

COMPARATIVE STUDY ON THE EFFICACY OF TOPICAL METRONIDAZOLE, TOPICAL NITROGLYCERINE, AND TOPICAL DILTIAZEM IN THE MANAGEMENT OF CHRONIC ANAL FISSURE

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Received: 02 December 2022, Revised and Accepted: 20 January 2023

ABSTRACT

Objective: Chronic anal fissure (CAF) is usually managed with surgical modalities but it imposes huge cost with recurrence rates. Hence, topical therapies are preferred in such cases which has a good patient acceptability rate. The present study aims to compare the topical metronidazole (MTZ), diltiazem (DTZ), and glyceryl trinitrate (GTN) in terms of healing rate and pain reduction in CAF patients.

Methods: This was a randomized and prospective study conducted on 90 patients with CAF. The patients were grouped as follows (n=30), Group 1; 1% MTZ gel, Group 2; 0.2% Nitroglycerin ointment, and Group 3 (n=30): 2% DTZ ointment. The patients were evaluated at 2, 4, and 6 weeks for pain using visual analogue score (VAS) and healing rate. The results were compared and $p < 0.05$ was considered as significant.

Results: The VAS scores between the groups was found to be non-significant ($p > 0.05$), however the VAS scores were markedly reduced within the group at 6 weeks. The healing rate was higher in MTZ group (90%) as compared to GTN (83.3%) and DTZ group (83.3%) but it was not significant. Regarding side effect, burning sensation was observed in MTZ and GTN, DTZ groups were devoid of side effects.

Conclusion: The MTZ was more effective with good healing rate but with few side effects. Regarding the pain reduction, all the groups displayed equivocal effects. Thus topical MTZ is a suitable agent for the faster healing of CAF and thus avoids the requirement of surgical options.

Keywords: Chronic anal fissures, Topical treatment, Metronidazole, Healing rate, VAS scores.

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INTRODUCTION

Anal canal is the terminal portion of the alimentary system and its main physiological role is the continence maintenance by complex sphincters which encompasses both internal and external sphincters [1]. The maintenance of anal tone by internal anal sphincter (IAS) is primarily due to the continuous partial contraction and the relaxation occurs only during rectal distension, meanwhile the external sphincter is mediated by the voluntary system [2]. During various conditions such as large bowel movement, excessive sphincter pressure during constipation, movement of dry bowel, or surgery causes excessive stress on the sphincter muscles. Hence, these one of the events causes a split or tear in the outermost skin of anal and leads to painful condition which is referred as anal fissure [3]. Majority of the anal fissures resolve within a short period and in some cases requires a conservative treatment for a period of 8-6 weeks. Anal fissures symptoms lasting for a few months are known as chronic anal fissures (CAF) [4].

The treatment modality for CAF varies based on the disease severity and the non-surgical management encompasses dietary modification, topical anti-inflammatory agents, Botulinum toxin injections, and sitz baths. In a systematic review and meta-analysis based on 148 trials, reveals that surgical management is more effective when compared to medical management but it imposes the risk of incontinence as well as post-operative pain and treatment cost [5]. For a quick and effective treatment, the first line agents such as topical nitroglycerin (NTG) and calcium channel blockers are preferred which decrease the IAS tone [6].

During the mechanical damage to sphincter, there is a chance for exposure to fecal bacteria and lead to an infection. Change in microbial flora (mixed pathogens) can lead to mucosal inflammation and causes defective anoderm in terms of loss of elasticity and flexibility and

leads to rupture. Further increased proinflammatory cytokines level in the anal tissue hinders the healing process and forms chronic ulcers. Hence, topical antibiotic is recommended in such cases in addition to conservative treatment for early recovery [7]. This study was designed to evaluate and compare topical Antibiotic (Metronidazole [MTZ] gel) with topical antispasmodics (NTG ointment, Diltiazem [DTZ]) in the treatment of CAF. In addition, the patient acceptability of these drugs in terms of side effect was also evaluated.

METHODS

This was a randomized and prospective study conducted in the Department of General Surgery, Sharda Hospital, Greater Noida during the period December 2019 to October 2022. The sampling of the patients was done by sealed sample method. In this study, 90 patients with the clinical diagnosis of primary anal fissure, who came to the Department of General Surgery, Sharda Hospital, were recruited for the study.

Inclusion criteria

All cases of primary anal fissure over 18 years were included in the study.

Exclusion criteria

Patients with secondary anal fissure due to tuberculosis, syphilis, Crohn's disease, ulcerative colitis and those with systemic conditions which delay the healing process, for example, diabetes and chronic renal failure were excluded from the study.

Methodology

In this study, the CAF patients (n=90) were grouped as follows,

- Group 1 (n=30): Treated with topical application of 1% MTZ gel.
- Group 2 (n=30): Treated with topical application of 0.2% NTG ointment.

- Group 3 (n=30): Treated with topical application of 2% DTZ ointment.

Patients were asked to apply their topical drug twice daily and they were evaluated at 2, 4, and 6 weeks. Analgesics, laxatives, and Sitz bath as required in all the three groups. Pain relief, healing, and side effects were noted. Pain relief was assessed using Visual Analog Score (VAS), Healing was assessed by looking re-epithelization of the fissure and side effects were noted as per patient's complaints.

Data analysis

The data were shown as mean (SD). To compare the data among the groups, one-way ANOVA and Chi-square test were applied. $p < 0.05$ was taken as significant.

RESULTS

The demographics variables between the three groups were found to non-significant ($p > 0.05$). The results are shown in Table 1.

Anorectal pain was reported among all (100.0%), blood in stool was seen in 62.2%, perianal swelling among 30%, constipation among 85.6%, and perianal itching among 82.2%. Diarrhea was observed in none of the cases. The results are shown in Table 2.

The distribution of PAIN (VAS) at presentation, at 2, 4, and 6 weeks was compared between Group A – MTZ, Group B – NTG, and Group C – DTZ using the Chi-square test. There was no significant difference in distribution of PAIN (VAS) at presentation, 2, 4, and 6 weeks between Group A – MTZ, Group B – NTG, and Group C – DTZ (Table 3).

The mean pain (VAS) in various groups was compared and there was no significant difference at various stages of treatment. The pain kept improving with treatment from 6.07, 6.03, and 6.0 in three groups to 0.27, 0.23, and 0.17 in three groups at the end of treatment. The results are shown in Fig. 1.

The distribution of healing at presentation at 2, 4, and 6 weeks was compared between Group A – MTZ, Group B – NTG, and Group C – DTZ using the Chi-square test. The distribution of healing at presentation 2, 4, and 6 weeks between the groups was found to be non-significant. The results are shown in Table 4.

Dizziness and burning sensation was compared between Group A – MTZ, Group B – NTG, and Group C – DTZ. Burning sensation was significantly more among Group A – MTZ compared to Group B – NTG, and Group C – DTZ. However, it was mild and did not affect acceptability. The results are shown in Table 5.

DISCUSSION

In the present scenario, the primary treatment modality for the symptomatic management of anal fissure is the topical administration of NTG or calcium channel antagonist nifedipine and DTZ [7-9]. Surgical modalities like lateral sphincterotomy is routinely used to mitigate pain during CAFs in patients with low response rate when managed with topical therapies. However, patients are hesitant to select this option due to huge surgical cost and risk of fecal incontinence [10]. Till date, no previous studies have been published comparing the topical MTZ, NTG and DTZ as an effective treatment for CAFs or anal pain.

In our study, the mean age was 32.13, 33.17, and 31.65 years in three groups. Our study was in corroboration with the previous reports where the most prevalent age for the occurrence of CAF was 30–40 years [11,12].

Most common symptom in our study was local pain, which was present in 100% cases. Other symptoms were constipation (85.6%), perianal itching (82.2%), blood in stool (62.2%), and perianal swelling (30%). Our results are in line with the study done by Acar *et al.* [13] pain as a result

Table 1: Comparison of demographic variables between the groups

Demographic parameters	Groups	Mean±SD	F	p-value
Age (years)	Group A–MTZ	32.13±7.33	0.422	0.657
	Group B–NTG	33.17±6.56		
	Group C–DTZ	31.63±5.79		
Weight (kg)	Group A–MTZ	75.97±6.38	0.166	0.847
	Group B–NTG	75.97±5.59		
	Group C–DTZ	75.20±5.83		
BMI (kg/m ²)	Group A–MTZ	23.79±2.66	0.859	0.427
	Group B–NTG	22.98±2.27		
	Group C–DTZ	23.20±2.51		

MTZ: Metronidazole, NTG: Nitroglycerin, DTZ: Diltiazem, BMI: Body mass index, SD: Standard deviation

Table 2: Symptoms among the study population

Symptoms	Frequency (%)
Anorectal pain	
Absent	0
Present	90 (100.0)
Blood in stool	
Absent	34 (37.8)
Present	56 (62.2)
Perianal swelling	
Absent	63 (70.0)
Present	27 (30.0)
Constipation	
Absent	13 (14.4)
Present	77 (85.6)
Perianal itching	
Absent	16 (17.8)
Present	74 (82.2)
Diarrhea	
Absent	90 (100.0)
Present	0
Site	
Posterior	90 (100.0)

of anal fissure in 97% of the subjects accompanied by high bleeding rate as a result of chronic condition of the anal fissure.

Topical glyceryl trinitrate (GTN) is widely used for the non-surgical management of CAF. GTN is a potent nitric oxide donor, which mediates the relaxation of internal sphincter. Application of GTN ointment or patch to the anal fissure area displayed significant healing of the fissures upto 50% [7]. However, the main side effect associated with GTN use is the headache and in a RCT conducted by Motie *et al.* [14] showed that postural dizziness and headache was more predominant during GTN treatment for anal fissures.

The smooth muscle IAS contraction depends on the increased level of calcium ions, mediated by influx of calcium ions through calcium channels or through activation of $\alpha 1$ -adrenoceptors. Hence relaxation of IAS muscles can be achieved by reducing the intracellular calcium concentration by antagonizing the calcium channels and enhancing the cGMP and cAMP levels [15]. Thus, calcium channels blockers such as DTZ are an effective management strategy for CAFs by decreasing the calcium influx into IAS and thus elicits muscle relaxation and decrease in resting anal pressure.

Another important factor for the chronicity of anal fissure is the local inflammation and infection due to the stool microbial flora populated with Gram-positive and negative organisms. In a study done by Grekova *et al.* [16] they stated that infection in the anal region is one of the important etiological factors for the development of CAFs. In some cases, localized infection in the subcutaneous area of anal fissure progresses

Table 3: Visual analogue score (pain) at different stages between the groups

Pain	Groups			χ^2	p-value
	Group A-MTZ (%)	Group B-NTG (%)	Group C-DTZ (%)		
At presentation					
4-7 (moderate)	30 (100)	30 (100)	30 (100)	0.000	1.000
At 2 weeks					
1-3 (mild)	9 (30.0)	11 (36.7)	8 (26.7)	2.797	0.834
4-7 (moderate)	21 (70.0)	19 (63.3)	22 (73.3)		
At 4 weeks					
0 (no)	8 (26.7)	10 (33.3)	8 (26.7)	1.502	0.826
1-3 (mild)	22 (73.3)	20 (66.7)	22 (73.3)		
At 6 weeks					
0 (no)	27 (90)	25 (83.3)	27 (90.0)	1.934	0.748
1-3 (mild)	3 (10.0)	5 (16.7)	3 (10.0)		

MTZ: Metronidazole, NTG: Nitroglycerin, DTZ: Diltiazem

Table 4: The distribution of healing at different presentation

Healing	Groups			χ^2	p-value
	Group A-MTZ (%)	Group B-NTG (%)	Group C-DTZ (%)		
At presentation					
Absent	26 (86.7)	27 (90.0)	26 (86.7)	0.207	0.902
Present	4 (13.3)	3 (10.0)	4 (13.3)		
At 2 weeks					
Absent	6 (20.0)	3 (10.0)	4 (13.3)	1.259	0.533
Present	24 (80.0)	27 (90.0)	26 (86.7)		
At 4 weeks					
Absent	5 (16.7)	2 (6.7)	4 (13.3)	1.450	0.484
Present	25 (83.3)	28 (93.3)	26 (86.7)		
At 6 weeks					
Absent	3 (10.0)	5 (16.7)	5 (16.7)	5.625	0.060
Present	27 (90.0)	25 (83.3)	25 (83.3)		

MTZ: Metronidazole, NTG: Nitroglycerin, DTZ: Diltiazem

Table 5: The distribution of side effect between the groups

Side-effects	Groups			χ^2	p-value
	Group A-MTZ (%)	Group B-NTG (%)	Group C-DTZ (%)		
Dizziness					
Absent	30 (100)	30 (100)	30 (100)	0.000	1.000
Burning sensation					
Absent	25 (83.3)	30 (100.0)	30 (100.0)	10.588	0.005
Present	5 (16.7)	0 (0.0)	0 (0.0)		

MTZ: Metronidazole, NTG: Nitroglycerin, DTZ: Diltiazem

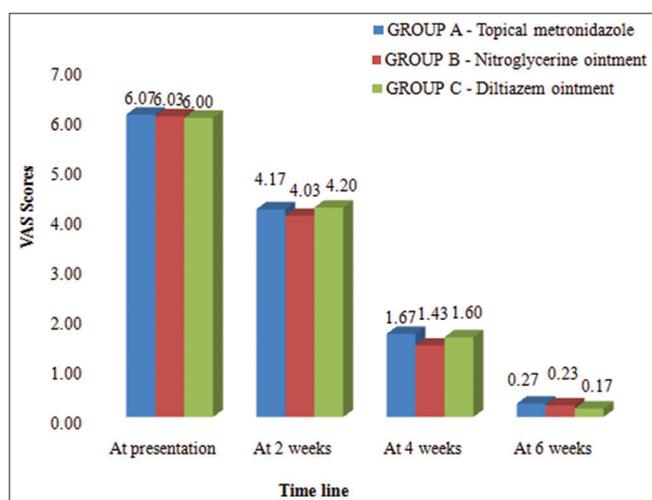


Fig. 1: Comparison of mean pain (VAS) between the groups

to form chronic symptoms [17]. Thus, a common phenomenon for delayed wound healing during anal fissure is ischemia accompanied by infection.

In the present study, at presentation, the wound rate was higher in MTZ and DTZ group as compared to GTN groups. Meanwhile, at the end of 6 weeks, the wound healing rate was higher in MTZ group (90%) as compared to DTZ (83.3%) and GTN groups (83.3%), respectively.

Meanwhile, in a study done by Suevarna *et al.* [18], the healing rates were significantly higher in DTZ as that of the GTN. In a study of Grekova *et al.* [16] after 4 weeks of treatment, in control group, the healing was improved in 71% of the patients meanwhile complete healing was achieved, 95.6% was achieved in patients treated with topical MTZ. Similar to our study, Mert *et al.* [19] reported that at 6th week the 42% of patients showed complete recovery after the treatment with topical DTZ while in topical MTZ group, 82% of patients showed complete recovery.

In the present study, there is no significant difference in the pain scores between the groups. However, there was marked reduction in the pain

scores before the treatment and at 6 weeks after the initiation of the treatment. In contrast in a study done by Shahid *et al.* [20] at the end of 6 weeks, the VAS scores was significantly decreased in MTZ group as compared to GTN. Likewise, in a study done by Karapolat *et al.* [21] at the end of 4th week, the mean VAS scores was significantly reduced in MTZ group as compared to lidocaine groups (1.36 vs 2.47; p<0.001).

In our study, however, none of the patients reported headache or dizziness. Five out of 30 patients in the MTZ group reported burning sensation. Likewise, in a study done by Ansari *et al.* [22], majority of the subjects had no side effects during GTN and DTZ therapy.

CONCLUSION

The present study concludes that healing rate was more profound in MTZ group as compared to GTN and DTZ. Thus, topical anti-infective with MTZ is an effective approach with a good safety profile for the mitigation of anal fissure pain with good healing potential.

ACKNOWLEDGMENTS

Nil.

CONFLICTS OF INTEREST

Nil.

FUNDING SOURCES

Nil.

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