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Original Research Article

A comparative study between combination of topical metronidazole and diltiazem vs diltiazem alone in treatment of acute anal fissure

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ABSTRACT

Background: Anal fissure is a common anorectal condition characterized by severe pain and bleeding. Topical diltiazem is a widely used treatment, but its efficacy can be enhanced by combining it with metronidazole. To compare the efficacy of topical diltiazem with metronidazole versus topical diltiazem alone in treating acute anal fissure.
Methods: This non-randomized clinical trial was conducted among 174 patients with acute anal fissure. Patients were allocated into two groups: combination group (topical diltiazem with metronidazole) and diltiazem alone group. Patients were followed up at 1, 2 and 4 weeks.
Results: The combination group showed significant pain reduction (7.30±0.89 to 0.48±0.21, $p<0.05$) and higher healing rates compared to the diltiazem alone group. The requirement for surgery was significantly lower in the combination group (8% vs 20.7%, $p<0.05$).
Conclusions: The combination of topical diltiazem with metronidazole is a safe and effective treatment for acute anal fissure, offering rapid and sustained pain relief, improved healing rates and reduced need for surgery.

Keywords: Anal fissure, Healing rates, Metronidazole, Pain relief, Surgery, Topical diltiazem

INTRODUCTION

An anal fissure is a superficial tear in the stratified squamous epithelial tissue of the anal skin distal to dentate line. Generally, anal fissure is located commonly at the anal verge at midline posteriorly, however, in few cases, they may be located in anterior midline. It is one of the most common cause condition of anorectal region and visit to emergency department.[1-3] The annual incidence of Anal fissures is documented to be 1.1 cases per 1000 person years and is reported in higher proportions of females as compared to males according to recent literature.[4] The prevalence of anal fissure in central India was found to be 18% amongst patients presenting with anorectal complaints.[5] Anal fissure is characterized by severe excruciating pain in the anal area during defecation, which may be associated with bleeding or rectal haemorrhage, decreased work productivity as well as impaired quality of life.[6-8] Only the epithelial tissue is damaged in an acute anal fissure, resulting in anal pain with defecation and bleeding. In addition to the symptoms mentioned above, a chronic anal fissure is distinguished by skin tags at the distal end, hypertrophied anal papillae at the proximal end and exposed internal anal sphincter fibers at the base.[9]

Majority of anal fissures are acute and most of these cases resolve spontaneously or after 6 to 8 weeks of treatment. Conservative management in the form of fiber rich diet, frequent sitz bath, adequate fluid intake, stool softeners, analgesics, regular toilet habits, muscle relaxants and blood flow enhancing drugs (e.g., diltiazem) etc. are used for acute anal fissures.[10-12] Calcium channel blockers, such as diltiazem and

nifedipine, have been shown to effectively lower mean anal resting pressure and promote healing of anal fissures by reducing calcium influx in smooth muscle cells.[13,14] A study comparing topical diltiazem and glyceryl trinitrate for chronic anal fissure treatment found that both treatments had a healing rate of over 68%.[15] However, recent literature suggests that subclinical infection, mainly attributed to anaerobic bacteria, may be present in anal fissures.[16,17] Controlling this infection with metronidazole has been shown to promote wound healing and reduce pain.[9] This study aims to compare the efficacy of combining topical metronidazole and diltiazem with topical diltiazem alone in treating acute anal fissure.

METHODS

The present study non-randomized clinical trial was carried among 174 patients diagnosed with acute anal fissure who presented to the outpatient department at the study site during the study period. The study was conducted at the Department of General Surgery, People's College of Medical Sciences and associated People's Hospital, Bhopal. The study period spanned 18 months, from November 1, 2022, to April 30, 2024. The study was registered with the Clinical Trials Registry of India (CTRI) with the registration number CTRI/2023/01/048866.

Inclusion criteria

The inclusion criteria for this study consisted of patients with acute anal fissure who presented with complaints of less than 6 weeks duration and were aged 18 years or older.

Exclusion criteria

The exclusion criteria for this study consisted of patients with chronic anal fissure, those with multiple fissures, patients who were already receiving topical treatment and patients with internal hemorrhoids greater than grade 1, perianal fistula and abscess, inflammatory bowel disease, immune deficiency or those receiving oral immunosuppressive drugs or steroids. Additionally, patients with anal stenosis, those on oral anti-coagulants or with ischemic heart disease were excluded. Pregnant females and patients who did not provide consent for the study were also excluded from participation.

Written consent was obtained from all the study participants after explaining them nature and purpose of study. They were ensured that confidentiality will be maintained and option to withdraw from the study was always kept open. Data regarding sociodemographic variables was obtained and all the patients were subjected to thorough history taking regarding their presenting complaints, duration of symptoms, nature and severity of pain, duration, amount and color of bleeding, associated history of constipation. Apart from this, relevant past medical and surgical history was obtained and documented in proforma. Rectal examination was done with respect to location of fissure, associated bleeding, tenderness, mass, anal sphincter tone etc.

All the patients were allocated into either of two groups using non random sampling. For purpose of grouping, patients on Mondays and Wednesdays were prescribed combination therapy while standalone therapy on rest of the days.

Group A (Combination group)

Patients were prescribed combination of Topical Metronidazole 1% Diltiazem 2% thrice a day for a period of 4 weeks. Each patient was instructed how to apply the drug locally using the tip of index finger at the site of fissure and around it.

Group B (Diltiazem alone group)

Patients were prescribed topical diltiazem 2% thrice a day for a period of 4 weeks. Each patient was instructed how to apply the drug locally using the tip of index finger at the site of fissure and around it.

The cost of topical metronidazole was taken care by the investigator. Each patient was advised to take sitz bath twice a day and stool softener at night for at least a period of 2 weeks or till the significant pain persists. Patients were asked for follow-up visits at 1 week, 2 weeks and 4 weeks. During each visit, pain relief was assessed using VAS score and examination of fissure done to assess the healing.

Statistical analysis

Data was compiled using Ms Excel and analysis was done using IBM SPSS software version 20. Categorical data was expressed as frequency and percentage whereas continuous data was expressed as mean and standard deviation. Patients of two groups were compared using chi square test for categorical variables and independent t test for continuous variables. Repeated measure ANOVA was used to compare the pain score at various interval within the group. P value of less than 0.05 was considered statistically significant.

RESULTS

Mean age of patients enrolled in combination group was 33.29±8.82 years and that of patients belonging to Topical diltiazem alone group was 35.55±11.37 years. Majority of patients in combination group belonged to 31 to 40 years of age (46%), whereas majority i.e., 41.4% cases in topical diltiazem alone group belonged to less than 30 years of age. However, the observed difference in age composition between two groups of patients was statistically insignificant ($p>0.05$). Mean VAS score in patients with fissures treated with topical diltiazem with metronidazole at baseline was 7.30±0.89, which reduced

over the period of 4 weeks to 0.48±0.21, combination therapy was significantly effective in reducing the pain ($p<0.05$). Similarly, we reported significant pain reduction following diltiazem alone from baseline to final follow up (7.26±0.86 to 1.45±0.58, $p<0.05$).

Intragroup analysis revealed that mean pain score were comparable at baseline, however, pain scores were significantly lower in patients of combination group receiving topical diltiazem with metronidazole as compared to topical diltiazem alone from 1st week of treatment ($p<0.05$). As observed from the above table, we found no significant difference in epithelization and healing between two groups ($p>0.05$). However, at 2nd week and 4th week following treatment, rate of partial epithelization and heading was significantly higher in cases belonging to combination group as compared to diltiazem alone group whereas significantly higher proportions of patients in diltiazem alone group underwent surgery ($p<0.05$). Overall, 20.7% cases in diltiazem only group and 8% cases in combination group required surgical intervention and the observed difference in requirement of surgery between the groups was statistically significant ($p<0.05$).

In present study, side effects of the drugs were noted in 12.6% cases in combination group (headache in 8% and itching in 4.6%) and 14.9% cases in topical diltiazem alone group (headache and itching in 9.2% and 5.7% cases respectively), but the observed difference was statistically insignificant ($p>0.05$). There was no reoccurrence in any of the patients in both the groups.

Table 1: Comparison of age distribution between two groups.

Age (in years)	Topical diltiazem with metronidazole (n=87)		Topical diltiazem (n=87)	
	N	%	N	%
≤30	35	40.2	36	41.4
31-40	40	46	34	39.1
41-50	10	11.5	9	10.3
>50	2	2.3	8	9.2
Mean	33.29±8.82		35.55±11.37	
$\chi 2$	4.15			
P value	0.245			

Table 2: Comparison of pain scores (VAS) between the groups.

Pain	Topical diltiazem with metronidazole (n=87)		Topical diltiazem (n=87)		t value	P value
	Mean	SD	Mean	SD		
Baseline	7.30	0.89	7.26	0.86	0.25	0.796
1st week	2.10	0.77	4.93	0.88	22.35	0.001
2nd week	1.8	0.88	3.10	1.16	13.68	0.001
4th week	0.48	0.21	1.45	0.58	4.73	0.001
Repeated measure ANOVA	21.09		24.67			
P value	0.001		0.001			

Table 3: Comparison of degree of epithelisation between the groups.

Degree of epithelization		Topical diltiazem with metronidazole(n=87)		Topicaldiltiazem value(n=87)		χ^2	P
		N	%	N	%		
1st week	Not healed	66	75.9	70	80.5	0.53	0.463
	Partial epithelisation	21	24.1	17	19.5		
	Completely healed	0	0	0	0		
2nd week	Not healed	16	18.4	34	39.1	14.69	0.005
	Partial epithelisation	48	55.2	39	44.8		
	Completely healed	21	24.1	9	10.3		
	Requirement of surgery	2	2.3	5	5.7		
4th week	Not healed	10	11.5	18	20.6	20.68	0.001
	Partial epithelisation	16	18.4	12	13.8		
	Completely healed	56	64.4	44	50.6		
	Requirement of surgery	5	5.7	13	14.9		

Table 4: Comparison of requirement of surgery between the groups.

Requirement of surgery	Topical diltiazem with metronidazole (n=87)		Topical diltiazem (n=87)	
	N	%	N	%
No	80	92	69	79.3
Yes	7	8	18	20.7
$\chi 2$	5.65			
P value	0.017			

Table 5: Comparison of side-effects between the groups.

Side effects	Topical diltiazem with metronidazole (n=87)		Topical diltiazem (n=87)	
	N	%	N	%
Headache	7	8	8	9.2
Itching	4	4.6	5	5.7
None	76	87.4	74	85.1
$\chi 2$	0.21			
P value	0.903			

DISCUSSION

The mean age of patients in the topical diltiazem with metronidazole group was 33.29±8.82 years, with the majority belonging to the 31-40 years age group. Similarly, the mean age of patients in the topical diltiazem group was 35.55±11.37 years. Both groups were comparable in terms of age composition (p>0.05). These findings suggest that most patients with anal fissures are young to middle-aged individuals presenting in the second and third decade of life. The present study's findings are consistent with previous studies that reported a similar age range for patients with anal fissures.[9,18] Mert et al, found a median age of 32-32.5 years, while Gupta et al, (2023) reported a mean age of 31.63-33.17 years.[9,19] However, some studies, Garg et al, Karapolat et al, Shahid HM et al, (2022) reported a slightly higher mean age range of 34.2-39.18 years.[10,20,21]

In our study, topical diltiazem with metronidazole significantly reduced pain scores in patients with anal fissures, from 7.30±0.89 at baseline to 0.48±0.21 at 4th week follow-up (p<0.05). Similarly, topical diltiazem alone also reduced pain scores, but to a lesser extent. Pain control was significantly better in the combination group compared to the diltiazem alone group after 1 week of treatment (p<0.05). Our study's findings on pain reduction with topical diltiazem and metronidazole are supported by previous studies.

Mert et al, reported a significant decrease in VAS scores in patients receiving combination therapy compared to monotherapy.[9] Similarly, Elgendy et al, found that pain control was significantly better in patients receiving metronidazole in addition to GTN.[22] These studies suggest that adding antibiotics to topical treatments can enhance pain relief in patients with anal fissures. Further, studies by Gupta et al, Karapolat et al, Shahid et al, and Saba et al, also reported significant pain reduction with the addition of metronidazole to topical treatments suggesting that combining metronidazole with topical treatments can enhance pain relief in patients with anal fissures.[19-21,23] In present study, we assessed degree of epithelialization during each follow up. After first week of treatment, partial epithelialization was noted in 24.1% cases in topical diltiazem with metronidazole group as compared to 19.5% cases in topical diltiazem group and the difference was statistically insignificant (p>0.05). After 2nd and 4th weeks of treatment, the rate of healing was significantly better in combination group as compared to topical diltiazem alone group (p<0.05). The findings of present study were supported by the findings of Elgendy et al, (2024).[22]

The authors documented significantly earlier healing in patients receiving combination of GTN and metronidazole as compared to GTN alone, i.e., majority of patients in GTN with metronidazole healed within 11 to 20 days (50%), whereas complete healing time was 21 to 30 days in 62% cases receiving GTN alone. About 4 and 14% cases in respective group showed no healing and thus required surgical intervention. Similar findings were reported by Mert et al, where complete recovery was noted in 8% cases in monotherapy group and 24% cases in combination therapy group and the difference was insignificant (p<0.05) after 4 weeks of treatment.[9]

However, after 6 weeks, recovery rate was almost double in combination therapy group as compared to monotherapy group (82% vs.42%; p<0.05). Thus, the authors documented that patient in combination group had considerably greater rates of epithelization and healing after the first week than those in group given diltiazem alone (p<0.05). Our study's findings on healing rates with topical diltiazem and metronidazole differ from those of Gupta et al, which found no significant difference in healing between metronidazole and diltiazem groups.[19] However, our findings are supported

by studies that reported improved healing rates with the addition of metronidazole to topical treatments.[16,19,20,22] These studies suggest that combining metronidazole with topical treatments can enhance healing rates in patients with anal fissures.

Our study found that the combination group (topical diltiazem with metronidazole) had a significantly lower requirement for surgery (8%) compared to the topical diltiazem alone group (20.7%) ($p<0.05$). This is consistent with previous studies, Hussein et al, Mert et al, that suggest the use of antibiotics, such as metronidazole, can improve the efficacy of conventional treatments and reduce the need for surgery in patients with anal fissures.[9,24] Surgical treatments may be required based on the severity, complications, recurrence and failure of medical therapy.[24]

Our study found that 12.6% of patients in the combination group (topical diltiazem with metronidazole) and 14.9% in the topical diltiazem group experienced side effects, with no significant difference between the groups ($p>0.05$). These findings are supported by Gupta et al, but contrast with Mishra et al, which reported a higher incidence of headache in the diltiazem group.[19] Suvarna et al, noted that headache is a significant side effect of calcium channel blockers, but diltiazem had a lower incidence compared to GTN.[18,25]

Patients were followed up for short period of time i.e., only 1 month and thus, the recurrence rates could not be observed.

CONCLUSION

In conclusion, this study demonstrates that the combination of topical diltiazem with metronidazole is a safe and effective treatment for anal fissures, offering rapid and sustained pain relief, improved healing rates and a reduced need for surgery. The results showed that combination therapy significantly reduced pain scores and improved healing rates, with a lower requirement for surgery (8% vs 20.7%, $p<0.05$). Both groups had similar side effect profiles. The findings suggest that the addition of metronidazole to topical diltiazem may be a useful strategy in the management of anal fissures, particularly in patients who are at high risk of complications or who have failed to respond to monotherapy.

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