

A Prospective Comparative Observational study in treatment of anal fissure – Topical Diltiazem vs Topical Nitroglycerin

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Abstract

Background: Anal fissure is a common condition in surgical practice. The treatment is usually conservative. Topical calcium channel blockers are used to decrease the tone of anal sphincter. **Material and Methods:** The prospective observational study was carried out on 60 cases on out-patient basis. The study population was divided into two groups of 30 patients each. Group A was treated with topical application of 2% diltiazem per rectally twice daily. Group B was treated with topical application of 0.2% nitroglycerin/ Glyceryl trinitrate twice daily. The treatment was given for a period of 6 weeks along with sitz bath and oral antibiotics. The two groups were compared for degree of symptom relief, healing, any adverse drug effect and recurrence if any. Statistical analysis was done on SPSS software version 21. P value of <.05 was considered significant. **Results:** On completion of therapy at 6 weeks healing was observed in 26(86.6%) patients in group A and in 21(70%) patients in group B, so there was no statistically significant difference between two groups. At 2 weeks and 6 weeks follow up headache was significantly higher in group B as compared to group A (p<.05). **Conclusion:** Chemical sphincterotomy with topical 2 % Diltiazem gel is an effective first-line treatment for anal fissures, achieving symptom relieving and healing rates comparable to those achieved with 0.2 % Nitroglycerin ointment but with relatively few, generally acceptable side effects as compared to distressing adverse effects of nitroglycerin as headache.

Keywords: Anal fissure, Calcium Channel Blockers, Nitroglycerin, Constipation.

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INTRODUCTION

Fissure-in-ano is defined as a longitudinal split in the anoderm of the distal anal canal which extends from the anal verge proximally towards, but not beyond, the dentate line.^[1] Anal fissure or fissure-in-ano is a common condition in surgical outpatient door. It can be a very troubling and distressing problem because the severity of pain and discomfort disproportionate to the severity of physical lesion. It may be so severe that patient may avoid defecation.^[2] In 90% of cases, it occurs in the posterior midline.^[3] Site is also peculiar, in males it is seen in mid posterior aspect while in females it is also seen in mid anterior and lateral aspect.^[4] The pathogenesis of anal fissure is poorly understood. Most anal fissures are idiopathic with no underlying disease process and there is no simple and unified theory to explain their genesis.^[5] The primary aim of the treatment of chronic anal fissures is to decrease internal sphincter tone and hence increase the blood flow for tissue healing. Treatment includes pharmacological and surgical modalities. Sphincterotomy results in a sustained reduction of maximum resting anal pressure.^[6] But The internal sphincterotomy carries a significant rates of fecal or flatus incontinence, fecal urgency and soiling of perianal area.^[7] Because of the possible pathogenesis that spasm of the internal sphincter and reduced blood flow to the sphincter play important role

in formation and chronicity of anal fissure, chemical sphincterotomy has been tried by using a variety of agents which include topical glyceryl trinitrate, calcium channel blockers such as nifedipine or diltiazem which can interrupt pathogenesis.

The present study is carried out with the aim of comparing the efficacy and adverse effects of topical application of 2% diltiazem with 0.2% nitroglycerin in treatment of anal fissure.

MATERIALS AND METHODS

The prospective observational comparative study was done at tertiary care centre on out-patient basis (OPD) in Department of Surgery between Jan 2018 and Aug 2020. The study was approved by institutional ethics committee. Informed consent was taken from the patients.

Sample size was estimated based on previous study, the two

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independent groups to be compared were equal size n , and to be drawn from population. Below α is the level of significance and equal to 0.05. Similarly, β is the Type-II Error whose complement is the power of 80%. Sigma is the common variance. Delta (Δ) is the difference between the two groups. $Z_{1-\alpha/2}$ and $Z_{1-\beta}$ are the respective tail area under the standard normal curve. We have taken $\alpha=0.05$, $Z_{1-\alpha/2}=1.96$, $Z_{1-\beta}=0.8416$, Power= $1-\beta=0.80$. $\Sigma=2.32$, and $\Delta=1.38$

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \cdot \sigma^2}{\Delta^2} = \frac{2 \cdot 2.562(1.96 + 0.8416)^2}{1.96^2} = 27$$

As our $n=27$, so we take sample size =30 for each group to increase the power of the study. The study population was divided into two groups.

The study was carried out on 60 patients. The study population was divided into two groups of 30 patients each. Grouping was done using computer generated randomization.

Group A: This group of patients were be treated with topical application of 2% diltiazem per rectally twice daily for a period of 6 weeks with sitz bath and oral antibiotics.

Group B: This group patients were treated with topical application of 0.2% nitroglycerin/ Glyceryl trinitrate application over the anal verge twice daily for a period of 6 weeks along with sitz bath and oral antibiotics.

Inclusion Criteria

- Patients aged between ≥ 18 yrs and ≤ 65 years;
- Presence of anal fissure that had failed to resolve with simple measures such as laxatives & high fiber diet
- Patients giving informed consent.

Exclusion Criteria

- Patients who had previous surgery for anal fissure

- Patients who require anal surgery for any concurrent disease like hemorrhoids
- Pregnant women
- Patients with significant cardiovascular condition will be excluded from present study.
- Patients with fissures secondary to other diseases like Crohn's disease, ulcerative colitis, tuberculosis, anal warts, malignancy, sexually transmitted diseases

Patients in each group were advised to consume fibre rich, high-water-content diet and to apply 3 grams of ointment per dose circumferentially 1 cm inside the anus, near the internal anal sphincter, every 12 hours for 6 weeks. Follow up is done by means of regular OPD visits at 2 weeks and 6 weeks and were assessed for degree of relief of symptoms (pain, itching, bleeding), healing, adverse effects and recurrence if any. Healing was defined as resolution of symptoms and absence of fissure on examination. Patients were further followed up after 3 months for examination for recurrence.

Statistical analysis was done using SPSS software version 21 and Microsoft excel sheet version 2021. A value of $P < 0.05$ was considered significant.

RESULTS

The majority of patients belong to younger age group with majority of patients lying in age group of 19-28 years. The mean age was 35.30 ± 9.93 years in Group A and 34.00 ± 9.75 years in Group B. The difference was not significant ($p = .611$). Male to female ratio was 1.5 in Group A and 1.2 in Group B. The male to female ratio in study was 1.3 (Table 1). The difference between two groups with respect to gender was not significant ($p=.232$).

Table 1: Demographic Profile

Age group (years)	Group A			Group B		
	Male	Female	Total	Male	Female	Total
19-28	6	4	10	6	4	10
29-38	8	3	11	4	5	9
39-48	3	3	6	5	4	9
>49	1	2	3	1	1	2
Total	18	12	30	16	14	30
Mean $\pm$ SD (years)	35.30 $\pm$ 9.93			34.00 $\pm$ 9.75		
P value	0.611					

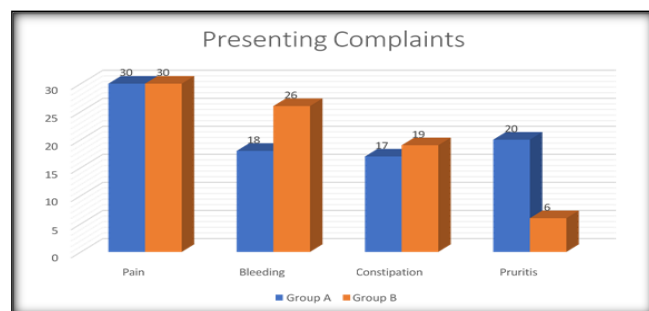


Figure 1: Presenting Complaints

All the 60 (100%) patients presented in the OPD with complaint of pain. Duration of pain varied from 2-6 weeks. Bleeding was observed in 44 (73.33%) patients, out of

which 18(60%) in diltiazem group (Group A) and 26(86.67%) in nitroglycerin group (Group B). Constipation was present in 36(60%) patients, out of which 17 (56.67%) were present in diltiazem group and 19(63.33%) in nitroglycerin group. Pruritus was present in 26 (43.33) patients, out of which 20 (66.67%) were in diltiazem group and 6(20%) were in nitroglycerin group [Figure 1]. The difference between two groups were not significant ($p=0.36$).

On local examination position of fissure was mostly at posterior site in 52(86.66%) patients, out of which 25 (83.33%) were present in diltiazem group and 27(90%) were present in nitroglycerin group. Anterior anal fissure was present in 5(8.33%) patients, out of which 3(10%) were in diltiazem group and 2(6.67%) were present in nitroglycerin group. Lateral anal fissure was present in 3 (5%) patients, out of which 2 (6.67%) were in diltiazem group and 1 (3.33%) was in nitroglycerin

group. The difference in position of fissure was not significant ($p=0.32$). Sentinel pile was present in 33(55%) patients, out of which 14 (46.67%) were in group A and 19(63.33%) were in group B. On local examination induration of some degree was present at the edges of anal fissure in total 37(61.66%) patients, out of which 16(53.33%) were in group A and 21(70%) were in group B [Figure 2].

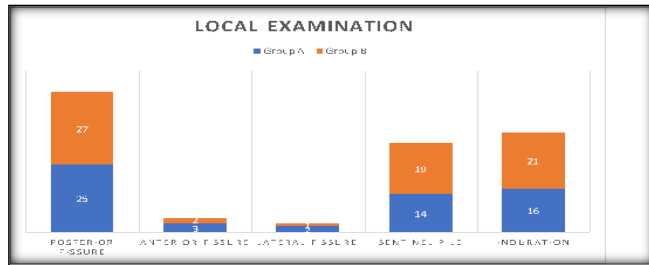


Figure 2: Local Examination

Table 2: Response to Treatment

Relief from Symptoms	Group A		Group B		P value
	2 weeks	6 weeks	2 weeks	6 weeks	
Pain	14	27	14	26	0.935
Bleeding	11	16	15	25	0.789

There were minor side effects observed during treatment. At 2 weeks follow up there was no statistically significant difference between diltiazem and nitroglycerin group in adverse effect profiling except headache which came out as

statistically significant in group B with presence of headache in 12 patients in group B. At 6 weeks follow up headache occurred in 15 patients, out of which 1 was in group A and 14 were in group B, which is a statistically significant difference [Table 3].

Table 3: Adverse Effects

Side Effects		Group A	Group B	P value
Headache	2 weeks	1	12	0.039
	6 weeks	1	14	0.015
Itching	2 weeks	2	0	0.93
	6 weeks	3	1	0.937

Follow up 3 months showed recurrence in 5 (8.33%) patients, out of which 2 (6.67%) were in group A and 3 (10%) were in group B. The result was not significant ($p=0.051$).

DISCUSSION

Resolution of symptoms of anal fissure and healing can be attained by invasive interventions or by chemical sphincterotomy. Because of the complications associated with operative lateral internal sphincterotomy and the risk of incontinence, medical alternatives of surgery have thus been tried. Chemical sphincterotomy is non-invasive, precludes the need for general anaesthesia, and could be applied at home by the patient itself. A first line use of medical therapy cures most chronic anal fissures economically and conveniently. Diltiazem remains the standard chemical sphincterotomy against which other treatments are compared.

Most of fissure were found in age group between age 19-38 years, that is 63.3% and mean age in our study was 34.5 years. Mean age that was reported in different studies ranges from 30-45 years which is almost same in our study.

In our study mean age is 35.3 in group A and 34 in group B. Similar results were observed in study conducted by Khan et al,^[8] with average age being 43 years and by Venkatesh et al,^[9] in which average age was 38 years. Mapel et al found higher incidence among old patients as compared to young patients.^[10]

In our study, there was male preponderance in occurrence of anal fissure, showing 43.3% in females and 56.6% in males. The lower number of female (43.3%) patients in this study and other studies illustrated below may be due to the conservative attitude of females, especially for perianal diseases. These observations were compared with the studies conducted by Khan et al,^[8] in which 66.3% were male and 33.7% were female patients and Venkatesh et al,^[9] showing 51% of male patients and 49% female patients. However, Wani et al reported that female patients had higher incidence of fissure than males (52.43% vs. 47.56%).^[11] Mapel et al also found higher incidence among females as compared to males.^[10] The reason could be due to dietary and regional differences.

The pain associated with chronic anal fissures is usually marked, and together with bleeding and irritation, it causes considerable morbidity and reduction in quality of life in these patients. Patients of anal fissure presents mostly with chief

complaints of pain, bleeding and pruritus ani. The common symptoms in our study were anal pain during and after defecation (100% patients), bleeding in 73.3% patients. These observations were compared with the studies conducted by Venkatesh et al,^[9] showing bleeding in 82% of patients and in study conducted by Hisham et al,^[12] showed bleeding in 76% patients.

In our study in 86.6% patients had fissures posteriorly, only 8.3% of patients had anterior fissure and 5% patients had lateral anal fissure. These observations were compared with the studies conducted by Venkatesh et al,^[9] showing 83% posteriorly lying anal fissure. Wani et al also reported that majority of patients (70%) had posterior anal fissures.^[11]

In the present study a comparative evaluation of diltiazem (2%) and GTN ointment (0.2%) was performed to assess the effectiveness in terms of pain relieve and healing and adverse effects of these two pharmacotherapies in the management of anal fissure. The results were comparable to studies conducted by Ala et al,^[13] and Sanei et al,^[14]. In our study, healing of anal fissure at the end of 6 weeks, in group A was 86.6% and in group B was 70%, which was statistically insignificant. These results were comparable to studies done by Ansari et al,^[15] and Venkatesh et al,^[9] Topical Diltiazem 2% is found to be equally effective as that GTN ointment with fewer side effects.^[16] Comparable results were also concluded by Sanei et al, as complete remission of anal fissure was occurred in 66.7% patients in diltiazem group.^[14] Pasha et al observed cure rate of 83.3% with diltiazem ointment which comparable to current study.^[17] Similarly cure rates of 78.2% was observed by Al-Jbory et al with nitroglycerine in anal fissure.^[18] The studies are comparable to current study.

Headache was the side effect experienced by patients treated by GTN ointment. Although 46.6% of patients treated with GTN experienced headache at some point during treatment. Headache was present in 3.3% in group A patients and 46.6% in group B patients which was statistically significant and comparable to the studies conducted by Venkatesh et al,^[9] in which 46% patients taking GTN suffered from headache and Ansari et al,^[15] showing headache in 16% of patients with GTN. However, Pangtey et al do not find any side effects observed with diltiazem after 3 months of treatment and found it as effective treatment for anal fissure.^[19] Al-Jbory et al found minimal side effects with nitroglycerine in 9.3% of patients.^[18]

Recurrence of anal fissure was assessed in present study at follow up after therapy in both the groups. In group A recurrence was noted in 6.6% of patients and 10% of group B patients which was statistically insignificant. Pasha et al observed recurrence rate of 13.33% with diltiazem ointment.^[17] Recurrence rate of 5% was observed by Pangtey et al with diltiazem ointment which is comparable to current study.^[19]

The study was conducted at single centre in limited time duration. It can further be improved with multicentric studies and longer duration follow ups.

CONCLUSION

Although there was no significant difference in outcomes of treatment with diltiazem and nitroglycerin. However, with minor side effects occurred during treatment with nitroglycerine, diltiazem is safer option and can be helpful in proper compliance of the patient.

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Conflicts of interest

There are no conflicts of interest.

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