Efficacy of local metronidazole with glyceryl trinitrate versus topical glyceryl trinitrate alone in the treatment of acute anal fissure: a randomized clinical trial

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Introduction
Anal fissure is one of the most common diseases of the anorectal region that is frequently encountered in surgical practice, equally affects both women and men. Acute anal fissures last shorter than 6 weeks. The American Society of Colon and Rectal Surgeons favors conservative management of anal fissure as the first line of treatment. A rectal ointment containing 0.2% glyceryl triturate (GTN) can be recommended to promote the healing of anal fissures and decreasing sphincter spasm. Metronidazole is a 5-nitroimidazole derivative antibiotic with a cytotoxic bactericidal effect particularly on anaerobic bacteria.
The purpose of the present study was to investigate whether local metronidazole antibiotic cream is effective and safe to use in reducing the symptoms and improving the healing process of acute anal fissure.
Patients and methods
This study was performed in Mansoura University Hospital, surgery outpatient clinic from the period of July 2022 till July 2023. This study was a single-blinded, randomized controlled trial.
Total 100 patients were included in this study and randomly divided into two groups, 50 patients in each group. First group (group 1) treated by combination of local metronidazole 10% with 0.2% GTN while the second group treated only with GTN.
Results
Anal pain were present in both group in all patients with acute anal fissure while constipation were 88% in group 1 and 76% group 2. To lesser extent itching, bleeding, and diarrhea were presented in both group.
Visual analog scale for pain intensity were equal in both groups at the time of first clinical examination. After 1 week and 1 month of treatment there were statistically significant difference between both groups thus the visual analog scale were lower in group 1 than group 2 (0.001 and $<$0.001, respectively).
Healing of acute anal fissure was assessed clinically at variable interval for all patients there is statistically significant difference between both group (0.004) as regard healing, first group showed earlier and faster healing and fewer number of nonhealing of the fissure at the end of follow up.
Conclusion
Adding local metronidazole 10% to the classic GTN treatment will improve the symptoms of acute anal fissure specially pain and discomfort and markedly accelerate healing process.

Keywords:
acute anal fissure, glyceryl trinitrate, local metronidazole

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Introduction

Anal fissure is one of the most common diseases of the anorectal region that is frequently encountered in surgical practice, equally affects both women and men [1].

It is a longitudinal tear of anal mucosa that is lined with stratified squamous epithelium, distal to the dentate line, and its usual position is in midline posteriorly [2].

Acute anal fissures last shorter than 6 weeks. They are superficial, limited to anoderm, and have sharp, fresh mucosal margins with granulation tissue at the base [3].

Treating acute fissures is by maintaining soft, regular, and easily passed stool. Laxatives and high-fiber diet must be used. Effective pain management is also essential by local anesthetics, such as lidocaine 5% ointment, are beneficial for short-term usage. A rectal ointment containing 0.2% or 0.4% glyceryl triturate (GTN) or diltiazem gels can be

recommended to accelerate the healing of anal fissures and decreasing sphincter spasm [4].

The American Society of Colon and Rectal Surgeons (ASCRS) favors conservative management (chemical sphincterotomy) of anal fissure as the first line of treatment [5].

It is identified that different types of microorganisms are found in base of acute anal fissure. Anaerobic organisms are present in almost 50% of cases of anal fissure. Microbial colonization of anal fissures results in its delayed healing. Reducing the bacterial count using topical antibacterial helps in accelerating the healing of anal fissure [6].

Durai *et al.* [7], concluded that local application of povidone–iodine solution in anal fissure associated with improvement of the symptoms.

Garg *et al.* [8], revealed that marked symptomatic improvement was achieved in more than 90% of cases with anal fissure with the use of oral ciprofloxacin and ornidazole for only 5 days.

The same authors reported in 2014 that the local application of metronidazole cream for 3 months in addition to the above regimen maintain the symptomatic relief achieved and help cure of chronic anal fissure in up to 90% of patients [9].

Metronidazole is a 5-nitroimidazole derivative antibiotic of with a cytotoxic bactericidal effect particularly on anaerobic bacteria [10].

The purpose of the present study was to investigate whether local metronidazole antibiotic cream is effective and safe to use in reducing the symptoms and improving the healing process of acute anal fissure.

Patients and methods

This study was performed in Mansoura University Hospital, 8th Department of Surgery outpatient clinic from the period of July 2022 till July 2023.

This prospective randomized control study was registered at Institutional Research Board (IRB) of Mansoura Faculty of Medicine with proposal code 'R.23.08.2294.R1.'

Informed consent was obtained from all patients to be included in the study. Patients with acute anal fissures, aged 18–79 years of both sexes, were included.

An acute fissure was defined by the first time duration of symptom's appearance for less than 6 weeks. Exclusion criteria were chronic anal fissure (symptoms present for >6 weeks) and the presence of anal sphincter fibrosis or skin tag. Patients with coexisting anal fistula, perianal abscess, with a history of hemorrhoids or hemorrhoidectomy or associated inflammatory bowel disease, and receiving oral immunosuppressive drugs or steroids; also pregnant female and lost patient during follow-up were excluded.

This study was a single-blinded randomized controlled trial, and patients have not disclosed the exact treatment they were getting.

Total 100 patients were included in this study and randomly divided into two groups, 50 patients in each group. First group (group 1) treated by combination of local metronidazole 10% with 0.2% GTN while the second group treated only with GTN.

Collected data included were demographic data, symptoms, duration of symptoms, pretreatment and posttreatment visual analog scale (VAS) after 1 and 4 weeks.

In both groups, preventing hard stools by high-fibers diet and lactulose syrup 30 ml twice per day were prescribed.

All patients underwent detailed medical history and physical examination before treatment was started. All patients were advised to locally apply a pea-sized amount of each drug to their anal margin three times per day for 4 weeks.

Baseline assessment included recording, maximum severity of pain during defecation according to a VAS, and fissure healing. After the starting of treatment, each patient was called for follow-up at 1 week, fourth week. After complete healing of the fissure, treatment was stopped. The primary endpoint was fissure healing, confirmed by finding a scar at fissure site. While the secondary outcome was maximum pain on defecation according to VAS.

Statistical analyses

All statistical data analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 17.0 for Windows software (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were used for comparisons. Student's t test, Mann–Whitney U test, and χ^2 test were used to

assess independent samples. A *P* value less than 0.05 was accepted as statistically significant.

Results

The mean age were 33.7 years in the first group and 30.2 years in the second group.

There were 48% male and 52% female in group 1 while the ratio were 56% male and 44% female in group 2

Ninety four percent of the anal fissure were posterior midline in group 1 while it was 86% in group 2 (Table 1).

Anal pain were present in both group in all patients with acute anal fissure while constipation were 88% in group 1 and 76% group 2. To lesser extent itching, bleeding and diarrhea were presented in both group (Table 2).

The mean duration of presenting symptoms were from 10.7 to 30.4 days in the first group while it varies from 8 to 28.6 days in group 2 (Table 3).

As seen in Table 4 and Fig. 1, VAS for pain intensity were equal in both groups at the time of first clinical examination. After 1 week and 1 month of treatment there were statistically significant difference between both groups thus the VAS were lower in group 1 than group 2 (0.001 and <0.001) (Fig. 1).

As regard Table 5, healing of acute anal fissure was assessed clinically at variable interval for all patients there is statistically significant difference between both group (0.004) as regard healing, first group showed earlier and faster healing and fewer number of nonhealing of the fissure at the end of follow up.

Table 1 Demographic data and location of the fissure

	Group 1	Group 2
Age (mean±SD)	33.72±14.30	30.20±12.88
Sex [*n* (%)]		
Male	24 (48)	28 (56)
Female	26 (52)	22 (44)
Location of fissure [*n* (%)]		
Anterior	2 (4)	3 (6)
Posterior	47 (94)	43 (86)
Lateral	–	1 (2)
Multiple	1 (2)	3 (6)

Table 2 Symptoms of acute anal fissure

Symptoms	Group 1 [*n* (%)]	Group 2 [*n* (%)]
Anal pain	50 (100)	50 (100)
Constipation	44 (88)	38 (76)
Itching	29 (58)	26 (52)
Bleeding	7 (14)	8 (16)
Diarrhea	1 (2)	2 (4)

Table 3 Duration of symptoms of acute anal fissure

Mean duration of symptoms	Group 1	Group 2
Pain (days)	18±7.9	21.2±8.6
Constipation (days)	30.45±6.8	28.66±4.45
Itching (days)	13.98±4.57	14.33±5.12
Bleeding (days)	10.73±5.44	13.3±4.6
Diarrhea (days)	12.7±4.8	8

Discussion

Few studies with a small sample size have been done utilizing topical metronidazole in treatment of acute anal fissure. The purpose of this study was to determine whether the use of topical metronidazole 10% with GTN could speed up the healing process of acute anal fissure in comparison to the use of GTN 0.2%, which has been used for years in the treatment of acute anal fissure.

The most common age of presentation in patients with anal fissure is 20–40 years. We observed that mostly patients were in 30 s years of age which co relates with findings of other studies [11].

Results achieved in a study concerning the pharmacological sphincterotomy prove to be an effective noninvasive, tolerant method of treatment of chronic anal fissure particularly for those who are surgically unfit, who refuse surgery, and those who had recurrence after previous surgery [12].

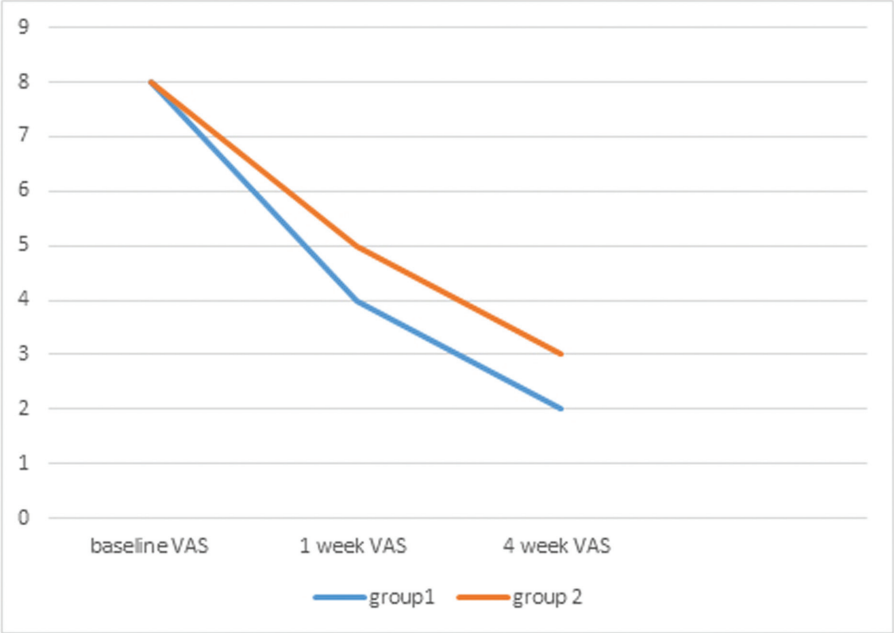
Our results showed that topical metronidazole combined with traditional therapy (GTN) has a faster pain relief (according to VAS) in acute anal fissures. Earlier healing (96%) in metronidazole combined with nitroglycerine 0.2% after 1 month of treatment while it was 86% in GTN alone group in agreement with Grekova *et al.* [13], stated that those patients who had anaerobic bacteria in their swab test and subsequently treated with topical metronidazole, their pain relieved earlier and 95.6% had healing of their wound, concluded that topical metronidazole

Table 4 Visual analog scale on first visit, 1 week, and 4 weeks after treatment

	Group 1	Group 2	*P* value
Baseline VAS	8 (6–10)	8 (6–10)	0.845
1 week VAS	4 (2–7)	5 (3–8)	0.001*
4 week VAS	2 (0–5)	3 (2–6)	<0.001*

VAS, visual analog scale. Baseline *p* 0.845 . . . non significant. 1 week *p* value 0.001 . . . . significant. 4 week *p* value <0.001 . . . significant.

Figure 1



Difference in VAS between the two groups. VAS, visual analog scale.

Table 5 Time of complete healing of acute anal fissure

Time of complete healing (day)	Group 1 [*n* (%)]	Group 2 [*n* (%)]	*P* value
0–10	3 (6)	0	
11–20	25 (50)	12 (24)	
21–30	20 (40)	31 (62)	0.004*
No healing	2 (4)	7 (14)	

ointment could be effective in patients with anal fissures.

In our study VAS dropped from 8 to 2 in metronidazole group after 1 month of treatment. In the a study by Saba and Saqib [14], observed that combination of local metronidazole and 0.2% GTN ointment for acute anal fissure resulted in a significant relief of symptoms especially pain (VAS was significantly less in patients who underwent metronidazole treatment). VAS in the metronidazole group dropped from 7.4 to 1.86 over 6 weeks duration of treatment. A study done by Karapolat [10] found that in combination with traditional medical therapies, topical metronidazole is an efficient, safe, quick, painless, and simple-to-use therapy that reduces pain and accelerates healing of anal fissure.

Mert [15] showed that infection plays an important role in the pathogenesis of anal fissures. Using topical metronidazole as an addition to GTN may reduce the chronicity of acute anal fissures and prevent surgical interference with reducing complications.

Nicholson and Armstrong [16] suggested that the antimicrobial and anti-inflammatory effects would be stronger in tissues if taken orally as the drug will be more bioavailable.

No side effects appeared in our patients in both groups except for nitroglycerine-related headaches.

The limitations of the present study include small sample sizes, short follow-up time, and the study having been conducted in a single site. Therefore, the long-term recurrence rates of the patients remain unknown.

Conclusion

Adding local metronidazole 10% to the classic GTN treatment will improve the control of acute anal fissure

symptoms specially pain and discomfort and markedly accelerate healing process this due to its anti-inflammatory and antimicrobial action of metronidazole.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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