LOCAL GLYCERYL TRINITRATE VERSUS LATERAL INTERNAL SPHINCTEROTOMY IN MANAGEMENT OF ANAL FISSURE

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Abstract

Introduction: Anal fissure is a common benign condition that can cause severe anal pain after defecation and bleeding. Symptoms from fissure cause considerable morbidity and reduction in quality of life. The aim of treatment is to reduce anal hypertonia, which may improve anodermal blood flow and heal the fissure.

Aim of the work: This study aimed to evaluate the effectiveness of local glyceryl trinitrate (GTN) versus surgical lateral internal sphincterotomy in the management of acute and chronic anal fissure.

Patients and methods: In our present study we compared topical application of GTN on liposomal base with the surgical procedure i.e. internal lateral sphincterotomy and according to the method of treatment the patients were divided into two groups: group 1 which included 40 patients with anal fissure and agreed to have the medical treatment with topical GTN 0.2% applied to the anoderm twice daily. Group 2 also included 40 patients and treated with lateral internal sphincterotomy.

Results:

In group 1, healing of fissures occurred in 85% of patients after 8 weeks therapy. Headache as a side effect developed in 65% of patients but no patient ceased to apply the ointment due to headache. In group 2, healing occurred in 97.5% of patients after 8 weeks. Incontinence to flatus occurred in 3 patients (7.5%) and mild soiling occurred in 2 patients (5%), but all were temporary and there was no gross incontinence and one patient with wound infection. The improvement in group 2 faster than group 1 but at the end of 8 weeks both groups become equal in pain score. The main anal resting pressure (MARP) assessment changes in the two groups were nearly equal.

Conclusion: We concluded that topical application of nitroglycerin represents a new easily handled and effective alternative in the treatment of anal fissure.

KEYWORDS: GLYCERYL TRINITRATE
INTRODUCTION

Anal fissure is one of the most painful conditions encountered in surgical practice, and cause considerable morbidity and reduction in quality of life. (1)

Anal fissure is a linear tear in the lining of the distal anal canal below the dentate line. It is a common condition affecting all age groups, but is seen particularly in young and other wise healthy adults, with equal incidence across the sex. The classical symptoms are of anal pain during or after defecation accompanied by the passage of bright red stool. In addition, purities ani may accompany up to 50% of anal fissure. (2)

Subcutaneous lateral sphincterotomy remains the golden standard for management of chronic anal fissure because of its simplicity of procedures, rapid healing and low recurrence rate. However, disadvantages of lateral sphincterotomy including; disturbance of continence, bleeding, fistula, abscess, persistent wound pain, cost and time of recovery (3) have led to search for mode of therapy or pharmacological way to create a temporary or reversible sphincterotomy, one that would lower sphincter pressure only until the fissure had healed. (4)

Local GTN can reduce the increased anal canal pressure caused by a hypertonic internal anal sphincter and improving anodermal blood flow, as surgical lateral sphincterotomy. Reversible chemical sphincterotomy produced by local GTN has been used successfully to healing in anal fissure, with minimal side effect and avoid the need for operative intervention. (5)

Topical GTN can be used with liposomal base as a delivery system, liposomes are most useful for being able to transfer and deliver active ingredient to application site which lead to more efficacy of the drug. In view of this, and the fact that the optimal therapeutic strength of GTN is still to be determined, we aimed to evaluate the use of topical GTN versus surgical lateral internal sphincterotomy in the management of anal fissure. (6)

AIM OF THE WORK

The present study aimed to study the effectiveness of local GTN versus surgical lateral internal sphincterotomy in the management of acute and chronic anal fissure.

PATIENTS AND METHODS

The study is a clinical prospective randomized controlled study hospital based, and was carried on patients who were diagnosed clinically with anal fissure attended to outpatient clinic of surgical department, Suez Canal University Hospital.

The study was carried on male and female patients aged 18-60 years who diagnosed clinically with acute and chronic anal fissure. Patients with complicated anal fissure, with other anal problem (as piles), with previous anal surgery, with systemic diseases (diabetes mellitus, chronic liver disease and collagen diseases), and patients under treatment with nitrates for other diseases, e.g. ischemic heart diseases were excluded from the study. Pregnant and children were also excluded.

Methods and procedures:

Full detailed history especially about symptoms of anal fissure including anal pain during and after defecation, bleeding, discharge and itching and duration of these symptoms were obtained from the patients. Possible cause of anal fissure as history of constipation and anal trauma were also reported. Digital rectal examination was done to palpate for presence of spasm and tenderness. The presence of linear ulcer in the distal anal canal, indurations and sentinel skin tag, with the previous symptoms was enough for clinical diagnosis.

According to out come, fissures were classified as; (a) acute, anal fissure with less than 6 weeks of duration, and (b) chronic anal fissure, more than 6 weeks of duration with preserved of the symptoms (pain–bleeding), marginal indurations and sphincter muscle.

Each patient must be agreed to participate in the study after being informed in detail of the aim of the study and fully informed written consent was obtained from each patient prior to entry into the study.

According to the method of treatment, the patients were divided randomly into two groups:

Group (1), which included 40 patients with acute and chronic anal fissure who agreed to have the medical treatment with local GTN 0.2% cream (in lipsomal base). Each patient was
instructed to apply about 0.5 g "per size amount" of GTN manually at distal anal canal (lower half of the anal canal and anal verge) twice daily for eight weeks. All patients advised to receive stool softeners and fiber supplements diets.

N.B. Patients in the group 1 with persistent fissure after treatment, or those unable to tolerate treatment with the GTN, at this time surgical sphincterotomy was offered. This patient was excluded from the study (failure of GTN treatment).

**Group (2),** which included 40 patients with acute and chronic anal fissure who agreed to have surgical treatment with lateral internal sphincterotomy. All patients were treated by the same surgeons using a uniform method in the lithotomy position with the same technique of internal lateral sphincterotomy.

**Assessment of the patients in the two groups:**

**MARP assessment:**

The pressure changes in the anal sphincter MARP was recorded in the patient in each group using anal manometry at the first visit (before treatment), and repeated after 20 min of application of topical GTN and after surgical lateral internal sphincterotomy.

**Follow up assessment:**

All patients in each group were followed up at 2–weeks intervals for 8 weeks, in order to evaluate the improvement as following:

1- Pain assisted by visual analogue score (VAS) in all patients. Patients asked to indicate a point on 100 mm line, one end of the line represent no pain on defecation and the other represent worst pain that they could imagine.

2- Bleeding for absent or present.

3- Fissure healing: the anus was examined by inspection to assess healing of the fissure which means complete epithelization of the fissure or persistence of the fissure and the time of complete healing.

4- Appearance of any adverse effect.

All patients were reassessed after one month and three months for evidence of recurrence of the fissure and the presence of possible side effects.

**RESULTS**

**Group 1:**

Patients treated with local application of GTN 0.2%. This group consists of 40 patients; 20 patients (50%) with acute anal fissure and 20 patients (50%) with chronic anal fissure. Sixteen patients (40%) were male and the other 24 patients (60%) were females. The age ranged from 18 to 60 years with median age of 36 years.

Those who presented with anal pain were 40 patients (100%), with anal pain and constipation were 28 patients (70%) and who presented with anal pain and bleeding were 16 patients (40%). Thirty five patients (87.5%) have posterior anal fissure and one patient (2.5%) with anterior anal fissure and 4 patients (10%) with posterior and anterior anal fissure.

**Group 2:**

Patients who underwent lateral internal sphincterotomy. This group also consisted of 40 patients; 20 patients (50%) with acute anal fissure and 20 patients (50%) with chronic anal fissure. Twenty patients of them (50%) were males and 20 patients of them (50%) were females. The age ranged from 18 to 60 years with median age of 36 years.

Those who presented with anal pain were 40 patients (100%), with anal pain and constipation were 30 patients (75%) and those who presented with anal pain and bleeding were 14 patients (35%). Thirty one patients (77.5) have posterior anal fissure and 9 patients (22.5%) with anterior and posterior anal fissure.

**MARP assessment:**

The main pre treatment MARP in group 1 was 122 ± 44 cm H$_2$O and 120± 44 cm H$_2$O in group 2, this was comparable in both groups. The mean value of MARP dropped by 40.5% to 72 ± 31.1 cm H$_2$O after application of GTN in group 1, this post treatment drop in pressure of 49.5 cm H$_2$O was statistically highly significant (P value < 0.0001). In group 2 the mean MARP dropped by 43.3% to 68.2±31.3 cm H$_2$O this drop of 51.8 cm H$_2$O was also statistically highly significant (P value < 0.0001). The difference in reduction of MARP between topical GTN and sphincterotomy (4.3 cm H$_2$O) was not statistically significant showing that both modality of treatment were equally effective in reducing the MARP in anal fissure.

**Follow up assessment:**
Follow up after 2 weeks in group 1:
Pain score falls from 100 at the beginning of treatment to 70 at the end of the 2 weeks. Absence of bleeding increased from 60% (24 patients) at the beginning of treatment to 85% (34 patients) at the end of 2 weeks. Twelve patients (3 chronic and 9 acute) (30%) showed complete healing by inspection after 2 weeks. At the beginning of the treatment 26 patients (65%) develop headache as a side effect of the treatment. Although usually moderate to mild tolerable, often diminishing in intensity and duration with continued application.

Follow up after 4 weeks in group 1:
Pain score fall from 70 after 2 weeks to 40 at the end of 4th week. Absence of bleeding increased from 85% (34 patients) at the end of 2 weeks to 95% (38 patients) at the end of the 4th week. Twenty patients (5 chronic and 15 acute) (50%) showed complete healing by inspection after 4 weeks. Only 8 patients (20%) have mild tolerable headache at the end of the 4th week.

Follow up after 6 weeks in group 1:
Pain score falls from 40 after the end of the 4th week to 20 at the end of 6th week. Absence of bleeding increased from 95% (38 patients) at the end of 4th week to 97.5% (39 patients) at the end of the 6th week. Twenty seven patients (8 chronic and 19 acute) (67.5%) become healed at the end of 6th week. Only 4 patients (10%) have continues mild tolerable headache.

Follow up after 8 weeks in group 1:
Pain score fall to 10 at the end of the 8th week and absence of bleeding become 97.5 (39 patients) at the end of course of treatment. Thirty four patients (14 chronic and 20 acute) (85%) become completely healed of anal fissure (by inspection) at the end of the 8th week. The headache stopped after the 6th week and no patients have headache after the 6th week.

Follow up after one month in group 1:
There was no relapse or complications.

Follow up after 3 months in group 1:
One patient have recurrence of symptoms and surgical intervention was done (lateral internal sphincterotomy) with no complication.

Follow up assessment:
Follow up after 2 weeks in group 2:
Pain score fall from 100 before the operation to 40 at the end of the 2 weeks after operation. Absence of bleeding increased from 65% (16 patients) before operation to 97.5% (39 patients) after 2 weeks from operation. Thirty patients (10 chronic and 20 acute) (75%) show complete healing by inspection after 2 weeks of operation. Three patients (7.5%) complaining from incontinence to faults, two patients (5%) complain of mild soiling, one patient with wound infection. No gross incontinence occurred.

Follow up after 4 weeks in group 2:
Pain score fall to 20 after 4 weeks from the operation. Absence of the bleeding became in 97.5. (39 patients). Thirty eight patients (18 chronic and 20 acute) (95%) show complete healing by inspection after 4 weeks from operation. One patient had mild soiling. One patient had continence to faults.

Follow up after 6 weeks in group 2:
Pain score fall to 10 after 6 weeks from operation. Absence of bleeding became in 97.5% (39 patients). Thirty nine (19 chronic and 20 acute) (97.5%) show complete healing after 6 weeks from operation. No complication only one patient had incontinence to flatus.

Follow up after 8 weeks in group 2:
Pain score around 10 after 8 weeks from operation. Thirty nine (19 chronic and 20 acute) (97.5%) show complete healing. No complication and only one patient had incontinence to flatus.

Follow up after one and 3 month in group 2:
No relapse and no complication. Only one patient had incontinence to flatus.

Figure 1: Pain score improvement comparison between the two groups after 2nd, 4th, 6th, 8th
week of treatment. At the end of 2\textsuperscript{nd} week of treatment, pain score in group 1 fall to 70 as compared to score in group 2 falls to 40 (p=0.0032). This clear indicate that lateral sphincterotomy relive pain much earlier as compared to GTN. However, by the end of 8\textsuperscript{th} week of treatment the pain score in both groups became 10. Hence, after 8 weeks of treatment, pain score with GTN is comparable to that after lateral sphincterotomy.

**DISCUSSION**

Most patients with a chronic anal fissure have raised resting anal pressures caused by hypertonicity of the internal anal sphincter (IAS) and this seems to play an important role in pathogenesis of anal fissure. Local ischemia may also be important, as there is a relative hypoperfusion at the posterior commissure of the anal canal in most people.\(^{(7)}\)

The aim of treatment is to reduce anal hypertonia, which may improve anodermal blood flow and heal the fissure. Until approximately 5 years ago, lateral internal sphincterotomy was the gold 'standard' in treatment, producing rapid symptom relief and healing rates of over 90\%, but it is now less popular as disturbances in continence can occur in up to 30\% of patients.\(^{(8)}\)

This has led to the search for alternative non surgical treatment and various pharmacological agents have been shown to lower resting anal pressure and heal fissure without threatening anal continence.\(^{(9)}\)

Recognition of organic nitrates as the non-adrenergic, non-cholinergic neurotransmitter mediating relaxation of the internal anal sphincter has initiated the widespread use of organic nitrates in the treatment of chronic anal fissure. These agents are metabolized at a cellular level to release NO which, in turn, mediate relaxation of the internal anal sphincter by increasing cGMP level within the smooth muscle cells. Preparations of GTN have been used with success and most studies report healing in the majority of cases.\(^{(10)}\)

In our present study we found that 20 patients of the 20 patients with acute anal fissure (100\%) get benefit of using a pea-sized of 0.2\% GTN cream on liposomal base applied to distal part of anal canal and the anal verge and showed complete healing at the end of 8 weeks therapy versus 14 patients of 20 patients with chronic anal fissure (70\%) receiving also topical GTN cream on liposomal base and become healed at the end of 8 weeks. Guillemt et al.\(^{(11)}\) reported that topical GTN ointment rapidly reduced the resting pressure in the upper anal canal in normal subjective and patient with constipation.

Loder et al.\(^{(12)}\) applied GTN 0.2\% ointment to the anodermal of 10 patients presenting for physiological assessment of a variety of anal disorders, including one patient with anal fissure. A significant decrease in MARP was observed by 20 min after application of the ointment, which was sustained for at least 9h after application of ointment. A recent randomized controlled trial showed that topical GTN brought a bout a dramatic drop in the MARP in chronic anal fissure, and it causes pain relief and healing, which was superior to xylocaine, proctosedyl or placebo.\(^{(13)}\)

Lund and Scholefield,\(^{(14)}\) showed that topical GTN has been shown to be an effective treatment for chronic anal fissure, healing over two thirds of patients after 8 weeks of treatment. Such a relative high success rate with chronic fissure in our study may be attributed uses of...
liposomal base which increase penetration of GTN in the muscle and mucosa of IAS.

Pitt et al. (15) have an opinion like us and they added that the presence of a sentinel pile adversely affect the outcome of treatment of chronic anal fissure with GTN ointment, and fissures with a history of more than six months were unlikely to heal initially.

Marion et al. (16) stated that topical 0.2 percent GTN ointment has a short-lived effect on resting anal pressure and twice application of topical 0.2% GTN heals two-third of fissures after eight weeks which is similar to our procedure but they added that the short duration of action of GTN may indicate that more frequent application might heal more fissures, more rapidly. Bacher et al. (17) stated that topical application of nitroglycerin represents a new, easily handled, and effective alternative in the treatment of anal fissure. All of their patients reported a dramatic reduction in acute anal pain which is also consistent with our study in which pain score falls from 100 pre-treatment to 70 after 2 weeks then to 10 at the end of 8 weeks. Also Gorfine, (18) reported that 30% of patients experienced headache when treated with topical 0.3% GTN ointment but that all were able to continue treatment.

On the other hand, Hyman and Cataldo, (19) treated anal fissure with topical 0.3% nitroglycerin ointment applied to the anoderm three times per day. They found that it was only effective in approximately one-half of patients with an anal fissure and often cause a headache (75%) than treats the symptoms of anal fissure. This study has a very high incidence of adverse reaction than our study and we think that this is attributed to the high concentration (0.3% GTN) than ours (0.2% GTN) and also for being applied to the anoderm three times per day compared to 2 times only in our study.

Despite the recent interest and the good results obtained with topical GTN in the nonsurgical management of chronic anal fissure, there have been surprisingly few studies comparing it with the standard lateral sphincterotomy in the format of a randomized clinical trial.

Oettle, (20) randomized 24 patients for treatment with sphincterotomy or local GTN; all 12 patients healed following sphincterotomy while 10 of 12 patients healed with local GTN (P = 0.239). Anal pressure recordings were not recorded or compared in that study. He concluded that local application of GTN could avoid surgery in more than 80% of patients with chronic anal fissure.

A multicenter trial involving 82 patients (38 patients in the sphincterotomy group and 44 patients in the GTN group) was conducted by Richard et al. (21) that study concluded that internal sphincterotomy was superior to topical GTN in the treatment of chronic anal fissure because of a higher rate of healing, fewer side-effects, and a low risk of early incontinence. Another study that randomized 60 patients into lateral sphincterotomy (27 patients) and GTN (33 patients) concluded that GTN heals the majority of chronic anal fissures. However, because a significant minority had little improvement or developed side-effects and required conventional surgical treatment. GTN was not shown to be superior to lateral sphincterotomy.

A recent trial randomized 70 patients to GTN ointment or sphincterotomy and resolution of symptoms and healing of fissures were assessed after 24months. They concluded that many anal fissures heal with topical GTN; lateral sphincterotomy remains effective but should be reserved for patients who fail to respond to initial GTN. (22)

The present study showed that in patients with fissure in ano a highly significant and comparable drop in MARP was brought about by both GTN and sphincterotomy. Sphincterotomy relieves pain much earlier as compared to GTN, but after 4 weeks of treatment, pain relief in the two groups is comparable. Healing in the sphincterotomy group was also much earlier as compared to GTN. But this initial advantage was lost by 8 weeks of treatment. Lateral sphincterotomy has a significant incidence of minor short-term complications of bleeding, wound infection and incontinence, which are usually self-limiting. It also requires surgical expertise, theater, time, and day care beds. GTN, on the other hand, is a
safe and simple procedure with mild and tolerable side-effects of headache and local burning sensation. Because it was a short-term study, no conclusions can be drawn about long-term recurrences with either treatment modality.

Because topical GTN is safe and well-tolerated, and because pain relief and healing are comparable with lateral sphincterotomy at the end of 6-8 weeks, we suggest that conservative treatment with GTN should be the initial treatment for chronic anal fissure. Lateral sphincterotomy should be reserved for patients with severe disabling pain (because pain relief is much faster), and for those patients not responding to at least 4 weeks of conservative therapy with GTN.

We also observed that the use of GTN as local application in the patients with early symptomatic hemorrhoids has beneficial for the patients with early symptomatic hemorrhoids.

CONCLUSION
Topical application of GTN with liposomal base anew, easily handled, low costs and effective alternative treatment of anal fissures and effectively heal about100% of acute anal fissure and 70% of chronic anal fissure and can reduce the number of cases requiring sphincterotomy. Also, chemical sphincterotomy with GTN is reversible and therefore avoids permanent division of part of the sphincter and the consequent disturbance of continence mechanism.

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