Original Article

Comparative Study to Assess the Effectiveness of Topical Nifedipine and Diltiazem in the Treatment of Chronic Anal Fissure

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Abstract

Background: Chronic anal fissure is a common condition which is classically treated by surgery which may lead to incontinence. Recently medical treatment in form of calcium channel blockers (CCB) has gained interest. **Aims:** The aim of this study is to compare the effectiveness of local Nifedipine and Diltiazem with lignocaine as control. We also aimed to observe the clinical pattern of chronic anal fissure. **Material and Method:** Patients of chronic anal fissure were divided into three groups. First group received topical Nifedipine, second received topical Diltiazem, and the control group received only local lignocaine for 1 month. Their clinical data was recorded. The intensity of pain and bleeding was assessed from a visual analogue score (VAS). On the 4th week patients were examined for healing. **Statistical Analysis:** Statistical analysis was done by Medcalc statistical software v14. Student's *t*-test and Chi-square test was used accordingly. **Results:** Mean age was 35.89 with a male female ratio of 1.7:1. Most common clinical feature was pain (100%), followed by constipation, bleeding, and pruritus. Most common location was posterior. VAS scores for pain of the Nifedipine group and Diltiazem group was significantly better than control group ($P < 0.0001$). VAS scores for bleeding in the Nifedipine group ($P = 0.0091$) and Diltiazem group ($P = 0.0045$) was significantly better than control group. The healing rate for NFD group was 93.33% ($P < 0.0001$), that of DTZ group was 86.67% ($P = 0.0002$), which was statistically better than control group (36.67%). There was no significant difference between the two CCBs. **Conclusion:** Adding topical Nifedipine or Diltiazem in the treatment of anal fissure is far superior to treatment with only topical Lignocaine.

Keywords: Calcium channel blockers, chronic anal fissure, Diltiazem, fissure-in-ano, Nifedipine

Introduction

An anal fissure is a longitudinal tear or defect in the skin of the anal canal distal to the dentate line. It was first described in 1934 by Lockhart-Mummery.[1] Although the exact incidence is unknown, it is a common disorder, with equal gender distribution. Fissures can occur at any age but are usually seen in younger and middle-aged adults with mean age of onset being 39.9 years.[2] The pathophysiology of anal fissures is not entirely clear. It is hypothesized to be because of an acute injury to the anoderm during the passage of hard or large stool, diarrhoea, anorectal surgery, and anal intercourse, which leads to local pain and spasm of the internal anal sphincter resulting in high resting anal sphincter pressure.[3] This in turn leads to reduced blood flow and ischemia and delays healing of fissure.[4] This vicious cycle has to be broken or else the fissure will persist. In almost 90% of cases, fissures are identified in the posterior midline, but

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can be seen in the anterior midline in up to 10% of cases. This is probably due to poor blood supply to this region. Fissures occurring in lateral positions should raise suspicions for other disease processes.[5] Anal fissures are classified as acute or chronic. Acute fissures are a shallow tear in the anoderm. Symptoms associated with acute fissures include anal pain, spasm, and/or bleeding with defecation. Chronic fissures are present for more than 6–8 weeks and are characterized by exposed fibres of internal anal sphincters at the base, hypertrophied anal papilla, and sentinel pile. Treatment of anal fissure has been classically surgical. Anal dilatation was first described by Recamier in 1838 for the treatment of proctalgia fugax and anal fissure.[6] Later in 1939, Miles published his paper on the treatment of anal fissure by sphinterectomy.[7] Initially it was a midline sphinterectomy but later due to high incidence of complications,[8] Eisenhammer described lateral internal sphincterotomy (LIS) in 1959.[9] LIS has been the mainstay of treatment since then but lately in the 90s topical nitro-glycerine has been studied extensively and found significantly good healing rates of upto 80%. The major drawback was associated headache.[10] The effect of calcium channel blockers (CCBs) on the anal sphincter was first evaluated by Chrysos *et al.* in 1996 and observed a reduction of anal resting pressure by almost 30%.[11] Various authors studied CCBs like Diltiazem (DTZ) and Nifedipine (NFD) for the treatment of acute anal fissure with healing rates significantly superior to placebo and with minimal side effects.[12-14] Relief from symptoms of anal fissure without the risk of incontinence or adverse effects like severe headaches have attracted surgeons toward CCBs worldwide. Although Nifedipine and Diltiazem have been studied separately quite a few times, on web search of various databases, we were unable to find any study which compares the two CCBs in the treatment of chronic anal fissure. This is the first study to compare topical Diltiazem and Nifedipine in the treatment of chronic anal fissure.

Thus, we did this study with the aim to compare the effectiveness of local application of Nifedipine ointment (0.3%) and Diltiazem ointment (2%), both in combination with Lignocaine ointment, and with Lignocaine ointment alone as control arm. We also aimed to observed the clinical pattern of chronic anal fissure in our institute.

Material and Method

Design

This was a prospective comparative, randomized, open labelled study conducted at Rajendra Institute of Medical Sciences, Ranchi between 1st April 2018 and 31st march 2019.

Methodology

Data was collected from 105 patients treated in OPD in our hospital during this period. Out of these five patients were lost in allocation. The remaining patients were divided into three groups. Group-A consisted of 33 patients under treatment with 0.3% nifedipine cream and 2% lidocaine cream, Group-B consisted of 33 patients and were treated by 2% diltiazem ointment and 2% lidocaine cream, and the control group consisted of 34 patients and received only symptomatic treatment with 2% lidocaine cream. All the three groups used medication three times daily for minimum 1 month. The cream application was with the patients' tip of the index finger to just inside and 1 cm around the anus circumferentially. The patients were encouraged to follow a high-fibre diet and use warm sitz baths. The intensity of pain was assessed from a visual analogue score (VAS). Every patient was instructed how to mark daily the level of pain during defecation on charts. Bleeding was assessed by VAS for bleeding during follow-up every week. Side effects were recorded. On the 4th week patients were examined to record if the wound has healed or not and thus healing rate in various groups were calculated and compared statistically. When healing occurred after the initial 4-week period, the patients were consequently followed up in clinic at 2, 6, and 12 months, or earlier if symptoms relapse. Data was collected in proforma and analysed. A total of 10 patients were lost in follow-up thus at last in each group we had 30 patients.

Inclusion criteria

1. Age group 16–75 years.
2. Patients of both sexes, with a definitive diagnosis of chronic anal fissure who had symptoms lasting for more than 4 weeks.
3. Patients whose symptoms will fail to resolve with conservative therapy consisting of stool softeners, high fibre diet, and warm sitz bath.
4. Physical examination will reveal anal ulcer with indurations at the edges and skin tag.

Exclusion criteria

1. History of reaction to topical agents.
2. Patients whose symptoms will resolve within 4 weeks with conservative therapy consisting of stool softeners, high fibre diet, and warm sitz bath.
3. Recurrent anal fissures
4. Associated condition or disease such as severe anemia, cancer, fistula, abscess, Crohn's disease, HIV-related anal ulcer, tuberculosis ulcer, leukemic ulcer, pregnancy, third- and fourth-degree hemorrhoids, and Diabetes Mellitus and Hypertension.

Statistical analysis

Statistical analysis was done by Medcalc statistical software v14. Student's *t*-test was used to test for significant differences in the VAS of pain and bleeding between the three groups at different intervals. Chi-square test was used to test significance in healing rate, adverse effects in different groups. $P < 0.05$ will be considered statistically significant.

Results

In our study of 90 patients, 57 patients were males and 33 patients were females. Male–female ratio being 1.7:1.

The age at diagnosis ranged between 16 and 68 years with mean age of 35.89 years and median age of 33.5 years. Vast majority of the patients (n = 62, 68.9%), were in their youth between 21 and 40 years of age. [Table 1]

Most common clinical feature, which was present in all of the patients, was pain (n = 90, 100%). Pain was intense and burning in nature. It started during the act of defecation and continued for some time after it. Constipation was observed to be the second most common symptom (n = 86, 96%). Bleeding was present in 48 subjects (53.33%) and Pruritus was present in only 14 (15.56%) patients. [Figure 1]

In our study of 90 cases, anterior fissure was seen in 10 patients (11.11%) and posterior fissure in 79 (87.78%) patients. 1 (1.11%) patient had both anterior and posterior fissure. Sentinel Piles was present in 51 (56.67%) patients.

One of the most common adverse reaction encountered was headache. Most of the patients who reported headache were from Diltiazem group. One patient was from Nifedipine group and none from control group. All the patients who developed perianal dermatitis were from Diltiazem group. Hypotension was seen two patients. On statistical comparison it was observed that incidence of perianal dermatitis (P = 0.0314) was significantly more in DTZ group than the other two groups. Difference in incidence of headache (P = 0.1967) and hypotension were not statistically significant (P = 0.5997). [Table 2]

VAS of pain and bleeding have been tabulated in Table 3. On comparison of VAS scores for pain of the Nifedipine group to that of the Diltiazem group it was observed that there was no significant difference between the two groups even after 4 weeks of treatment (P = 0.4738). But on comparison of VAS scores for pain of the Nifedipine group to that of the control group we observed that pain scores on the Nifedipine arm were significantly better than control from the first week of treatment itself (P < 0.0001). Pain scores on the Diltiazem group too were significantly better than that of the control group just after the first week of treatment (P < 0.0001). [Table 4]

When we compared the VAS scores for bleeding of the Nifedipine group to the control group we observed that the bleeding stopped in most patients and the scores improved significantly in the Nifedipine group, after two weeks of treatment (P = 0.0091). The control group took four weeks to achieve similar bleeding scores. Similarly, Diltiazem group too showed significantly better bleeding scores in comparison to control group after two weeks of treatment (P = 0.0045). There was no significant difference between the two calcium channel blockers in terms of improvement in bleeding (P = 0.5769) [Table 5].

After 4 weeks of treatment the healing rate of fissure for NFD group was found to be 28 of 30 (93.33%), that of DTZ group was 26 of 30 (86.67%), and for Control group was 11 of 30 (36.67%). On comparing the healing rates of different groups, it was observed that there is no statistically significant difference between the NFD and the DTZ groups. But on comparison of the NFD group with the Control group it was observed that the healing rate of NFD group (93.33%) was significantly higher than that of the Control group (36.67%) (P < 0.0001). Similarly, on comparison of the DTZ group with the Control group it was observed that the healing rate of DTZ group (87.67%) was significantly higher than that of the Control group (36.67%) (P = 0.0002). [Figure 2]

Discussion

This prospective comparative, randomized, open-labelled study was designed to test the hypothesis that combining local application of calcium channel blockers like Nifedipine and Diltiazem is significantly better than topical Lignocaine and Sitz bath alone, in terms of pain relief, control of bleeding and

Table 1: Age wise incidence of Chronic anal fissure

	Age distribution					
Group	**10-20**	**21-30**	**31-40**	**41-50**	**51-60**	**61-70**
NFD	2	10	8	4	4	2
DTG	0	12	10	3	3	2
Control	2	13	9	4	1	1
Total	4	35	27	11	8	5
%	4.4%	38.9%	30.0%	12.2%	8.9%	5.6%

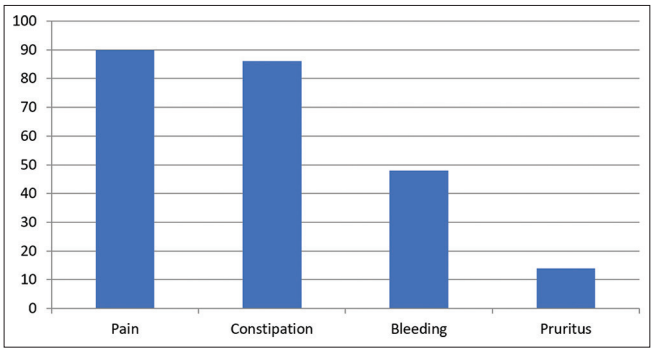

Figure 1: Showing frequency of various symptoms of chronic anal fissure observed

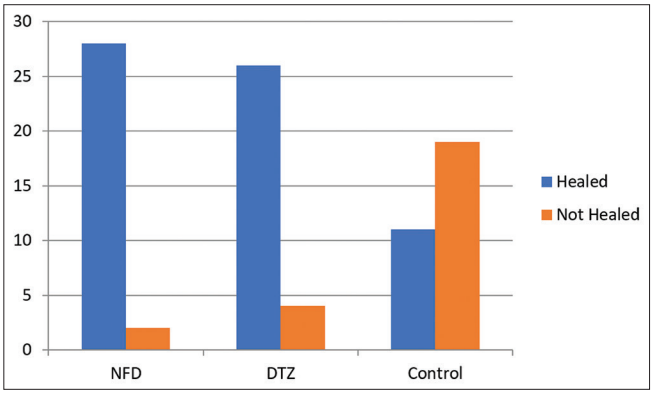

Figure 2: Showing healing rate in different groups

healing, in the treatment of chronic anal fissure. This study also aimed to observe the clinical pattern of chronic anal fissure in our area. Our findings clearly indicate that combining topical Nifedipine or Diltiazem gives much better results in terms of pain relief, controls bleeding faster, and felicitates faster healing. We also observed that there was no statistical difference between the two CCBs namely, Diltiazem and Nifedipine, on these parameters but Diltiazem was found to be associated with significantly greater incidence of perianal dermatitis than Nifedipine. We also observed that the incidence was more in males than in females and majority of patients were in the age group between twenty to forty years.

On comparing the VAS scores for pain on the Nifedipine and Diltiazem groups to that of the control group we observed that pain scores on the Nifedipine and Diltiazem arms were significantly better than control arm, just after one week of treatment. VAS scores of bleeding improved significantly after two weeks of treatment in both Nifedipine and Diltiazem groups. Control group took four weeks to achieve similar scores. After 4 weeks of treatment we observed 93% of patients achieved complete healing in the Nifedipine group, 87% in Diltiazem group and 37% in the control group. Most adverse reactions in terms of headaches and perianal dermatitis were observed in the Diltiazem group.

Topical CCBs as a treatment modality for chronic anal fissure found place in various studies since late 90s. Antropoli *et al.*, in 1999 observed that topical nifedipine was superior to 1% lidocaine plus 1% hydrocortisone in a randomized multicentre study in 283 patients. Fissure healing was seen in 95% of the nifedipine group vs. 50% of the comparator group.[15] In a prospective, randomized, double-blind study by Perrotti *et al.* in 2002, 55 patients with anal fissure received treatment with topical nifedipine ointment 0.3% plus 1.5% lidocaine, while 53 others received topical Lidocaine 1.5% plus 1% hydrocortisone acetate. Healing occurred in 94.5% of the Nifedipine group compared to 16.4% of the control group (P = 0.001).[13] Golfam *et al.* in

Table 2: Adverse reactions observed in various groups

Complications during treatment							
Complication	**NFD**	**DTZ**	**Control**	**Total**	**%**	χ^2	***P***
Headache	1	5	0	6	6.67%	1.667	0.1967
Hypotension	1	1	0	2	2.22%	1.023	0.5997
Dermatitis	0	6	0	6	6.67%	4.63	0.0314

Table 3: Means of VAS scores of Pain and Bleeding at various time intervals

	0 week		**1 week**		**2 weeks**		**3 weeks**		**4 weeks**	
	Pain	**Bleeding**	**Pain**	**Bleeding**	**Pain**	**Bleeding**	**Pain**	**Bleeding**	**Pain**	**Bleeding**
Nifedipine Group	9	1.2	5.77	0.6	3.3	0.1	1.43	0	0.17	0
Diltiazem Group	8.9	1.07	5.7	0.57	3.3	0.07	1.4	0	0.36	0
Control Group	8.9	1.63	7.5	1	5.93	0.6	4.37	0.33	2.93	0.13

Table 4: Comparison of Pain scores in different groups at different time intervals

Comparison of Pain scores					
NFD vs. DTZ					
	0 week	**1 week**	**2 weeks**	**3 weeks**	**4 weeks**
Difference	-0.1	-0.06	0	-0.03	0.2
Standard error	0.209	0.286	0.426	0.362	0.277
95% CI	-0.519-0.319	-0.632-0.512	-0.853-0.853	-0.755-0.695	-0.355-0.755
Test statistic t	-0.478	-0.21	0	-0.0829	0.721
DF	58	58	58	58	58
Significance level	*P*=0.6346	*P*=0.8345	*P*=1.0000	*P*=0.9342	*P*=0.4738
NFD vs. Control					
Difference	-0.1	1.74	2.6	2.93	2.77
Standard error	0.188	0.232	0.369	0.446	0.474
95% CI	-0.476-0.276	1.276-2.204	1.861-3.339	2.038-3.822	1.821-3.719
Test statistic t	-0.532	7.501	7.04	6.572	5.84
DF	58	58	58	58	58
Significance level	*P*=0.5967	*P*<0.0001	*P*<0.0001	*P*<0.0001	*P*<0.0001
DTZ vs. Control					
Difference	0	1.8	2.6	2.96	2.57
Standard error	0.195	0.252	0.419	0.493	0.528
95% CI	-0.39-0.39	1.296-2.304	1.761-3.439	1.972-3.948	1.513-3.627
Test statistic t	0	7.149	6.202	6	4.868
DF	58	58	58	58	58
Significance level	*P*=1.0000	*P*<0.0001	*P*<0.0001	*P*<0.0001	*P*<0.0001

Table 5: Comparison of bleeding scores in various groups at different time intervals

Comparison of VAS Scores for Bleeding					
NFD vs. DTZ					
	0 week	**1 week**	**2 weeks**	**3 weeks**	**4 weeks**
Difference	-0.14	-0.04	-0.04	0	0
Standard error	0.322	0.192	0.0713	2.58E-09	2.58E-09
95% CI	-0.785-0.505	-0.425-0.345	-0.183-0.103	5.168412317012E-009-5.168412317012E-009	5.168412317012E-009-5.168412317012E-009
Test statistic t	-0.435	-0.208	-0.561	0	0
DF	58	58	58	58	58
Significance level	*P*=0.6654	*P*=0.8361	*P*=0.5769	*P*=1.0000	*P*=1.0000
NFD vs. Control					
Difference	0.43	0.4	0.5	0.32999999	0.12999999
Standard error	0.379	0.26	0.185	0.109544512	0.091287093
95% CI	-0.328-1.188	-0.121-0.921	0.129-0.871	0.110722826-0.549277154	-0.0527309799-0.31273096
Test statistic t	1.135	1.537	2.697	3.012	1.424
DF	58	58	58	58	58
Significance level	*P*=0.2609	*P*=0.1298	*P*=0.0091	*P*=0.0038	*P*=0.1598
DTZ vs Control					
Difference	0.57	0.43	0.54	0.329999999	0.129999999
Standard error	0.372	0.268	0.183	0.109544512	0.091287093
95% CI	-0.175-1.315	-0.107-0.967	0.174-0.906	0.1107228352-0.5492771628	-0.05273097087-0.3127309689
Test statistic t	1.531	1.604	2.953	3.012	1.424
DF	58	58	58	58	58
Significance level	*P*=0.1312	*P*=0.1142	*P*=0.0045	*P*=0.0038	*P*=0.1598

their randomized single-blind study published in 2010 compared topical nifedipine 0.5% with standard therapy using topical Lidocaine 2% in 110 patients. After 4 weeks, healing occurred in 70% of the Nifedipine group and 12% of the standard therapy group ($P < 0.005$).[16] Long-term results of Diltiazem treatment for chronic anal fissure was reported by Nash *et al.* for 112 patients, given a 6-week course of 2% diltiazem cream twice daily. The initial success rate was 67.9%.[17] Giridhar *et al.* in their study in 2014 observed pain relief rate of 78% and healing rate of 88% after treatment with topical Diltiazem.[18] Findings of all these studies was in agreement to that of our study and opined that topical calcium channel blockers can be used as the first line treatment modality. We could not find any study published in medical literature which has compared topical Nifedipine and Diltiazem in the treatment of anal fissure.

Previous studies by Mapel *et al.*[19] and Giridhar *et al.*[18] observed male female ratio of 1:1.3 and 1.4:1, respectively. Our study of a slight male predominance, similar to Giridhar *et al.*, may be due to the social stigma in India where females are shy to come out with complains associated with private parts. Both these authors also observed that mostly youth were affected which is similar to findings of our study.

The results of our study show that the most common clinical feature is pain followed by constipation, bleeding and pruritus. Hananel *et al.* observed similar finding when they observed pain as the most common symptom, present in 90.8% of patients. They also observed that bleeding was also a common symptom, found in 71.4% of cases.[2] In our study we observed posterior fissure in 87.78% patients which was in concurrence with other authors like Giridhar *et al.*, who also observed that the majority of the fissures were posterior in location (92%).[18] Our study also observed presence of sentinel piles in 56.67% of patients similar to 46.6%, which Giridhar *et al.* observed.[18]

Conclusion

Our study clearly demonstrates that adding topical Nifedipine or Diltiazem in the treatment of anal fissure is far superior to treatment with only topical Lignocaine. It is significantly better in control of pain, has better healing rates and is more effective in control of bleeding. Although both Nifedipine and Diltiazem are almost identical in these parameters, Nifedipine is better tolerated with lower incidence of adverse reactions.

Thus, we recommend the topical use of CCBs as first line therapy in the management of anal fissures.

Key-Message

Topical Calcium channel blockers like Nifedipine and Diltiazem have gained interest in the treatment of chronic anal fissure. These show excellent relief from pain, bleeding and show great healing rates of ulcers.

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Conflicts of interest

There are no conflicts of interest.

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