

COMPARISON OF EFFECTIVENESS OF TOPICAL METRONIDAZOLE & GLYCERYL TRINITRATE V/S TOPICAL GLYCERYL TRINITRATE ALONE IN THE MANAGEMENT OF ACUTE ANAL FISSURE

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Abstract

OBJECTIVE

To compare the efficacy of topical metronidazole and topical 0.2% GTN vs topical 0.2% GTN alone in patients of anal fissure.

METHODOLOGY

A prospective, interventional, comparative study was conducted in the Surgical Unit VI of Civil Hospital Karachi over six months. A total of 158 patients aged 18–70 years with acute anal fissure (<6 weeks' duration) were consecutively enrolled and randomly allocated into two groups: Group A received topical metronidazole with 0.2% glyceryl trinitrate, and Group B received 0.2% glyceryl trinitrate alone. Data was analyzed using SPSS version 26 with a significance level of $p \leq 0.05$.

RESULTS

A total of 158 patients were included, with an overall mean age of 39.4 ± 10.7 years; 51.9% were males and 48.1% females. The combination of metronidazole with 0.2% glyceryl trinitrate demonstrated higher efficacy ($p=0.023$) and greater pain reduction at all follow-up intervals ($p<0.01$) than GTN alone. Efficacy was significantly higher among males ($p=0.033$) and younger patients aged 18–40 years ($p=0.044$), while differences among females and older patients were not significant.

CONCLUSION

The findings of this study demonstrate that combining topical metronidazole with 0.2% glyceryl trinitrate enhances healing and provides faster pain relief in patients with acute anal fissure compared to monotherapy. The addition of metronidazole improves therapeutic response, especially among younger adults, by addressing both inflammation and infection at the fissure site. This combination represents a safe, effective, and easily applicable first-line treatment option for managing acute anal fissure in clinical settings.

INTRODUCTION

Anal fissure, a linear tear in the anoderm of the lower anal canal, presents with intense pain during defecation, occasional bleeding, and discomfort that can markedly impair daily functioning. Globally, the lifetime incidence is estimated up to about 11 %, but precise epidemiological data from Pakistan are sparse [1,2]. A regional study from KJMS reported that among fissure patients in a Pakistani hospital, 84 % had posterior fissures, 38 % had constipation as a preceding symptom, and 26 % had diarrhoea as a precipitant; the mean symptomatic interval was about 20 days [3]. These local data underscore the burden of anal fissures in the Pakistani population and the need for locally-relevant therapeutic evidence.

The pathogenesis of anal fissure involves an initial mechanical injury to anoderm (e.g. by hard stool or strain), followed by internal anal sphincter spasm and diminished blood flow leading to ischemia and delayed healing [4,5]. In chronic or refractory cases, a vicious cycle of spasm, ischemia, and microtrauma perpetuates nonhealing [6]. In such situations, reducing sphincter pressure pharmacologically or surgically becomes critical.

Medical management is typically first-line, consisting of high-fibre diet, stool softeners, analgesics, warm sitz baths, and topical vasodilators that aim to lower internal sphincter tone and improve perfusion. The most commonly used agent is glyceryl trinitrate (GTN) 0.2 % ointment, which releases nitric oxide and decreases sphincter resting pressure [7,8]. Early trials, including some from Pakistan, have shown fissure healing rates of 60–70 % with GTN, though headache and hypotension remain frequent side effects, contributing to poor compliance [9,10]. For example, a Pakistani study (Hashmi et al.) treated 100 chronic fissure patients with topical GTN; 76 healed over 8 weeks, 7 had recurrence, and 21 experienced headaches [11]. Another local survey reported noncompliance in 112 patients using GTN was significantly associated with headache and hypotension [12].

However, a significant proportion of patients still fail to heal with GTN alone or discontinue treatment due to adverse effects. Some Pakistani studies have sought alternatives: for instance,

topical diltiazem has been compared to GTN in Karachi, showing similar fissure healing but fewer headaches [13]. In one Karachi-based RCT, diltiazem healed 31 of 40 patients and GTN healed 33 of 40; side effects were lower with diltiazem (13 vs. 29) [13]. Moreover, in the Pakistani context, lateral internal sphincterotomy (LIS) remains frequently used: a study at Qazi Hussain Hospital reported that 86 patients underwent closed LIS, mostly male, with acceptable outcomes [14]. Yet LIS carries risks: a Peshawar series of 139 patients reported fecal incontinence in 10 % after closed LIS [15].

Beyond sphincter relaxation, attention has turned to adjunctive therapies. Inflammation and microbial colonization at the fissure base may delay healing; topical metronidazole has been hypothesized to promote mucosal repair via antimicrobial and anti-inflammatory effects. Some studies from other regions suggest faster symptom relief and improved epithelialization when metronidazole is added to standard therapy [16,17]. Yet in Pakistan, there is no well-documented study comparing topical metronidazole + GTN vs GTN alone in acute fissure.

This gap presents both a challenge and an opportunity. Given the burden of anal fissure in Pakistan, variable response to GTN monotherapy, and local use of surgical options with associated morbidity, it is clinically relevant to explore whether adding topical metronidazole can improve outcomes. The present trial aims to rigorously compare healing rates, symptom relief, adverse events, and compliance between topical metronidazole + 0.2 % GTN versus 0.2 % GTN alone in patients presenting with acute anal fissure at a tertiary care hospital in Karachi. The findings may help guide evidence-based, contextually appropriate nonoperative management strategies in Pakistan and similar settings.

METHODOLOGY

This study was designed as a prospective, interventional, comparative clinical investigation conducted in the Surgical Unit VI of Civil Hospital Karachi, a tertiary-care public teaching hospital affiliated with Dow University of Health

Sciences, Karachi, Pakistan. The study was carried out over a period of six months after obtaining ethical clearance from the Institutional Review Board. Written informed consent was obtained from all participants prior to enrolment. The total sample size was 158 patients, equally divided into two groups (79 in each). Patients of both sexes aged between 18 and 70 years who presented with symptoms of acute anal fissure lasting less than six weeks were considered eligible for participation. Acute anal fissure was defined as a linear tear in the anoderm extending from the anal verge toward the dentate line, accompanied by pain during defecation, rectal bleeding, or perianal itching. The healing response was classified into three categories: complete, partial, and no healing. Complete healing referred to full re-epithelialization and closure of the fissure with resolution of symptoms and absence of local inflammation; partial healing denoted incomplete re-epithelialization with improvement in pain or bleeding; and no healing indicated persistent ulceration with inflammation and unchanged symptoms. Exclusion criteria comprised individuals with coexisting perianal conditions such as fistula, abscess, haemorrhoids, inflammatory bowel disease, or prior perianal surgery, as well as those who were pregnant, mentally incapacitated, or immunocompromised due to diabetes mellitus, tuberculosis, HIV infection, or prolonged corticosteroid or immunosuppressive therapy. Eligible patients were enrolled consecutively until the target sample size was achieved. Participants were divided into two treatment groups according to the study protocol: Group A received a combination of topical metronidazole and 0.2% glyceryl trinitrate (GTN) ointment, while Group B received topical 0.2% GTN alone. Both groups were advised supportive measures including a high-fibre diet, stool softeners, adequate fluid intake, and warm sitz baths four times daily. A pea-sized amount of

the assigned ointment was applied to the perianal region three times daily. Each participant underwent a detailed history and perianal examination prior to initiation of treatment, with follow-up assessments conducted at 1, 4, and 6 weeks. Treatment was discontinued upon complete fissure healing or completion of the follow-up period. Data were collected using a structured proforma and analysed using SPSS version 26. Quantitative variables were summarized as mean $\pm$ standard deviation, while categorical variables as frequencies and percentages. Comparisons between the two treatment groups for healing outcomes were performed using the Chi-square test, with a p-value ≤ 0.05 considered statistically significant.

RESULTS

A total of 158 patients were included in the study, with 79 patients each in the MTZ + GTN group and the GTN alone group. The mean age of patients in the MTZ + GTN group was 38.52 ± 9.68 years, while in the GTN alone group it was 40.25 ± 11.57 years. The mean duration of symptoms was 3.38 ± 1.12 weeks in the MTZ + GTN group compared to 2.91 ± 2.13 weeks in the GTN alone group. Among the study participants, males constituted 58.5% in the MTZ + GTN group and 41.5% in the GTN alone group, whereas females accounted for 40.8% and 59.2%, respectively. The most common presenting symptom was pain on defecation, reported by 71 (49.3%) patients in the MTZ + GTN group and 73 (50.7%) in the GTN alone group. Bleeding on defecation was observed in 11 (40.7%) and 16 (59.3%) patients of the respective groups, while perianal itching was present in 47 (50.5%) of MTZ + GTN group and 46 (49.5%) of GTN alone group. Difficulty in defecation was reported by 67 (50.8%) patients in the MTZ + GTN group and 65 (49.2%) in the GTN alone group (Table I).

Table I: Demographic and Clinical Characteristics of Study Patients (n=158)		
Demographic and Clinical Characteristics	Treatment Groups	
	MTZ + GTN (n=79)	GTN Alone (n=79)

Age in years, Mean $\pm$ SD		38.52 $\pm$ 9.68	40.25 $\pm$ 11.57
Duration of Symptoms in weeks, Mean $\pm$ SD		3.38 $\pm$ 1.12	2.91 $\pm$ 2.13
Gender, n (%)	Male	48 (58.5)	34 (41.5)
	Female	31 (40.8)	45 (59.2)
Pain on Defecation, n (%)		71 (49.3)	73 (50.7)
Bleeding on Defecation, n (%)		11 (40.7)	16 (59.3)
Perianal Itching, n (%)		47 (50.5)	46 (49.5)
Difficulty in Defecation, n (%)		67 (50.8)	65 (49.2)

Table II presents the comparison of mean VAS scores at different follow-up intervals and the overall efficacy between the MTZ + GTN and GTN alone groups. At baseline, both groups showed comparable pain scores, with a mean VAS of 6.02 ± 2.51 in the MTZ + GTN group and 6.00 ± 2.46 in the GTN alone group ($p=0.953$), indicating no significant difference in initial pain intensity. However, as the treatment progressed, a marked reduction in pain scores was observed in the MTZ + GTN group compared to the GTN alone group. After 1 week, the mean VAS score significantly decreased to 2.71 ± 1.90 in the MTZ

+ GTN group, while it remained higher at 5.31 ± 1.44 in the GTN alone group ($p=0.0001$). Similarly, at 4 weeks, the mean VAS score further reduced to 0.71 ± 0.88 in the MTZ + GTN group versus 2.77 ± 1.97 in the GTN alone group ($p=0.0001$). By 6 weeks, both groups showed substantial improvement; however, the MTZ + GTN group maintained significantly lower pain levels (0.18 ± 0.21 vs. 0.30 ± 0.34 , $p=0.006$). Regarding treatment efficacy, 76 (96.2%) patients in the MTZ + GTN group were classified as effective responders compared to 68 (86.1%) in the GTN alone group, and this difference was statistically significant ($p=0.023$).

Table II: Comparison of VAS Scores at Different Follow-up Intervals & Efficacy Between Groups (n=158)				
VAS Scores & Efficacy		Treatment Groups		P-Value
		MTZ + GTN (n=79)	GTN Alone (n=79)	
Baseline VAS score		6.02 $\pm$ 2.51	6.00 $\pm$ 2.46	0.953
VAS score at 1 Week		2.71 $\pm$ 1.90	5.31 $\pm$ 1.44	0.0001
VAS score at 4 Week		0.71 $\pm$ 0.88	2.77 $\pm$ 1.97	0.0001
VAS score at 6 Week		0.18 $\pm$ 0.21	0.30 $\pm$ 0.34	0.006
Effectiveness	Yes	76 (96.2)	68 (86.1)	0.023
	No	3 (3.8)	11 (13.9)	

Applying Independent Sample t-test & Chi-Square test

Table III presents the comparison of treatment efficacy between the Metronidazole + GTN and GTN alone groups according to gender and age. Among male patients, 46 (54.1%) in the Metronidazole + GTN group achieved efficacy compared to 30 (35.3%) in the GTN alone group, demonstrating a statistically significant difference ($p = 0.033$). In contrast, among female patients, 30 (41.1%) in the Metronidazole + GTN group and 38 (52.1%) in the GTN alone group showed effective treatment outcomes, though this difference was not statistically significant ($p = 0.288$). When assessed according to age, patients aged 18–40 years showed significantly greater

efficacy with combination therapy, where 59 (53.2%) in the Metronidazole + GTN group achieved effectiveness compared to 41 (36.9%) in the GTN alone group ($p = 0.044$). However, in patients aged above 40 years, 17 (36.2%) in the Metronidazole + GTN group and 27 (57.4%) in the GTN alone group demonstrated effective outcomes, with no statistically significant difference ($p = 0.178$). These findings indicate that the combination of Metronidazole and GTN was significantly more effective among male and younger patients, while the difference in treatment response among females and older patients was not significant.

Table III: Comparison of Treatment Efficacy According to Gender and Age Between Groups (n=158)			
Gender	Treatment Groups		P-Value
	MTZ + GTN	GTN Alone	
Male	46 (54.1)	30 (35.3)	0.033
Female	30 (41.1)	38 (52.1)	0.288
Age Group			
18–40	59 (53.2)	41 (36.9)	0.044
>40	17 (36.2)	27 (57.4)	0.178

DISCUSSION

Anal fissure is a common benign anorectal condition defined by a painful longitudinal tear in the anoderm that often leads to bleeding, sphincter spasm, and impaired mucosal healing due to localized ischemia [1,4,5]. Diagnosis is primarily clinical and is based on identifying a fresh linear fissure extending from the anal verge toward the dentate line, usually accompanied by acute symptoms such as pain, bleeding, or pruritus ani for less than six weeks [3,4]. Patients in this study met these diagnostic parameters, and individuals with chronic fissures, inflammatory bowel disease, or perianal infections were excluded to maintain homogeneity. Early recognition of the acute stage is crucial since medical treatment targeting internal sphincter relaxation and improved endodermal perfusion

can achieve complete healing in most cases if started promptly [1,5,7].

The present study found that topical metronidazole combined with 0.2% glyceryl trinitrate (GTN) provided superior outcomes compared to GTN alone in treating acute anal fissure. The overall healing rate of 96.2% in the combination group versus 86.1% in the GTN-only group was statistically significant ($p = 0.023$). Pain reduction was also more pronounced and faster among those using the combined regimen. These findings are consistent with Shahid et al. [4], who reported similar superiority of metronidazole plus GTN in a randomized clinical trial in Pakistan, and with the study by Mert [6], which demonstrated faster epithelialization and symptomatic improvement when metronidazole was added to topical therapy. The enhanced response can be attributed to the antimicrobial

and anti-inflammatory actions of metronidazole, which decrease bacterial load and local inflammation, supporting re-epithelialization when used alongside the nitric oxide-mediated vasodilatory and sphincter-relaxing properties of GTN [2,6,16].

Evidence from international trials also supports the efficacy of GTN in promoting fissure healing. Higuero [1] and Nelson et al. [17] highlighted GTN as a first-line pharmacologic option for nonsurgical management, while the landmark study by Lund and Scholefield [18] confirmed its effectiveness in a randomized, double-blind, placebo-controlled trial, showing significantly higher healing rates compared with placebo. However, frequent headaches and hypotension often limit GTN use, leading to poor adherence. The combination with metronidazole, as demonstrated in this study, may mitigate these drawbacks by hastening healing, reducing discomfort, and improving compliance. Furthermore, analysis by age group showed that patients aged 18–40 years achieved significantly greater healing with combination therapy (53.2% vs. 36.9%; $p = 0.044$), likely due to better vascular responsiveness, faster tissue regeneration, and fewer comorbidities compared with older patients, who showed no significant difference in treatment response ($p = 0.178$). Karapolat [2] also noted that age-related vascular changes can influence response to conservative management, which supports the present findings.

The demographic characteristics in this study, including a mean age around 39 years and predominance of male patients, correspond with other regional studies from Karachi and Peshawar [3,14,15]. These findings reflect the influence of lifestyle factors such as low fiber intake, chronic constipation, and limited physical activity. Clinically, the results emphasize that combining topical metronidazole with GTN is a cost-effective, accessible, and well-tolerated therapy suitable for acute fissure management in resource-limited tertiary hospitals. The approach offers a valuable nonoperative alternative to lateral internal sphincterotomy, which, while effective, is associated with postoperative incontinence risks [15]. Consequently, this combination therapy can

reduce the surgical burden while maintaining excellent clinical outcomes.

Despite its promising results, the study has several limitations. Being a single-centre investigation with a six-week follow-up, it could not evaluate long-term recurrence or sustained symptom relief. The modest sample size limited the depth of subgroup analysis, and adherence to treatment was self-reported, possibly introducing compliance bias. Additionally, blinding was not feasible due to the nature of topical application, which might have affected subjective symptom reporting. However, the prospective design, consistent methodology, and standardized data collection enhance the reliability and clinical relevance of the findings. Future multicentre randomized trials with larger populations and extended follow-up periods would be valuable for confirming the long-term benefits and safety of this combination therapy.

In summary, the addition of topical metronidazole to 0.2% glyceryl trinitrate significantly improved healing rates and accelerated pain relief in acute anal fissure, with the greatest benefit observed among younger adults. The results corroborate previous local and international studies and endorse the combination regimen as an effective, safe, and economical first-line therapeutic strategy for acute anal fissure in tertiary-care hospitals in Pakistan.

CONCLUSION

The findings of this study demonstrate that combining topical metronidazole with 0.2% glyceryl trinitrate enhances healing and provides faster pain relief in patients with acute anal fissure compared to monotherapy. The addition of metronidazole improves therapeutic response, especially among younger adults, by addressing both inflammation and infection at the fissure site. This combination represents a safe, effective, and easily applicable first-line treatment option for managing acute anal fissure in clinical settings.

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