.1%) had recurrence of symptoms within six months after treatment. There was a significantly strong relationship between recurrence of symptoms and the duration of treatment (P-value was .015). The symptoms recurred more if the treatment was less than 6-8 weeks period.

The recurrence was mild in 12/26 patients (46.2%), treated either with traditional ointment or repeated GTN course; and was severe in 14/26 patients (53.8%), treated surgically by anal dilatation.

The duration of follow-up was less than six months in 12/54 patients (22.2%), six to twelve months in 11/54 patients (20.4%), and more than twelve months in 31/54 patients (57.4%).

DISCUSSION

Topical GTN ointment is an effective alternative to surgery in the treatment of chronic fissure in ano⁸. The GTN ointment is applied 2 to 3 times daily to the distal anal canal for up to 8 weeks but in some up to 12 weeks for the fissure to heal.

In this study, 82.4% of the chronic fissures in ano were either healed or healing in 6-8 weeks. The healing rate in 4-8 weeks course in other studies was 73% with 0.5% concentration, 68%, 65%, 62.5%, and 84% with 0.2% concentration^{1, 2, 4, 5, 7}. One study showed no difference in healing rates between 0.2% and higher concentrations⁶. Other studies concluded that two-thirds of their patients will heal, but over one-half will develop headache as side effects of the treatment³. The headache is usually mild, transient and tolerable, often diminishing in intensity and duration with continued application^{3,6}. In some cases, the headache may be sufficiently severe to reduce compliance or leads to cessation of treatment. One study showed better outcome with the use of higher concentration (73% with 0.5% vs. 64% with 0.2%)¹. This benefit occurs at the expense of more headache and lower compliance rate.

In this study, the healing rate was good with 0.2% concentration and non-compliance and headache were high in patients who stopped their course of treatment before 6-8 weeks. Furthermore, given the absence of a reliable dosage system, the actual dosage quantity is different in each patient¹.

An uncontrolled prospective study looked at the use of isosorbide dinitrate spray in the treatment of anal fissures². In 41 patients, studied 1.25 or 2.5 mg (one or two sprays) applied three times a day for four weeks produced healing in 83% of patients at four months. There was an 18% relapse after a mean follow-up of 11 months, all of which were successfully treated with a further four weeks course. Headache occurred in 19.5%.

Most studies reported healing in the majority of cases within eight weeks of treatment^{1, 2, 3, 4, 7}. In a review study, GTN had higher healing rates than placebo (11 trials). This also showed that GTN had lower healing rates than sphincterotomy (4 trials) but did not differ for minor incontinence. GTN did not differ from botulinum toxin injection (botox) (2 trials) or calcium channel blockers (1 trial)⁹.

The duration of treatment in our patients ranged between one week and 28 weeks. About 62.9% took the treatment for 6-8 weeks or more.

Other studies showed that fissures, which initially healed on GTN, will recur within 12 months but would respond to further courses of GTN⁶.

From this study and others, we conclude that less than eight weeks of treatment with topical GTN is likely to be unsuccessful in truly chronic fissures⁶.

The duration of follow-up in this study was significantly higher than other studies^{1,2}.

CONCLUSION

The use of GTN ointment in the treatment of chronic fissure in ano may be a safe and effective modality and can be considered as a good first-line treatment for this condition.

In this study, more than 80% of our patients had healing fissures at the end of 6-8 weeks course. The recurrence of symptomatic fissures and high incidence of headaches are limitation to its use. Standardisation of the method of application and the amount of ointment applied are also required to validate metanalysis in the future.

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