

A Prospective Randomized Comparative Evaluation of Oral Diltiazem and Topical Diltiazem (2%) Ointment in the Treatment of Chronic Anal Fissure

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Abstract: ***Objectives:** To evaluate and prospectively compare the efficacy of oral diltiazem and topical 2% diltiazem ointment in patients with chronic anal fissure in terms of improvement in sign and symptoms, time taken for healing, side effects and recurrence, if any. **Study design:** 50 patients with chronic anal fissure were randomly divided in two groups. In one group oral diltiazem was given and in another topical diltiazem ointment was given for treatment and comparative evaluation was done. **Results:** Complete healing was observed in 40% patients in oral diltiazem group and 80% patients in topical diltiazem group at the end of 6 weeks. Oral diltiazem group patients reported headache and nausea and vomiting whereas in topical diltiazem group one patient developed anal excoriation. Recurrence rate was more in oral diltiazem group than topical diltiazem group at 3 months of follow up. **Conclusion:** While considering medical management for treating chronic anal fissure topical diltiazem ointment may be the preferred first line treatment.*

Keywords: Chronic anal fissure, Diltiazem

1. Introduction

Anal fissure is a linear defect or laceration in the anoderm, located commonly in the posterior midline (women -90% - 99%). The incidence of anal fissure is around 1 in 350 adults and it occurs equally among men and women mostly in the age group of 15 to 40. It usually presents as anal pain upon defecation. Trauma to anal canal, due to passing hard stools, is probably the most frequent cause and initiating factor of fissure-in-ano¹.

Recamier (1829) recommended stretching of anal fissure based on the concept of loosening the sphincter muscle and increasing the blood flow to the anoderm but it was complicated by permanent incontinence of flatus and stool². Eisenhammer (1951) described internal sphincterotomy by dividing the sphincter in posterior midline³. In 1968 Lord described anal dilatation⁴. In 1969 Notaras further simplified open lateral subcutaneous anal sphincterotomy to closed lateral anal sphincterotomy⁵. Both anal dilatation and sphincterotomy are associated with asymmetry of anal canal and irreversible damage to the anal sphincter. As mainly young individuals are affected by anal fissure, there is increasing concern over the long term results and fecal incontinence after surgical procedures.

A variety of agents like botulinum toxin, glyceryltrinitrate (GTN), calcium channel blockers like nifedipine or diltiazem have been used till date and all these agents focus on breaking the cycle of pain, spasm and ischemia. O'Kelly et al⁶ (1993) demonstrated that nitric oxide is one of the most important nonadrenergic noncholinergic neurotransmitter mediating relaxation of internal anal sphincter. Nitroglycerine is a nitric oxide donor which causes relaxation of the internal anal sphincter and increases the blood flow.

A calcium channel blocker, diltiazem is widely and safely used in clinical practice as an antihypertensive and anti-angina agent on the principle that it causes relaxation of vascular smooth muscle and vasodilation. Applying the same principle, oral and topical preparations of diltiazem have been shown to lower anal resting pressure, probably by relaxing the internal anal sphincter.

Although the debate about optimum first line therapy for chronic anal fissure continues, treatment is becoming increasingly medical. Surgical techniques result in healing of the ulcer in majority of the patients but these surgical procedures may be complicated by non-healing wounds and a higher incidence of incontinence of flatus or mucus. Medical treatment avoids all the complications related to surgical procedures and it can be carried out as an outpatient. It is cost effective, does not require hospitalization and there is no wastage of man hours. Also, with the availability of better drugs and more and more studies supporting conservative management as a first line of treatment of anal fissure, patients now a days should be given a fair period of trial of medical management before subjecting him/her to surgical management. The present study was thus planned to comparatively evaluate the efficacy and complications of oral and topical diltiazem in the management of chronic anal fissure.

2. Material and Method

A total of 50 patients presenting with chronic anal fissure were included in the present study. They were divided into two groups by computer generated randomization. Group A included 25 patients treated with oral diltiazem (60 mg twice daily) and Group B included 25 patients treated with topical diltiazem ointment (2 % w/v twice daily). Patients in both groups were supposed to take medication for a period of six weeks. None of the patients in either group received

analgesic in any form during the course of treatment and follow up. Inclusion Criteria were:

- 1) Patients willing to give written informed consent.
- 2) All the cases of single anal fissure either anterior or posterior of more than 6 weeks duration.
- 3) All fissures with associated features of chronicity like sentinel piles or hypertrophied papillae or exposure of horizontal fibers of internal sphincter.

Patients on medication containing nitrate compound for medical condition like Ischemic heart disease or pregnant women, anal fissure with inflammatory bowel disease like ulcerative colitis & Crohn's disease, immune-compromise state like human immuno deficiency virus, tuberculosis were excluded. Also patients with history of previous allergic reactions or sensitivity to diltiazem or those with history of chronic headache were also excluded from the present study.

The intensity of pain during defecation was assessed by using Visual Analogue Scale (VAS). This visual analogue was a 10 cm line on which '0' represented no pain and 10 the most severe pain. All patients in both groups were encouraged for high fibre diet and stool softener. During the course of treatment patients were followed initially twice a week and then at the end of 3 weeks and 6 weeks. At each visit they were examined for symptomatic relief of pain (VAS), healing of fissure, side effect or complication of the treatment, if any. On complete healing of fissure, the patients were asked to stop application of ointment and continue high fibre diet. The healed fissures were then subsequently followed up at 3 months for recurrence, if any. The time required for symptomatic relief and complete healing of fissure was recorded in each case. Also the side effects of treatment particularly headache, postural hypotension, palpitation, dizziness were noted during each follow up. At each follow up the perianal region around the fissure was also examined for excoriation, if any, because of local application of ointment. Patients who did not show any improvement at 6 weeks treated by either of the treatment options were offered the opportunity to undergo surgical treatment in the form of lateral internal sphincterotomy. At the end of the study the data was collected and analysed statistically. The qualitative data presented in the form of numbered percentage. Chi-square test was used as a test of significance for qualitative data in terms of pain reduction and time taken for healing. Student t-test was used as a test of significance for quantitative data. A p value of < 0.05 was considered for significance. This study was reviewed and approved by the Institutional Ethical Board.

3. Observations

All 50 patients in both the groups were followed-up at twice weekly during first week and thereafter at 3 and 6 weeks to find the relief of pain on visual analog scale, fissure healing, side effects of the treatment, if any. The healed fissures were then subsequently followed up at 3 months to see any recurrence. The mean age in group A was 32.00±10.67 (18-85) and in Group B 30.64±9.53 (20-53). In group A, 16 were male and 9 females vs 15 males and 10 females in group B (p>.05). The mean duration of symptoms in group

A was 16.96±12.11weeks whereas in group B was 16.08±11.98 (P>.05). Both groups were comparable regarding mean pain score during defecation before treatment- group A 8.64±0.95 vs 8.44±1.19 in group B (p>0.05). Bleeding during defecation was present in 69% of group A and 76% of group B patients whereas constipation was present in 18 out of 25 (64%) patients in group A and 16 out of 25 (76%) patients in group B. In group A 21 (84%) patients had fissure in posterior midline and 4 (16%) had anterior midline fissure whereas in group B 19(76%) had posterior midline fissure while 6(24%) had fissure in anterior midline.

4. Pain Relief After Treatment

Median pain score decreased from 9 to 2 after treatment with oral diltiazem and from 9 to 0 after the application of diltiazem ointment at the end of six weeks. Patients in both the groups had perceptible pain relief as compared to pre-treatment levels. But there was statistically significant difference (p value < 0.05) in terms of pain relief at the end of 1st week between two groups, however, at the end of 3rd week and 6th week, there was no statistical difference (p value >0.05) in terms of pain relief in both the groups.

Table 1: Pain Relief after Treatment

Time of Follow-up	Group A	Group B	p value*	Statistical Significance
After 72 hrs	8(7-10)	8(6-10)	>0.05	Non Significant
At the end of 1 st week	8 (6-9)	6 (4-9)	<0.05	Significant
At the end of 3 rd week	5 (0-7)	4 (0-6)	>0.05	Non Significant
At the end of 6 th week	2 (0-5)	0 (0-7)	>0.05	Non Significant

*Chi-square test

Healing

Complete healing was observed in 40% patients in oral diltiazem group and in 80% patients in topical diltiazem group at the end of 6 weeks (p value <0.05). Patients with non healing fissures at the end of 6 weeks in both the groups were advised alternative method in the form of surgical treatment.

Recurrence

Although there were only 10 patients in oral diltiazem group (who had complete healing) at the end of 6 weeks, and 20 patients in topical diltiazem group (who had complete healing), but recurrence was observed in only 2 patients in each group at the end of mandatory 3 months follow up. This difference was not statistically significant (p value >0.05) between the two groups.

Table 2: Fissure Healing and Recurrence of Disease

Healing and Recurrence		Oral Diltiazem Group	Topical Diltiazem Group	p value
Fissure Healing	At the end of 3rd week	4 (16%)	6 (24%)	>0.05*
	At the end of 6th week	10(40%)	20(80%)	<0.05**
Recurrence		2(10%)	2 (20%)	>0.05*

* Fischer Exact test

** Chi Square test

Side effect/complication of the treatment

4(16%) patients in oral diltiazem group reported headache and 5 (20%) patients reported nausea and vomiting whereas no patient reported either of them in topical diltiazem group and only one patient developed anal excoriation (4%) while applying ointment. Overall 9 patients developed side effects in oral diltiazem group while only 1 patient developed side effects in topical diltiazem group (p value <0.05).. None of the patient in either group had to stop medication due to side effects.

Table 3: Side Effects of Treatment

Side Effects	Oral Diltiazem Group	Topical Diltiazem Group	p value*
Headache	4 (16%)	0	0.11
Nausea and Vomiting	5 (20%)	0	0.06
Perianal Excoriation	0	1 (4%)	1.000
Overall	9 (36%)	1 (4%)	<0.05

*Fischer Exact test

5. Discussion

Surgical treatments such as manual dilatation and internal sphincterotomy have been widely used for treating chronic anal fissure. Because of the disability associated with surgery for anal fissure and the risk of incontinence, medical alternatives to surgery have been sought. Pharmacologic methods that relax the anal smooth muscles accomplish reversibly what occurs in surgery and in turn help to obtain fissure healing. Topical diltiazem ointment has been studied extensively with effective healing in most cases. Oral diltiazem in the treatment of chronic anal fissure has not been studied much. Few studies available in literature show oral diltiazem as less effective in treatment of chronic anal fissure.

Both groups in the present study were comparable regarding age and sex. The most common symptoms were pain during defecation, bleeding per rectum and constipation. The pain associated with chronic anal fissures is usually marked and together with bleeding and irritation causes considerable morbidity and reduction in quality of life in these patients⁷. Patients in both the groups had perceptible pain relief as compared to pre treatment levels and the differences in decrease of median pain score between the groups were not statistically significant except at the end of 1st week of treatment. The relief in median pain score at the end of study was in conformity with the study undertaken by Marion Jonas et al⁸ in which 50 patients of chronic anal fissure showed no significant difference in reduction of mean pain score between the groups treated by oral diltiazem and diltiazem ointment for a period of 8 weeks.

Complete healing was observed in 10 (40%) patients in oral diltiazem group whereas 20 (80%) in topical diltiazem group had completely healed fissure at the end of 6th week. At the end of 3rd week, the difference was not statistically significant between the two groups but at the end of 6th week, the difference in fissure healing was statistically significant between the two groups. Although similar findings were observed in a study undertaken by

Marion Jonas et al⁸ in which 9 out of 24 (38%) patients treated with oral diltiazem and 17 out of 26(65%) in patients treated with diltiazem ointment(at the end of 8 weeks) had fissure healing but he observed no significant difference in the healing frequency between the two groups (p value-0.09). Jawaid et al⁹ showed 77% healing by diltiazem ointment in 2009 and similar results were reported by Kocher et al¹⁰ in 2002 with diltiazem ointment treatment.

Headache, nausea and vomiting were the side effects observed in the patients treated with oral diltiazem whereas in topical diltiazem group only 1 patient (4%) presented with anal excoriation. None of the patient in either group had to stop the medication due to side effects. The findings of the present study were in agreement with the study undertaken by Marion Jonas et al⁸ in 50 patients of chronic anal fissure, which reported side effects in 8 out of 24 (33%) patients treated with oral diltiazem and no patient reported with side effects in diltiazem ointment group. Study by Shrivastava et al¹¹ showed no case of headache in diltiazem ointment group. Kocher et al¹⁰ reported 3 patients with anal excoriation in their 31 patients in diltiazem ointment group.

Recurrence rates of present study were in conformity with the study conducted by Marion Jonas et al⁸ in 50 patients of chronic anal fissure who found a recurrence rate of 11.11% in oral diltiazem group and 5.88% in patients treated with diltiazem ointment at 8 months of follow up and the difference was not statistically significant. Srivastava et al¹¹ found 12.5% recurrence rate in patients using diltiazem ointment. Rithinsuvarna et al¹² reported recurrence in 6 out of 62 patients using diltiazem ointment.

Present study demonstrated that both oral and topical preparations of diltiazem lead to fissure healing in patients with chronic anal fissures, thereby avoiding surgery. However topical diltiazem group appears to be more effective than oral diltiazem healing 80% as compared to 40% of fissures respectively. Also for those patients who healed during study, there was no difference between the time taken for healing to occur with regard to oral and topical treatment. Another important observation noted in the present study was the absence of side effects with topical diltiazem which is an advantage for patients treated with topical diltiazem.

Four patients, two in each study group developed recurrence of fissure at three months of follow up on cessation of treatment at 6 weeks which was not statistically significant. However long term follow up is required to determine the true rates of recurrence after treatment of chronic anal fissure with oral and topical diltiazem and to evaluate the true efficacy of diltiazem in preventing recurrence of fissure.

Medical treatment avoids all the complications related to surgical procedures and it can be carried out as an outpatient. It is cost effective, does not require hospitalization and there is no wastage of man hours. The findings of the present study support a role for topical diltiazem as first line treatment for chronic anal fissure.

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