

Role of Adding Topical Metronidazole in the Treatment of Acute Anal Fissure

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Abstract

Background: An anal fissure is a longitudinal ulcer in the anoderm of the distal anal canal which extends from the anal verge proximally towards, but not beyond, the dentate line. Anal fissure is a disease characterized by severe pain in the anorectal region with constipation, per rectal bleeding and sometime itching. Recently, anaerobic bacteria are sorted out as a causative factor. **Objective:** This study investigates patient compliance in the treatment of anal fissure with adding topical metronidazole. **Materials and method:** A total number of 100 patients attended to the General Surgery Clinic of Delta Medical College Hospital, Department of Surgery, between December 2020 and May 2021 and diagnosed with acute anal fissure were included in this prospective study. Patients older than 18 years, including non-pregnant, pregnant and lactating women are recruited. Patients were randomly divided in two groups. One group (group: 1) was treated with topical glyceryl trinitrate [0.4% nitroglycerin ointment], and the other group (group: 2) was treated with topical glyceryl trinitrate [0.4% nitroglycerin ointment] and topical antibiotic [metronidazole 0.75%]. **Results:** There is no difference between the groups regarding age and symptoms. From week 1, fissure healing rates were high in group 2. Group 2 VAS score levels were lower than group 1 and achieved by group 1 only in week 4. Compliance of pregnant and lactating lady was more in group 2. **Conclusion:** Adding topical metronidazole to treatment of acute anal fissure reduces the duration and severity of pain, shortens healing time and increases the healing rate.

Keywords: Anal fissure; Topical metronidazole.

Delta Med Col J. Jul 2021;9(2):84-90

Introduction

An anal fissure (fissure in ano) is a longitudinal ulcer in the anoderm of the distal anal canal which extends from the anal verge proximally upto the dentate line.¹ This can be acute or chronic. An anal ulcer is a chronic fissure when mature, an ulcer is associated with skin tag (sentinel piles).^{2,3}

The cause of anal fissure, and the reason of posterior midline being frequently affected is not completely understood. The shearing forces acting at the posterior midline at defecation, combined with less elastic anoderm due to an increased density of longitudinal muscle extensions in that

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region of the anal circumference may contribute to the cause.¹

Fissure results from forceful dilatation of the anal canal, mostly during defecation. The anoderm is disrupted, exposing the underlying internal sphincter muscle which goes into spasm in response to exposure and fails to relax with next dilatation (bowel movement). This leads to further tearing, deepening of the fissure, and increased muscle irritation and spasm. There is relative ischemia of the overlying anoderm which inhibits healing.² Hormonal changes during pregnancy and puerperium, pressure by gravid uterus and vasodilatory effects of prostaglandins all cause decreased colonic motility and constipation. This constipation ultimately results in anal fissure.

Acute anal fissure is characterised by severe anal pain during defecation. A trace of blood is noticed on tissue paper after wiping and it usually lasts less than 2 months. Here only epithelial tissue is ruptured. Chronic fissure lasts longer than 6 to 8 weeks and is characterised by above mentioned features and exposed fibres of internal anal fissure at the base of the fissure, hypertrophied anal papilla internally and a sentinel tag externally.^{1,4}

The disease affects both sexes in all age group.⁵ Anterior anal fissure is more common in women and may arise after vaginal delivery.¹ Most anal fissures are acute and resolve spontaneously or within 6 to 8 weeks of treatment.⁶ After confirmation of the diagnosis, conservative management should result in the healing of almost all acute and majority of chronic fissure. Emphasis must be placed on normalisation of bowel habits. The addition of fibre to the diet to bulk up the stool, stool softeners and adequate water intake are simple and helpful measures. Warm baths and topical local anaesthetic agents relieve pain. Patients with normal bowel function and excessive straining at defecation might benefit from anorectal biofeedback to correct it. The mainstay of conservative management is the topical

application of pharmacological agents that relax the internal sphincter. If simple measure fails, treatment can be escalated to “chemical sphincterotomy” using agents that induce smooth muscle relaxation. Glyceryl trinitrate (GTN) is a nitric oxide donor. The cure rate with GTN is 50% but can be associated with some problems like headache.¹ Surgical lateral internal sphincterotomy is applied as the gold standard treatment in patients who do not respond to medical treatment. However, surgical risks and the incidence of late persistent incontinence are important postoperative complications.⁷⁻¹⁰

Recent studies have suggested that presence of anaerobic bacteria in the anal fissure region may cause subclinical infection, and the use of topical or oral antibiotics in addition to conventional medical treatment increases wound healing and reduces pain.^{7,11,12} In studies on this subject, the effect of local or systemic antibiotics was mostly performed on patients with anal fissure. In this study, our aim was to investigate whether the use of topical metronidazole, which is effective against anaerobic bacteria, in addition to GTN, that has been used for years in the treatment of acute anal fissure, are superior to the use of GTN alone.

Materials and method

A total number of 100 patients attended to the General Surgery Clinic of Delta Medical College, Hospital, Department of Surgery (between December 2020 and May 2021) and diagnosed with acute anal fissure were included in our prospective study. The study was performed with the approval of the clinical research ethics committee of Delta Medical College, Hospital. Informed consent was obtained from all patients. Patients older than 18 years, including non-pregnant, pregnant and lactating women with complaints of anal fissure for less than 4 weeks, with complaints of severe anal pain (knife – cutting) during defecation with trace of fresh

blood noticed on tissue paper after wiping and no findings suggestive of chronic anal fissure were included in the study. Patients with perianal fistula and perianal abscess with concomitant inflammatory bowel disease and immunodeficiency; taking oral immunosuppressant or steroids; with a history of haemorrhoidectomy; with chronic diseases such as ischemic heart disease, hypertension, or migraine are excluded from the study.

Patients were randomly divided in two groups. One group (group: 1) was treated with topical glyceryl trinitrate [0.4% nitroglycerin ointment], and the other group (group: 2) was treated with both GTN and topical antibiotic [metronidazole 0.75%]. Both groups included random selection of pregnant and lactating ladies. Demographic characteristics of all patients were recorded, a detailed anamnesis was taken, and physical examination was performed before the start of treatment. Pain complaints during defecation were evaluated with the visual analogue scale (VAS). All patients were instructed to circulate each pea sized drug 1-2 cm into the anus with the tip of the index fingers 2-3 times a day for 14 days. They were also advised to eat a fibre rich diet, stool softener until they have loose stool, and 20 minute luke warm water bath with salt 3-4 times a day. At the end of the 1st, 2nd and 4th weeks of treatment, the patients were called for control visits and examined, and their VAS scores were recorded.

The effectiveness of the treatment was evaluated according to the level of healing of the fissure and the severity of pain. The fissure was visually inspected and evaluated at each visit, while the degree of epithelialization was determined as follows: 0, no epithelialisation in the fissure; 1, there is epithelialization in the fissure; and 2, the fissure is fully healed. The VAS score was used to measure pain after defecation. The scale was divided into 10 equal parts; 0, indicated no pain and 10 indicated unbearable pain. Clinical improvement was considered as complete

reepithelialization of the anal canal mucosa and closure of the fissure without erythema or inflammation and relief of patient complaints. Appropriate statistical analyses were done.

Results

Of the 100 patients included in the study, all were female of different age group. The median age of the patients in group 1 was 26.5 years (18-45 years); and in group 2, it was 26 years (18-40 years). Among the 100, 6 patients were pregnant (26%) and lactating lady was 10 (10%). Pain symptoms were present in both groups, while defecate. Constipation and bleeding during defecation were detected in 62 (100%) and 60 (97%) patients in group 1 and in 35 (92%) and 33 (87%) patients in group 2. The medians of the duration of pain, bleeding time and constipation duration of the patients were detected by 1 week, 2 weeks and 4 weeks in both groups. There was no statistical difference between group 1 and 2 in terms of age, duration of pain, duration of bleeding and duration of constipation ($p > 0.05$).

Table I: Comparison of general characteristics in two study groups

Characteristics	Total (N=100)	Group 1 (n=62)	Group 2 (n=38)
Age in years (Median)	26.25	26	26.5
Pain on defecation			
No	0	0	0
Yes	100	62	38
Bleeding on defecation			
No	07	02	05
Yes	93	60	33
Constipation			
No	03	00	03
Yes	97	62	35
Pain duration (wk)	3.5(2-4)	4(2-4)	3(2-4)
Bleeding duration (wk)	4(2-4)	4(2-4)	3(2-4)
Constipation duration (wk)	4(2-7)	4(3-5.50)	4(3-5.50)

A. Pregnant lady

Model Summary^b

Model	R	R Square	Adjusted Square	R Std. Error of the Estimate	Durbin-Watson
1	.104 ^a	.681	.532	.219	2.068

a. Predictors: (Constant), GTN+Metro

b. Dependent Variable: pregnant lady

The adjusted R² value was 0.532. This indicated that 53.2% of the variations in pregnant lady could be explained by the predictor variables of GTN, GTN+Metro.

ANOVA^a

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	.051	1	.051	1.071	.003 ^b
	Residual	4.699	2	.048		
	Total	4.750	3			

- a. Dependent Variable: pregnant lady
- b. Predictors: (Constant), GTN+Metro

Table 2 shows that the total sum of squares is 4.750, with a 3 degree of freedom. The sum of square for regression is 0.051 with 1 degree of freedom. The mean square for regression is 0.051. The F Statistics is 1.071 and the corresponding p value is 0.003, which is below the typical significance level of 0.05, indicating the overall significance of the regression model and robust.

B. Lactating lady

Model Summary^b

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Durbin-Watson
1	.784 ^a	.625	.545	.303	2.05

- a. Dependent Variable: pregnant lady
- b. Predictors: (Constant), GTN+Metro

Table 2 shows that the total sum of squares is 4.750, with a 3 degree of freedom. The sum of square for regression is 0.051 with 1 degree of freedom. The mean square for regression is 0.051. The F Statistics is 1.071 and the corresponding p value is 0.003, which is below the typical significance level of 0.05, indicating the overall significance of the regression model and robust.

B. Lactating lady

Model Summary^b

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Durbin-Watson
1	.784 ^a	.625	.545	.303	2.05

- a. Predictors: (Constant), GTN+Metro
- b. Dependent Variable: lactating lady

The adjusted R² value was 0.625. This indicated that 62.5% of the variations in pregnant lady could be explained by the predictor variables of GTN, GTN+Metro.

ANOVA^a

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	.002	1	.002	.018	.032 ^b
	Residual	8.998	3	.092		
	Total	9.000	4			

- a. Dependent Variable: lactating lady
- b. Predictors: (Constant), GTN+Metro

Table 3 shows that the total sum of squares is 9, with a 3 degree of freedom. The sum of square for regression is 0.02 with 1 degree of freedom. The mean square for regression is 0.002. The F Statistics is .018 and the corresponding p value is 0.032, which is below the typical significance level of 0.05, indicating the overall significance of the regression model and robust.

C. Non-Pregnant lady

Model Summary^b

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Durbin-Watson
1	.753 ^a	.621	.544	.360	2.014

- a. Predictors: (Constant), GTN+METRO
- b. Dependent Variable: non-pregnant

The adjusted R² value was 0.621. This indicated that 62.1% of the variations in pregnant lady could be explained by the predictor variables of GTN, GTN+Metro.

All the equations were found to be robust with rejection of the null hypotheses. None of the equations were found to suffer from problems of autocorrelation as has been evident from the Durbin-Watson statistic lying between 1.60 and 2.40.

ANOVA^a

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	.072	1	.072	.554	.038 ^b
	Residual	12.678	2	.129		
	Total	12.750	3			

a. Dependent Variable: non-pregnant

Table 4 shows that the total sum of squares is 12.75, with a 3 degree of freedom. The sum of square for regression is 0.72 with 1 degree of freedom. The mean square for regression is 0.072. The F Statistics is .554 and the corresponding p value is 0.038, which is below the typical significance level of 0.05, indicating the overall significance of the regression model and robust.

At the end of the first week, only 2 patients (3.2%) in group 1 had complete recovery; while in group 2, 8 patients (21%) had complete recovery. At the end of 4th week 10 patients (16%) in group 1 and 14 patients (36%) had fully recovered. When the groups were compared in terms of physical examination findings and recovery rates, it was found that both epithelialization and healing rates of the patients in group 2 were statistically significantly higher than those in group 1 from the first week.

The median VAS score levels were found to be 8 (6-8) in group 1 and 8 (6-9) in group 2, respectively, on the day of enrolment. At the end of the first week of treatment, the median VAS score decreased from 8 to 5 (4-7) in group 1 and in group 2 while it decreased from 8 to 2 (1-3). At the end of the 1st week, 30.0% patients in group 1 still have VAS score above 7; while in group 2 about 11% VAS score below 5. At the end of 4th week, the VAS score decreased from a median of 8 to 3.5 (IQR, 2-5) in group 1 and VAS decreased from a median of 8 to 0 (IQR, 0-1) in group 2. At the end of the 4th week, the VAS score was still above 6 in 30% patients in group 1. When the groups were compared in terms of VAS score detected on the day of enrolment and follow up, it was found that the VAS scores of the patients in group 2

decreased much more rapidly after the 1st week, along with the physical examination findings. The VAS score of the group 1 was started to decrease slowly at the 1st week of treatment and at the end of the 4th week it reaches same as the group 2 in 1st week.

Table II: Comparison of treatment groups according to acute anal fissure healing status

Variable	Total (N=100)	Group 1 (n=62)	Group 2 (n=38)
Week 1			
Uncured	88	57	31
Epithelialized	12	7	5
Healed	10	2	8
Week 4			
Uncured	20	12	8
Epithelialized	56	40	16
Healed	24	10	14
Week 8			
Uncured	10	10	0
Epithelialized	28	19	9
Healed	62	33	28

Discussion

In our study, it was shown that the combined use of glyceryl trinitrate and topical metronidazole for the treatment of acute anal fissure, compared to the use of topical glyceryl trinitrate alone, reduced the severity of pain in a very short period of time and both shortened the healing time of the fissure and increase healing rate.

Here we studied only female patients along with pregnant and lactating lady. Result shows that pain and other symptoms are same among all of them. Typical presenting symptoms in acute anal fissure are sharp and excruciating pain occur during defecation may be accompanied by per rectal bleeding.¹³ Similar to the literature, all of our patients had complaints of pain at defecation, and pain scores were found to be very high before starting treatment. In addition, defecation was accompanied by bleeding in 90% patients.

Spasm is known to occur in the internal anal sphincter in acute anal fissure.¹⁴ Warm sitz bath

contributes to the relaxation of the internal anal sphincter and the healing of the anal fissure through the somatoanal reflex.¹⁵ Approximately half of acute anal fissures have been reported in studies to heal with only warm sitz bath and fibre diet intake.¹⁶ In studies on aetiology, due to the inadequate response of some patients to treatment, it has been shown that the bacteria found in the anal fissure area in 90% of patients do not match with the normal flora of the same patients. *Escherichia coli* was reported to be one of the main causes.¹² In light of Grekova et al.¹³, after 4 weeks of conventional treatment of chronic anal fissure, a 71% improvement was found in control group, while complete recovery was achieved in 95.6% of the patient group in which topical metronidazole was added to the conventional treatment. Unlike previous study, Karoplat reported that a 44% improvement was found in the control group with 4 weeks of topical lidocaine treatment in acute anal fissure, while an improvement of 86% was achieved in the group that added topical metronidazole to topical lidocaine ointment.⁷ In our study, similar to the literature, complete recovery was achieved in 90% of patients using topical glyceryl trinitrate and metronidazole. In addition, it was shown that the increase in the rate of complete recovery started from the 1st week of treatment compared to that in the control group.

Alvandipour et al.¹⁷ reported that the mean VAS score level of patients, who had received topical diltiazem treatment in the treatment of chronic anal fissure was 3.2 ± 0.25 at the beginning of the treatment, and the VAS score level was reduced to 2.32 ± 0.32 at the end of 1 month of treatment. On the other hand, in a study by Martellucci et al.¹⁸, evaluating patients with acute anal fissure, the median VAS score was 7.1 (range, 2-10) at the beginning of the treatment, and 1.7 at the end of 1 month of treatment. In a retrospective study of patients with acute anal fissure, Emile et al.¹⁹ reported that the mean VAS score level was 8.8 ± 0.96 before treatment, and the mean VAS score level was 0.47 ± 0.8 after 6 weeks of

treatment. Unlike the above studies, in patients with chronic anal fissure, Grekova et al.¹³ reported that the VAS score level decreased in a shorter period of time from the day the treatment was started in the patient group using topical metronidazole compared to the period required for a similar decrease in the non-user group. Carrying out similar treatment in patients with acute anal fissure, Karapolat⁷ reported that the VAS score levels of patients, who had received topical metronidazole treatment was significantly lower at the 2nd and 4th weeks of treatment compared to those of the patient group, who did not receive topical metronidazole treatment. In our study, similar to the literature, it was found that the VAS score level had decreased further in the patient group using topical metronidazole from the 1st week of treatment compared to the level of decrease in the group using glyceryl trinitrate alone. In addition, in our study, it was shown that the VAS score level attained by the patient group using topical metronidazole in the 1st week of treatment was only achieved in the 4th week by the group using glyceryl trinitrate alone.

Our study has several limitations. First, the long-term recurrence rates are unknown due to the short follow-up period. The second limitation is that most of the patients included in the study were female. Despite these limitations, we think that our study contributes to the treatment of acute anal fissure in the adult age group.

In conclusion, with the addition of topical metronidazole to conventional treatment, the reduction of acute anal fissure-related pain in a short period of time, the shortening of the healing time of the fissure, and the high rate of healing indicate that infection plays an important role in the aetiology of anal fissure. The use of topical metronidazole as an adjunct to conventional treatment may result in lower chronicity of acute anal fissures and avoidance of surgical interventions with high complication rates. We think that there is a need for new studies in which different topical antibiotic therapy options are employed.

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