Successful use of 0.2% Glyceryl Trinitrate ointment for anal fissures in Erbil city, Iraq

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Abstract

Aim of the study: To assess the clinical efficacy of 0.2% glyceryl trinitrate ointment in the management of acute and chronic anal fissures.

Patients and Methods: A prospective clinical study conducted on consecutive patients presented to the surgical clinic of Erbil teaching Hospital, Erbil city with acute and chronic anal fissures, from June 2009 till August 2012.

These patients were treated with topical 0.2% glyceryl trinitrate (GTN) paste in soft white paraffin three times a day. Patients were examined at regular intervals to evaluate the fissure status, adverse reactions, symptomatic control and recurrence. One hundred and fifty nine patients with acute and chronic anal fissures were evaluated in the study. Fifty one of them were lost to follow-up and 108 were remaining (94.7%)

Results: At the end of complete course (6-8 weeks), pain was completely relieved in 80.9 % and partially better in 7.4%, bleeding was absent in 83.7%, anal tone became normal in 80%, and in 80.3 % had healing. The course was completed or taken for longer duration in patients 62.9%. GTN was stopped before end of the course in 40 patients (37%) due to different causes, 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. It was seen that in two-thirds of the cases, the duration of treatment was less than 6-8 weeks. There was a highly significant positive relationship between duration of treatment and recurrence of symptoms. The recurrence was treated surgically in 53% patients, traditional ointments in 30.8% patients, and repeated GTN course in 15.4% patients.

Conclusion: The use of 0.2% GTN ointment induces rapid healing of anal fissures with an 80.3% 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 lower GTN concentration.

Key words: Glyceryl trinirate 0.2% ointment, acute and chronic anal fissures

Introduction

Anal fissure is a benign painful condition of the anoderm. Raised resting internal anal sphincter pressure is important in the pathogenesis of anal fissure, possibly by impairing tissue perfusion and leading to ischemic ulcer (1, 2, 3 4). Conservative management of the anal fissures traditionally involves stool softeners, warm sitz baths and the application of topical anesthetics. Chronic fissures tend to be more resistant to conservative management characterized by frequent recurrences (5) . Surgical procedures to reduce resting anal tone for the recalcitrant fissures are effective but carry a significant risk of permanent minor impairment of continence (6, 7). Manual anal dilatation may cause irreversible, uncontrolled injury to the internal and external anal sphincters (8) with the associated incidence of fecal incontinence being 39% (9). Lateral subcutaneous internal sphincterotomy leads to successful healing of the fissure in more than 90 % of patients but temporary incontinence for the flatus or feces occurs in 0-30 % of the patients (10). Such observations have fuelled attempts to develop non-operative measures for reducing internal sphincter spasm.

Nitric oxide has emerged as one of the most important neurotransmitters mediating internal sphincter relaxation. [10] Topical glyceryl trinitrate (GTN), a nitric oxide donor produces a successful chemical sphincterotomy and improves anodermal blood flow [10]. The aim of this study was to present a more pragmatic assessment of the ultimate usefulness of GTN in the treatment of acute and chronic anal fissures.

Materials and Methods

This is an uncontrolled prospective clinical study involving one hundred and eight patients with acute and chronic anal fissure. Most of the patients had tried traditional conservative treatment (such as ointments, suppositories and laxatives) for long duration, had presence on examination of signs of chronicity (skin tag and or anal polyp), or even previous surgical intervention such as anal dilatation with recurrence of symptoms and signs, but never used GTN. These patients had full explanation about chronic fissure in ano including pathogenesis and options of treatment, mechanism of action and side effects of GTN and how to overcome or tolerate them. These patients chose to take this option as the first choice instead of other modalities such as surgery or others. Only pregnant and lactating patients were excluded from this treatment. All patients above forty years of age had barium enema or colonoscopy during their course of treatment.

The study was prospective, and was done in Erbil Teaching hospital, out patient Department and private clinic during the period from June 2007 till August 2009. The data was registered in a pre-prepared form. This form was filled in on each visit (first time GTN ointment was prescribed, end of first week, end of second week, and at 6th -8th week). Some did come regularly for the follow-up visits, others did not. Those patients who were not coming regularly received phone calls to be able to fill out the forms. All patients had a phone call to update the data at the end of the study period (i.e August 2005). The follow up period for all the patients ranged between 4 months and 28 months.

All patients were evaluated regarding pain, bleeding, anal tone and fissure healing. Patients who stopped the treatment were evaluated for the cause. Patients who had recurrence of symptoms were evaluated regarding the duration elapsed since they finished their course and the severity of the recurrence and how it was treated. Patients who had severe recurrence (i.e similar to the presenting symptoms) were treated with anal dilatation or lateral sphincterotomy.

Glyceryl trinitrate 0.2% ointment was prescribed for three times per day for 6-8 weeks. Few patients extended their course to 12 weeks which is acceptable if needed according to the latest international literature. All patients received in addition supportive measures such as sitz baths and fiber laxatives.

Drug preparation

Glyceryl trinirate 0.2% ointment according to the invention was prepared by admixing 5 gm of 2% by weight nitroglycerin in white petrolatum, lanolin, and distilled water with 45 gm white petrolatum in a laboratory mixing vessel at room temperature. The resulting mixture comprised 50 gm of a 0.2% nitroglycerin ointment (11).

Statistical analysis

Data were analyzed using the Statistical Package for Social Science (SPSS version 15). The chi square test of association was used for categorical variables.

Results

One-hundred and eight patients took the GTN 0.2% ointment. Almost all; 106 patients (98.1%) were males. Age ranged between 18-70 years of age, and 50 patients (46.3%) were between 30-49 years of age.

At presentation all patients were complaining of pain (100%), only 84 patients (77.8%) had bleeding, and external anal skin tag. Chronic constipation was found in 93 patients (86.1%). Spastic colon was present in 19 patients (17.6%). Two patients had ulcerative colitis disease. On examination; all patients (100%) had fissure, 104 patients (96.3%) had anal spasm, and 86 patients (79.6%) had skin tag. Almost all, 106 patients (98.1%) were treated conservatively, and only 16 patients (14.8 %) were treated surgically before GTN course. (Table 1)

The response to treatment was analyzed at first week, second week, and 6th -8th week from the start of the treatment. Pain and bleeding showed significant improvement over the 6-8 weeks period. By the sixth to eighth week the pain was absent in 55 patients (80.9%), and was reduced in 8 patients (11.8 %). This means 63 patients (92.7%) showed good response to GTN treatment. Bleeding stopped in 72 patients (83.7%), and was reduced significantly in 6 patients (7%). Total good response was seen in 78 patients (92.9%).(Tables 2, 3).

Table 1: Symptoms of acute and chronic Fissure in 108 patients.

Symptoms	Frequency	%
pain	108	100.0%
bleeding	84	77.8%
skin tag	84	77.8%
chronic constipation	93	86.1%
spastic colon	19	17.6%
presence of fissure	108	100.0%
anal spasm	104	96.3%
presence of skin tag	86	79.6%
Pre-GTN medical treatment	106	98.1%
Pre- GTN surgical treatment	16	14.8%

Table 2: History of Pain in acute and chronic fissure.

History of Pain	Absent		Reduced		Same	
	No	%	No	%	No	%
Week one	12	20%	39	65	9	15
Week two	42	57.5%	23	31.1	10	13.5
Weeks 6-8	55	80.9%	8	11.8%	5	7.4%

Pearson Chi-square: 50.5, (P<0.001)

Table 3: History of bleeding acute and chronic fissure.

History of bleeding	Absent		Reduced		Same	
	No	%	No	%	No	%
Week one	73	67.6%	21	19.4%	14	13%
Week two	83	74.8%	15	13.5%	13	11.7%
Week six	72	83.7%	6	7%	8	9.3%

Pearson Chi-square: 7.64, (P<0.105)

Regarding anal tone, it became normal in 68 patients (80.5%) and was spastic in 17 patients (20 %) at the end of the treatment course.(Table 4) Fissures were also evaluated regarding signs of healing, where 80.3% were either healed or showing signs of healing. (Table 5).

Table 4: Anal tone in acute and chronic fissure of 108 patients.

Anal tone	Normal		Spastic	
	No	%	No	%
Week One	38	34.2%	73	65.8%
Week two	79	71.8%	31	28.2%
Week six	68	80%	17	20%

Pearson Chi-square: 51.44 (P<0.001)

Table 5: Healing efficacy of GTN in 108 patients with acute and chronic fissure.

Healing fissure	Not healed		Healing	
	No	%	No	%
Week One	34	37.4%	57	62.6%
Week two	35	32.1%	74	67.9%
Week six	14	19.7%	57	80.3%

Pearson Chi-square: 6.003 (P<0.05)

The duration of treatment ranged between 1 week and 28 weeks. Forty nine patients took the course for 6-8 weeks (45.3%) and 19 patients (17.6%) took the treatment more than 8 weeks and up to 20 weeks. (Table 6) This indicates that 68 patients (62.9%) did not stop the treatment and finished the course within 6-8 weeks.

Table 6: Duration of treatment with GTN in 108 patients with acute and chronic fissure.

	Frequency	Percent
1 - 5 weeks	40	37.0%
6 - 8 weeks	49	45.3%
> 8 weeks	19	17.6%

The duration of follow-up was less than six months in 24 patients (22.2%), six to twelve months in 23 patients (20.4%), and more than 12 months in 64 patients (57.4%). This indicates that almost half of our patients had follow-up for more than one year and more than two-thirds for 6 to 12 months (Table 7).

Table 7: Duration of follow-up in months in 108 patients with acute and chronic fissure treated with GTN 0.2%

	Frequency	Percent
< 6 months	24	22.2
6 - 12 months	23	20.4
> 12 months	64	57.4

The patients who stopped the GTN course early (40 patients), had multifactorial causes which were evaluated; such as side effects (mainly headache) in 25 patients (60%), noncompliance to dose, frequency or the drug finished before the end of the course in 39 patients (95%), and patients who claim no response to GTN course were 21 patients (50%) (Table 8).

Table 8: Causes of stopping treatment with GTN 0.2% in patients with acute and Chronic fissure

Causes	Count	Percent*
Side effects (headache)	25	60.0%
Non compliance	39	95.0%
No response	21	50.0%

* The percent was calculated from those who stopped treatment (20 patients)

There were 47 patients who had recurrence of symptoms within six months after finishing or stopping the course. The symptoms were either mild or severe. There was a significant strong relationship between recurrence of symptoms and the duration of treatment; the symptoms recurred in a shorter period if the treatment was taken for a shorter course, particularly if it was taken for less than a 6-8 weeks period (Table 9).

The severity of recurrence in these patients was mild in 18 patients (46.2%) and was treated either with traditional ointment or repeated GTN course and was severe in 29 patients (53.8%) and was treated surgically by anal dilatation.

Table 9: Treatment of recurrence in relation to severity

Type	Mild		Severe	
	No	%	No	%
Surgical	0	0%	29	53.8%
Repeat GTN	9	15.4%	0	0%
Using traditional ointments	9	30.8%	0	0%

Pearson Chi-square: 47 (P<0.001)

The percent was calculated from the patients who had recurrence within 6 months (26 patients).

Discussion

The present clinical trial establishes the clinical efficacy of 0.2% GTN ointment in the treatment of anal fissures. The published data of a high cure rate of 70-80% in various studies [3,6] with a paucity of significant side effects are encouraging Topical GTN ointment is an effective alternative to surgery in the treatment of chronic fissure in ano(8). Preparations of 0.2% GTN ointment is probably the most widely used first line treatment in the UK with successful results (3), but many patients experience troublesome headaches on this therapy. The ointment is applied 2-3 times daily to the distal anal canal for up to 8weeks but in some should be used up to 12 weeks for the fissure to heal.

In our study the chronic fissure in ano was either healed or healing in 80.3% in the 6-8 weeks period. The healing rate in 4-8 weeks course in other studies was 71% with 0.5% concentration (1), 67%, 65%, 62.5%, and 84% with 0.2% concentration (2, 3, 5,). There were other studies which showed no difference in healing rates between 0.2% and higher concentrations (6). Other studies have also concluded that two-thirds of their patients will heal, but over one-half will develop headaches as side effects of the treatment (3). 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 lead to cessation of treatment. One article claimed that better outcome was seen with the use of higher concentration (72% with 0.5% vs 64% with 0.2%). (1) This benefit, however, occurs at the expense of more headache and lower compliance rate. In our study the healing rate was high with only 0.2% concentration and non-compliance and headache were studied and found significantly high in patients who stopped their course of treatment before 6-8 weeks. What remains unclear in all published series is whether headaches are in part due to absorption of GTN via the finger, given that not all patients use gloves while applying the medication. Furthermore, given the absence of a reliable dosage system, the actual quantity may be different in each patient.(1)

An uncontrolled prospective observational study looked at the use of isosorbide dinitrate spray in the treatment of anal fissures.(2) In 81patients studied, symptoms had been present for two to 120 months with classical signs of chronicity present in only 61% of cases. All the patients had failed to heal after three weeks of conservative management. In this group of patients, isosorbide dinitrate 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 rate after a mean follow-up of 11 months, all of which were successfully treated with a further four week course. Headaches occurred in 19.5%.

In general, most studies report healing in the majority of cases within eight weeks of treatment (1, 3, 4 & 7). In one article a review through the Pub Med (1996-May 2003) and Cochrane Library (May 2003) for all reports that compared non-surgical therapy with surgery, showed that 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.

Early recurrence (less than 6 months) has occurred in 48% of patients. It does not appear to be a problem as it was mild in almost half and was treated conservatively either with traditional ointments or repeated GTN course. The recurrence was severe in 29 patients only and these were the ones who needed surgical treatment. In our results we found a significant strong relationship between the duration of treatment and duration of recurrence. This indicated that prolonged courses of treatment 8-12 weeks or more had better results and longer periods of free of symptoms.

Other series showed that fissures which initially healed on GTN will recur within 12 months but respond to further courses of GTN (6).

From our results and other studies we conclude that less than eight weeks of treatment with topical GTN is likely to be unsuccessful in truly chronic fissures as it takes chronic fissures eight weeks to heal; indeed some fissures may only partially heal within eight weeks but will fully heal if treated longer (6).

The duration of follow-up of our patients was significantly high which was not found in some other studies. (1,2)

Conclusion

GTN is a useful therapeutic modality in the management of acute and chronic anal fissures, with an 80.3% healing rate in this study, which are refractory to dietary modifications, fiber supplements and sitz baths. As GTN is safe and effective we suggest performing a randomized comparative study with surgical gold standard treatment.

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