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A RANDOMIZED CONTROLLED TRIAL ON THE EFFICACIES OF TOPICAL METRONIDAZOLE, DILTIAZEM AND LIGNOCAINE IN IDIOPATHIC CHRONIC ANAL FISSURE

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ABSTRACT

Aim and objectives: To evaluate and compare the effects of topical application of metrogyl ointment, diltiazem ointment and lignocaine in the healing of chronic anal fissure (CAF). **Materials and method:** This Randomised controlled trial was conducted in the Department of General Surgery, Swaroop Rani Nehru Hospital, Prayagraj, after obtaining clearance from hospital Ethics Committee. The drugs were applied over the fissure twice a day. Healing of the fissure in terms of complete epithelialization, and reduction of pain (measured by visual analogue score) were noted. VAS score was rated from 0-100 in terms of pain sensations as used in another similar study. Any side effects of the used drugs were recorded. The patients were followed up at 2, 4 and 8 weeks of initiation of treatment for assessing the outcomes. **Results:** It was noted that the VAS score were significantly lower with Metronidazole in comparison to Lignocaine at 4 weeks; whereas at 8 weeks, it was significantly lower in Diltiazem group as compared to Lignocaine group. There was a significant difference in the healing between Diltiazem and Lignocaine (p=0.0006) and Metronidazole and Lignocaine (p=0.007) but no statistical difference between Diltiazem and Metronidazole (p=0.667). Headache was significantly more in Diltiazem group (24%) and burning sensation was significantly more with the use of Metronidazole. (p=0.022). **Conclusion:** Diltiazem and metronidazole are equivalent to treat anal fissures for relieving pain and healing, both of which are better in comparison to lignocaine.

KEYWORDS

Anal fissures, Diltiazem, Lignocaine, Metronidazole, VAS score

INTRODUCTION

Anal fissures are longitudinal tears in the squamous epithelium of the anal canal distal to dentate line and most frequently lie on posterior midline in up to 90% of the cases.[1] Anal fissures are common and have a cumulative lifetime incidence of 11%.[2] Fissures are classified as acute, if they have been present for less than 6 weeks. They are often superficial and have well demarcated edges. If symptoms persist for more than 6-8 weeks, fissures are classified as chronic. They are wider, deeper and marked by ulcers with keratinous edges, presence of sentinel tag at external apex, hypertrophy at the anal papillae and exposes internal anal sphincter smooth muscle fibers.[3,4]

Healing of acute anal fissures is often spontaneous or through conservative management including high fiber diet, stool softeners, Sitz bath and does not require medical intervention.[5,6] CAF require chemical or surgical sphincterotomy for its resolution.[7] Since the incontinence rate after surgical interventions is found to be considerable, and sphincter hypertonicity and ischemia are considered as causes of CAF, the search to look for an efficacious medical therapy continues. Chemical sphincterotomy has been induced by different agents including botulinum toxin, glyceryl trinitrate, and calcium channel blockers, such as diltiazem and nifedipine (NIF).[8]

Glyceryl trinitrate (GTN) has been employed in various studies, and despite initial promising results, it is disfavoured due to high rate of side effects like headache and dizziness due to possible vasodilatation following systemic absorption, thereby leading to decreased compliance.[9,10]

Calcium channel blockers (CCBs), such as diltiazem (DTZ) and NIF, cause smooth muscle relaxation and vasodilation resulting in increased blood flow and tissue irrigation that promote wound healing. Factors that limit the use of topical nitrates are infrequent with CCBs making them an attractive alternative therapy.[11]

Among CCBs, diltiazem (DTZ) is the best documented drug out of the possible options, with most literature supporting its use and it has been reported that topical diltiazem is equal to or more effective than nitric oxide (NO) donors in healing CAF.[9,12,13]

Metronidazole is a 5-nitroimidazole derivative antibiotic of a lipophilic character with a bactericidal effect particularly on anaerobic pathogen bacteria. It is widely used in clinical practice against protozoon infections as well as for the treatment of ailments where mixed pathogen microorganisms are active. In the study by Karapolat Banu.,[14] it was seen that the topical antimicrobial treatment with metronidazole as an addition to the classical medical treatments in acute anal fissure was an effective and safe practice resulting in further reduction of pain and increased healing rate.

Further, local anesthetics are extensively used to alleviate symptoms and improve the life quality of patients with inflammatory anal diseases. Local anesthetics provide immediate relief of pain and itching after application and thus the use of Lidocaine is being increased either alone or in combinations with Corticosteroids.[15] Amide local anesthetics, such as lidocaine hydrochloride (LDH) are advantageous over ester-type since ester-type anesthetics that are metabolized to methyl-para benzoic acid causing allergic reactions and skin sensitization.[16] In accordance, the safety of repeated anorectal administration of 5% lidocaine ointment has been reported.[17]

All three categories of chemical treatments have their own advantages and efficacies but not many studies have been done to compare and assess the better drug. In this study we aimed to assess and compare the effects of individual topical application of lidocaine, diltiazem and metronidazole on healing of chronic anal fissures (CAF). This study shall help us to know the better chemical drug for healing of chronic anal fissures.

MATERIALS AND METHOD

This Randomised controlled trial was conducted in the Department of General Surgery, Swaroop Rani Nehru Hospital, Prayagraj, after obtaining clearance from hospital Ethics Committee. Informed written consent was obtained from each patient.

The minimum required sample size with 90% power of study and 5% level of significance is 21 patients in each study group. To reduce margin of error, total sample size taken is 75 (25 patients per group). Block Randomization with Sealed envelope system was used. In this, group A represents Diltiazem group, B represents Metronidazole group and C represents Lignocaine Group.

Study Population:

The study followed the patients who visit the general surgery OPD of the hospital for the presence of chronic anal fissure. All the patients visiting the general surgery O.P.D. of S.R.N. Hospital, Prayagraj with signs and symptoms suggestive of chronic anal fissure, willing to be a part of the study, Classic triad of hypertrophied anal papilla, skin tag

and exposed internal sphincter muscle fibres and Patients aged between 18 to 65 years.

The study excluded patients with Acute anal fissure (symptoms present for less than 6 weeks), Patients with cardiovascular diseases, heart failure, diabetes and cancer, Recurrent fissures, Patients with haemorrhoids, anal fistulae, other anal pathologies or previous anal surgeries, Patients with diseases like ulcerative colitis, Crohn's disease, syphilis, tuberculosis which cause secondary anal fissure, Anal sphincter fibrosis and Pregnant females.

Methodology

The complete demographic, personal and clinical history was taken. A history of co-morbidities such as hypertension, diabetes, and smoking status was determined. The preliminary history and examination details were filled in the study proforma.

The drugs were applied over the fissure twice a day and were followed up three times, after a fortnight for the first two times and after a month for the third time. Healing of the fissure in terms of complete epithelialization, and reduction of pain (measured by visual analogue score) were noted. VAS score was rated from 0-100 in terms of pain sensations as used in another similar study. Any side effects of the used drugs were recorded. The patients were followed up at 2, 4 and 8 weeks of initiation of treatment for assessing the outcomes.

Statistical analysis

SPSS version 25.0 analyzed the Excel data when it was loaded. Quantitative (numerical variables) data was given as mean and standard deviation, whereas qualitative (categorical variables) data was provided as frequency and percentage. The student t-test was used to compare the two groups' mean values, while the chi-square test analyzed their frequency differences. If p0.05, it was statistically significant.

RESULTS

Table 1 showing demographic characteristics of the study population

		Diltiazem (n=25)	Metronidazole (n=25)	Lignocaine (n=25)	P-value
Age in years	19-20	2 (8%)	3 (12%)	3 (12%)	NS (> 0.05)
	21-30	8 (32%)	7 (28%)	8 (32%)	
	31-40	9 (36%)	9 (36%)	9 (36%)	
	41-50	3 (12%)	2 (8%)	2 (8%)	
	51-60	3 (12%)	4 (16%)	3 (12%)	
	Mean ± SD	34.56±10.71	34.52±11.5	33.44±10.66	NS (> 0.05)
	Median (IQR)	33 (27-38)	33 (26-38)	32 (26-38)	
	Range	19-56	19-58	19-56	
Gender	Female	12 (48%)	13 (52%)	12 (48%)	NS (> 0.05)
	Male	13 (52%)	12 (48%)	13 (52%)	
Duration	Mean ± SD	4.36 ± 3.09	4.46 ± 2.77	3.78 ± 3.52	NS (> 0.05)
	Median (IQR)	3 (2-6)	4 (2-6.5)	2.5 (2-4)	
	Range	1-12	1-10	1-18	
Complications	Bleeding	19 (76%)	19 (76%)	18 (72%)	NS (> 0.05)
	Constipation	21 (84%)	21 (84%)	20 (80%)	NS (> 0.05)
	Pruritis	15 (60%)	15 (60%)	15 (60%)	NS (> 0.05)

No significant difference was seen in the distribution of age (years) between diltiazem, metronidazole and lignocaine. (p value>.05) Age group was 31-40 years in majority of patients; 36% in diltiazem, 36% in metronidazole and 36% in lignocaine. Proportion of males was 52% in diltiazem, 48% in metronidazole and 52% in lignocaine and proportion of females was 48% of patients in diltiazem, 52% of patients in metronidazole and 48% of patients in lignocaine with no significant difference between them. Presenting complaints was constipation in majority of patients; 84% in diltiazem, 84% in metronidazole and 80% in lignocaine followed by bleeding in 76% of patients in diltiazem, 76% of patients in metronidazole and 72% of patients in lignocaine. Presenting complaints was pruritis in 60% of patients in diltiazem, 60% of patients in metronidazole and 60% of patients in lignocaine with no significant difference in distribution between them.

Table 2 showing the comparison of pain between diltiazem, metronidazole and lignocaine

	Pain	Diltiazem (n=25)	Metronidazole (n=25)	Lignocaine (n=25)	P value
At presentation	Mean ± SD	5.08 ± 1.73	4.36 ± 2.02	4.52 ± 1.83	0.321 DTZ vs MTG:0.158 DTZ vs LIG:0.261 MTG vs LIG:0.707
	Median (IQR)	5(4-6)	4(2-6)	5(3-6)	
	Range	2-8	2-9	2-8	
At 2 weeks	Mean ± SD	1.92 ± 1.68	2.24 ± 1.9	2.44 ± 1	0.409 DTZ vs MTG:0.668 DTZ vs LIG:0.244 MTG vs LIG:0.277
	Median (IQR)	2(0-3)	2(1-3)	2(2-3)	
	Range	0-5	0-7	1-4	
At 4 weeks	Mean ± SD	0.88 ± 1.33	0.72 ± 1.46	1.24 ± 0.93	0.038* DTZ vs MTG:0.478 DTZ vs LIG:0.103 MTG vs LIG:0.012*
	Median (IQR)	0(0-2)	0(0-0)	1(0-2)	
	Range	0-5	0-5	0-3	
At 8 weeks	Mean ± SD	0.2 ± 0.71	0.4 ± 0.87	0.64 ± 0.91	0.047* DTZ vs MTG:0.253 DTZ vs LIG:0.015* MTG vs LIG:0.190
	Median (IQR)	0(0-0)	0(0-0)	0(0-1)	
	Range	0-3	0-3	0-3	

Significant difference was seen in pain at 4 weeks and 8 weeks between diltiazem, metronidazole and lignocaine.(p value <.05) Median (IQR) of pain at 4 weeks in metronidazole was significantly lower as compared to lignocaine and no significant difference was seen in pain of diltiazem with metronidazole and lignocaine. Median (IQR) of pain at 8 weeks in diltiazem was significantly lower as compared to lignocaine and no significant difference was seen in pain of diltiazem with metronidazole and lignocaine.

Table 3 showing the comparison of healing between diltiazem, metronidazole and lignocaine

Healing	Diltiazem (n=25)	Metronidazole (n=25)	Lignocaine (n=25)	P value
At 2 weeks				
Absent	23 (92%)	25 (100%)	25 (100%)	0.324 DTZ vs MTG:0.49 DTZ vs LIG:0.49 MTG vs LIG: 1.000
Present	2 (8%)	0 (0%)	0 (0%)	
At 4 weeks				
Absent	16 (64%)	18 (72%)	21 (84%)	0.274 DTZ vs MTG:0.544 DTZ vs LIG:0.196 MTG vs LIG:0.496
Present	9 (36%)	7 (28%)	4 (16%)	
At 8 weeks				
Absent	2 (8%)	4 (16%)	14 (56%)	0.0002* DTZ vs MTG:0.667 DTZ vs LIG:0.0006* MTG vs LIG:0.007*
Present	23 (92%)	21 (84%)	11 (44%)	

Significant difference was seen in the distribution of healing at 8 weeks between diltiazem, metronidazole and lignocaine. (p-value < 0.05) Healing at 8 weeks was present in 92% of patients in diltiazem and 84% of patients in metronidazole which was significantly higher as compared to 44% of patients in lignocaine.

Table 4 showing the comparison of side effects between diltiazem, metronidazole and lignocaine

Side effects	Diltiazem (n=25)	Metronidazole (n=25)	Lignocaine (n=25)	P value
Headache	6 (24%)	1 (4%)	0 (0%)	0.014* DTZ vs MTG: 0.098 DTZ vs LIG: 0.022* MTG vs LIG: 1
Dizziness	0 (0%)	0 (0%)	0 (0%)	1.000
Burning sensation	2 (8%)	6 (24%)	0 (0%)	0.062 DTZ vs MTG: 0.247 DTZ vs LIG: 0.49 MTG vs LIG: 0.022*

Proportion of patients with headache was 24% of patients in diltiazem which was significantly higher as compared to 0% of patients in lignocaine and was comparable with 4% of patients in metronidazole. Proportion of patients with burning sensation was 24% of patients in metronidazole which was significantly higher as compared to 0% of patients in lignocaine and was comparable with 8% of patients in diltiazem.

DISCUSSION

The mean age of the patients in our study were comparable among the three groups (34.56 ± 10.71 in Diltiazem, 34.52 ± 11.5 in Metronidazole, 33.44 ± 10.66 in Lignocaine, p=0.919). The age group was comparable to the study of *Karapolat B et al*.,[14] where the mean age was 34.2±4.1 years in Group 1 (lidocaine promade) and 36.6±3.8 years in Group 2 (lidocaine promade plus metronidazole) (p=0.0.510). Overall also, anal fissure are mostly seen in individuals aged between 20 and 40 years which is seen in the literature.[18,19]

In our study, even the gender distribution was statistically comparable with 12 females in Group Diltiazem and Lignocaine and 13 females in Group Metronidazole (p value 0.948). This was in line with other studies which showed no significant difference in the gender among the comparing groups. As for example in the study by *Karapolat B et al*.,[14] there were 40 (80%) female and 10 (20%) male patients in Group 1 and 38 (76%) female and 12 (24%) male patients in Group 2 (p=0.412)

The anal fissures are characterised by symptoms such as bleeding constipation and pruritus as was seen in our study. These presenting symptoms were seen in all the three groups in similar proportions (p>0.05). Similarly other studies also showed pain and bleeding during defecation as the commonest symptoms with other minor symptoms being constipation and itching.[14]

The pain associated with chronic anal fissures together with bleeding and irritation causes considerable morbidity and reduction in quality of life of the patients. So it becomes important to take that into account during the treatment.[20]

In our study, we found that VAS scores were significantly lower with Metronidazole in comparison to Lignocaine at 4 weeks; whereas at 8 weeks, it was significantly lower in Diltiazem group as compared to Lignocaine group, indicating that both Diltiazem and Metronidazole showed good response in comparison to Lignocaine at 4 and 8 weeks of follow up.

Among other studies, the effectiveness of Metronidazole in reducing the pain (VAS score) was seen in the study by *Karapolat B et al*.,[14] which found a statistically significant difference in the mean VAS scores at 2 and 4 weeks. The findings were similar to our study in showing better pain relief with Metronidazole in comparison to Lignocaine at week 4 for anal fissures treatment follow up. This might be because Metronidazole keeps the local infection under control and thereby leading to decrease in pain as was demonstrated by decreases in the VAS scores at the end of weeks 2 and 4 of treatment. Besides Metronidazole, this mechanism of pain relief with antibiotics and infection control has been revealed in the literature with different drugs. *Grekova et al*.[21] found that patients with chronic anal fissure and anaerobic bacteria in their swabs who received topical metronidazole treatment experience rapid relief of pain and anal sphincter spasm

The effectiveness of Diltiazem as seen in our study have been confirmed in the previous studies by *Jonas et al*.,[20] *Alvandipour M et al*.[22] and *Shrivastava et al*.,[23] who showed that diltiazem is effective in reducing pain associated with anal fissures.

The healing was assessed in view of the complete epithelisation of the anal fissures which showed that at 8 weeks, it was more with Diltiazem (92%), intermediate with Metronidazole (84%) and least with Lignocaine (44%). There was a significant difference in the healing between Diltiazem and Lignocaine (p=0.0006) and Metronidazole and Lignocaine (p=0.007) but no statistical difference between Diltiazem and Metronidazole (p=0.667)

The effectiveness of Metronidazole in better healing of anal fissures over lidocaine has been shown in the study by *Karapolat B et al*.,[14] where at week 4, the healing was 46% in Group 1 and 68% in Group 2 (p=0.004). This might be because Metronidazole helps decreasing the bacterial load with topical application and accelerates fissure healing. *Grekova et al*.[21] found that patients with chronic anal fissure and anaerobic bacteria in their swabs who received topical metronidazole treatment showed enhanced fissure healing (healing rate: 95.6%).

Further, chronic anal fissure have raised resting anal canal pressure, secondary to hypertonia of the internal anal sphincter, and Diltiazem (CCB) is mainly targeting to lower the anal resting pressure, producing a "chemical sphincterotomy" without causing permanent damage to the anal sphincter mechanism.[20]

We found that Diltiazem is effective in anal fissures healing to the best effect as compared to Lignocaine and with comparable effect to Metronidazole. This has been noticed in the previous studies by *Jonas et al*.,[20] who found that any formulation (oral or topical) Diltiazem provided good healing in 4-8 weeks of follow up. In the study by *Carapeti et al*.,[24] Diltiazem provided 67% healing which was slightly less than our study which may be due to a shorter follow-up.

It was seen that headache was significantly more in Diltiazem group (24%) and burning sensation was significantly more with the use of Metronidazole. (p=0.022) The findings are in line with the previous studies that show CCB (GTN or Diltiazem) carry side effects of headaches (predominantly) and others that include nausea, vomiting, rash and perianal itching.[20,25] However, it was noted that Diltiazem have significantly less side effects as compared to GTN but remains high in comparison to Lignocaine. It was interesting to note that none of the patients in our study had incontinence with the use of the drugs as was seen in a previous systematic review suggesting the importance of 'chemical sphincterotomy' over surgery.[26]

The limitations of the present study include short follow-up time, small sample sizes of the three groups, and the study having been conducted in a single site. Therefore, the long-term recurrence rates of the patients could not be determined.

CONCLUSION

All the three drugs – Diltiazem, lignocaine and metronidazole, are effective in relieving pain and healing the anal fissures but amongst themselves Diltiazem and metronidazole are equivalent to treat anal fissures for relieving pain and healing , both of which are better in comparison to lignocaine. However the safety remains a concern with the use of Diltiazem and metronidazole as they are associated with side effects such as headaches and burning sensations while lignocaine shows no such side effects.

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