

# Comparative Study to Know Efficacy of Topical Minoxidil (2%) Versus Topical Diltiazem (2%) in Chronic Anal Fissure Healing

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## ABSTRACT

**Introduction:** Chronic Anal fissure (CAF) is an elliptical ulcer in the anal canal extending from dentate line to the anal verge with sentinel pile or hypertrophied papilla. It is associated with hypertonia of the internal anal sphincter and pain; surgery to reduce internal anal sphincter hypertonia has been the standard treatment for anal fissure. Since, minoxidil, a potassium channel opener, induces smooth muscle relaxation and vasodilatation. It has been found that this drug could hasten the healing of anal fissure. The objective of the present study was to compare and evaluate the efficacy of topical minoxidil (2%) versus topical diltiazem (2%) in management of CAF.

**Material and methods:** This prospective comparative study was conducted in 100 patients with CAF. They were randomly divided into two groups, A and B. Group A received local application of ointment containing 2% minoxidil and group B received 2% diltiazem.

The patients were advised to visit the hospital every alternate week for a period of 6 weeks.

**Results:** Complete fissure healing rate was 74.5% in minoxidil group against 50% in diltiazem group with p value 0.030. The pain relief was also good as 65.9% patients in minoxidil group and 15.9% patients in diltiazem group got relieved from this painful symptom over the 6 weeks time. Minoxidil controls bleeding per rectum (BPR) in 91.5% patients while 91.1% patients got relieved from BPR in diltiazem group. Recurrence rate was found 6.4% in minoxidil group as compared to 11.4% in diltiazem group. Minoxidil produce side effects like hypertrichosis, headache and perianal dermatitis. Minoxidil produce headache in 2.12% of the patients as compared to Diltiazem in 4.54% of the patients.

**Conclusion:** Minoxidil 2% topical application is a good alternative in CAF healing in place of Diltiazem 2% with few side effects which could be ignored in regard to benefit of CAF healing.

**Keywords:** Chronic anal Fissure, Diltiazem, Minoxidil.

about 6% patients.<sup>4,5</sup> Acute anal fissure (AF) usually heals with simple measures such as stool softeners and dietary modifications. But chronic AF usually doesn't respond to such measures and a treatment is usually required, that is aimed at reducing the internal sphincter spasm with minimal complications.<sup>6</sup> Chronic AF has traditionally been treated by surgical sphincterotomy.<sup>7,8</sup> However, concerns have been raised about the risk of permanent anal incontinence.<sup>6,9</sup> Chemical Sphincterotomy (CS) for therapy of AF would mimic surgical sphincterotomy, again by reducing anal resting pressure and causing its healing. CS performed with botulinum toxin (BTX) injections or the topical application of ointments such as calcium channel blockers, nitric oxide donors, a potassium channel agonist (minoxidil), inhibitors of angiotensin-converting enzyme, phosphodiesterase inhibitors, cholinomimetic (bethanechol) and an alpha-adrenoreceptor antagonist (indoramin) usually reduce anal resting pressures but with a diminished healing rate compared to lateral internal sphincterotomy (LIS).<sup>10</sup>

In a studies which were conducted by Bhardwaj et al<sup>11</sup> (2000) and Carapeti et al<sup>12</sup> (1998) treated patients with CAF with topical diltiazem, three times daily for 16 and 8 weeks respectively. Mean anal resting pressure was reduced by 24% in both studies and anal fissure healing in 73% and 67% of the patient respectively. Knight JS et al<sup>13</sup> (2001) reported a healing rate of 75% after 8-12 weeks treatment with Diltiazem 2% ointment. Griffin N et al<sup>14</sup> (2002) in a study reported a low, 48% healing rate with topical Diltiazem in 8 week follow up. Topical 2% diltiazem is an effective and safe treatment for chronic anal fissure in patients who have failed topical 0.2% GTN. The need for sphincterotomy can be avoided in up to 70% of cases.

Muthukumarassamy et al<sup>15</sup> (2005) using 0.5% Minoxidil ointment, 10 (29.4%) out of 34 patients developed complete fissure healing at 6<sup>th</sup> week follow up. 14 (41.2%) out of 34 patients achieved partial healing in at 6<sup>th</sup> week follow up. We therefore compared the efficacy of local application of

## INTRODUCTION

An anal fissure also called a fissure in ano, is a traumatically induced longitudinal split or ulcer in the squamous epithelium of the distal anal canal. It typically extends from the anal verge cephalad towards the dentate line. It can occur at any age, but is usually a condition of young adults.<sup>1</sup> If an anal fissure does not heal in at least six weeks, it may be recognized as chronic anal fissure.<sup>2-4</sup>

The exact etiology of anal fissure is unknown but trauma caused by hard faecal mass and hypertonicity of the internal sphincter are thought to be the initiating factors. However only 25% patients with chronic anal fissure have constipation.<sup>5</sup> Diarrhoea is a predisposing factor in

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**How to cite this article:** Rachan Lal Singla, Sanjay Yadav, Paras Kumar Pandove, Bimaljot Singh. Comparative Study to Know Efficacy of Topical Minoxidil (2%) Versus Topical Diltiazem (2%) in Chronic Anal Fissure Healing. International Journal of Contemporary Medical Research 2018;5(2):B1-B4.

Minoxidil 2% with Diltiazem 2% in chronic anal fissure healing.

## MATERIAL AND METHODS

This prospective study was conducted in 100 patients with CAF. A written informed consent was obtained from the patients and they were given the choice to pull out from the study at any point if they wished to. Patients of CAF of either gender aged between 15-60 years presenting to Out Patient Department of Surgery in Rajindra Hospital, Patiala were taken up for this study and randomly divided into two groups A and B. Group A received local application of ointment containing 2% Minoxidil and group B received 2% Diltiazem. Healing of anal fissure at 6 weeks was used as the primary end-point.

### Inclusion criteria

- Patient of chronic anal fissure with either sex aged in between 15-60 years included in this study.
- Symptoms lasting more than one month.
- Induration of the fissure.
- Visible fibers of sphincter muscle at floor of fissure,
- Presence of sentinel pile or hypertrophied papilla.
- Patients willing to participate in this study.

### Exclusion criteria

- Patient with cardiovascular disease.
- Pregnant and lactating mothers
- Patients with anal disease that warranted surgery (abscess or fistula).
- Atypical fissures associated with inflammatory bowel disease or cancer or infection.
- Acute fissure in ano.
- Fissure in children less than 15 years old.
- Patients aged more than 60 years old.
- Patients refused to participate in this study.

100 Patients who satisfied the selection criteria were randomly divided into two groups A and B, group A was applied 2% Minoxidil ointment and group B was applied 2% Diltiazem topically. Patients were advised to apply about 0.5 gram of the ointment circumferentially around and inside anus every 8 hourly for 6 weeks.

No laxative or stool softeners were prescribed during the trial period. The patients were advised to visit the hospital every alternate week for a period of 6 weeks.

Anal pain was assessed before starting treatment and at every alternate week follow-up visits using a linear visual analogue pain score (VAS, range 0-10, with 0 representing no pain and 10 representing the worst possible pain).

Patients main presenting features like painful defecation, bleeding per rectum, constipation and per rectal examination findings like location of feature, internal anal sphincter (IAS) tone, associated sentinel pile or hypertrophic papilla were assessed subjectively at baseline and recorded in pre-designed proforma. Pain score, fissure healing, bleeding per rectum, recurrence of fissure and side effect profiles were assessed at each alternate week respectively. Pulse rate, blood pressure and any side effects associated with treatment

were recorded at each visit.

Complications that were specifically looked for were postural hypotension, perianal dermatitis, hypertrichosis, and allergy to the Minoxidil and headache and gastrointestinal upsets for Diltiazem.

The primary end point was complete healing of fissure, defined as presence of scar at 6 weeks of treatment. Partial healing was defined as persistence of fissure but with improvement in symptoms (pain relief and /or control of bleeding). At the end of trial, patients who did not responded to conservative management of either group were advised surgical treatment.

## STATISTICAL ANALYSIS

Patients data (demographic, disease, treatment, outcome, and follow-up) were collected on pre-designed proforma and observations obtained were tabulated and analysed using the SPSS, version 17 software. The p values were calculated by using the Chi-square test.

## RESULTS

Majority of patients were in between 21-50 yrs of age in both the groups. There was male predominance in chronic anal fissure cases in both the groups. In our analysis, painful defecation was the most common symptom 94% in group A and 82% in group B. This was followed by bleeding per rectum and constipation in 62% and 38% in group A while 56% and 46% in group B respectively (Table1).

In the present study the presence of posterior anal fissure was noted to be 80% in group A and 76% in group B. Anterior anal fissure was noted in 16% patients in group A while 20% patients in group B. 4% each in both groups were those having both anterior as well as posterior fissure.

In our study 70% patients in group A and 74% patients in group B were having sentinel tag. 58% patients in group A and 60% patients in group B were having hypertrophic papilla. In group A 72% patients and 66% patients in group B were having spasm of internal anal sphincter on per rectal examination (Table1).

Characteristics	Group A Minoxidil% age (n)	Group B Diltiazem% age(n)
Male	60%(30)	56%(28)
Female	40%(20)	44%(22)
Age in years	15-60	15-60
Symptoms:		
Pain	94%	82%
BPR	62%	56%
Constipation	38%	46%
Local findings:		
Posterior midline	80%(40)	76%(38)
Anterior midline	16%(8)	20%(10)
Ant. + post. midline	4%(2)	4%(2)
Sphincter spasm	72%(36)	66%(33)
Sentinel tag	70%(35)	74%(37)
Hypertrophic papilla	58%(29)	60%(30)

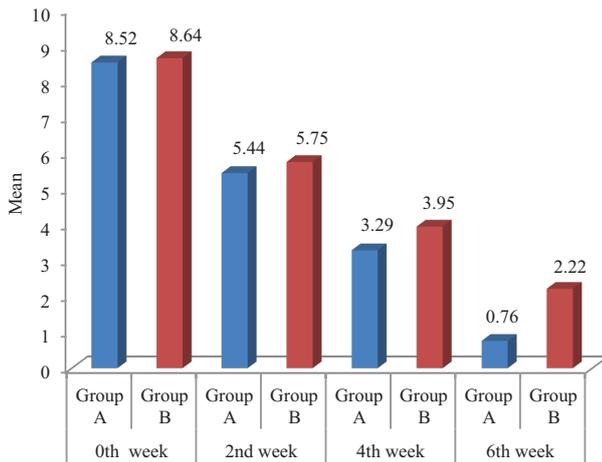
**Table-1** Clinical details of the patients (n= no. Of patients)

Weeks	Group A Minoxidil % age	Group B Diltiazem % age
2 <sup>nd</sup>	8	6
4 <sup>th</sup>	59.2	46.9
6 <sup>th</sup>	74.5	50

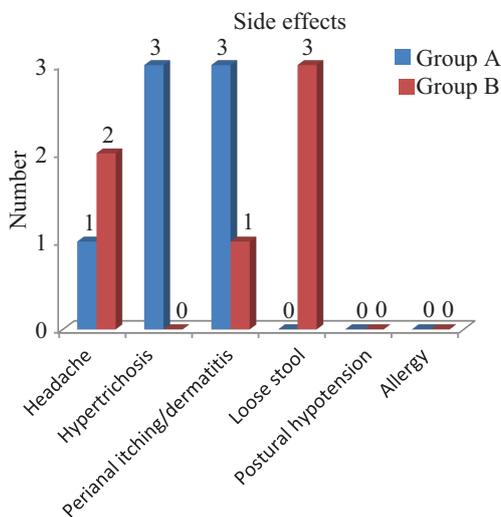
**Table-2** Complete fissure healing rate.

At 6 <sup>th</sup> week	Group A Minoxidil %age (n)	Group B Diltiazem %age (n)
'0' VAS score	65.9%(31)	15.9%(7)

**Table-3:** Patients with '0' VAS score (n= no. Of patients)



**Figure-1:** Mean VAS score



**Figure-2:** Side effect profile

At the end of the 2<sup>nd</sup>, 4<sup>th</sup> and the 6<sup>th</sup> weeks follow up, the following parameters were evaluated and compared in both the groups. At 4<sup>th</sup> week follow up 1 patient in group A and 1 in group B did not reported for follow up. At 6<sup>th</sup> week total 3 in group A and 6 in group B respectively did not reported for follow up.

**Fissure healing:** In the present study fissure was completely healed in 74.5% patients by 6<sup>th</sup> week in group A and 50% in group B while 32.6% partial healing was achieved at 4<sup>th</sup> week in group A and 24.5% in group B. P value 0.030, was found significant. In group A 4 (8%) out of 50 patients were

present with complete fissure healing while in group B 3 (6%) out of 50 had completely healed fissure at 2<sup>nd</sup> week follow up. (Table 2)

**Pain relief:** Pain score at the time of presentation and at 2<sup>nd</sup> week follow up were not found significant on statistical analysis in both the groups.

At 4<sup>th</sup> week mean pain score in group A was 3.29 as compared to 3.95 in group B on statistical analysis p valve 0.033 was significant.

At 6<sup>th</sup> week in group A mean pain score was 0.76 as compared to 2.22 in group B. On statistical analysis this study was highly significant with p value <0.001(Figure 1).

In the present study at the end of 6 weeks follow up 31(65.9%) out of 47 patients were having no pain with VAS score '0' in group A while 7 (15.9%) out of 44 patients were having no pain in group B. On statistical analysis p value was <0.001 found highly significant (Table 3).

**Effect on BPR:** In the present study 43 (91.5%) out of 47 patients in group A while in group B 40 (91.1%) out of 44 patients got relieved from bleeding per rectum at the end of 6 weeks follow up. On statistical analysis p value was not found significant.

**Recurrence:** In the present study the recurrence rate was 6.4% in group A while 11.4% in group B after 6 weeks follow up. On statistical analysis p value 0.030, was found significant.

**Side effects:** In the present study 1 (2.12%) out of 47 patients in group A reported headache which was mild in nature and got relieved its own. While 2 (4.54%) out of 44 patients in group B affected with headache, mild to moderate nature and required analgesics. In the present study we found that 3 (6.38%) out of 47 patients in group A while only 1(2.27%) out of 44 patients in group B developed perianal itching in the form of local irritation as a complication of topical application. In the present study the most common side effect, specific to the Minoxidil is hypertrichosis, was present in 3 (6.4%) out of 47 patients. Loose stool was the most common and specific side effect to the Diltiazem and was present in 3 (6%) out of 50 patient in group B and it was not a distressing symptoms. None of the patients were found to have postural hypotension or allergy to the drug in both groups (Figure 2).

## DISCUSSION

Fissure-in-ano is a common problem across all parts of the world, causing considerable morbidity and affecting the quality of life of the patients. This necessitates the prompt treatment of the condition with suitable, cost-effective methods. The posterior midline is the commonest site, followed by the anterior midline, particularly in females.<sup>16</sup> Fissure is often initiated by constipation.<sup>12</sup> In females, it frequently occurs during pregnancy and following childbirth.<sup>12</sup> There is an associated spasm of the underlying internal sphincter muscle which results in severe pain and impaired fissure healing. An acute fissure (less than a month's duration) usually heals

spontaneously or with simple measures like a high fibre diet, adequate water intake, and warm sitz baths.<sup>12,13</sup> The chronic anal fissures are not usually amenable to the aforementioned simple conservative measures.<sup>13</sup>

The rationale of treating this condition lies in reducing the internal anal sphincter tone, relieving the spasm and thereby improving the local circulation which is necessary for the healing of the ulcer (fissure). Lateral internal sphincterotomy (LIS) has been considered as the gold standard in the treatment of anal fissure, wherein, there is partial division of the internal anal sphincter away from the fissure site. Chemical sphincterotomy (CS), a medical line of treatment, is now being accepted as the first line of treatment for chronic anal fissures at various centres. CS with the injection of botulin toxin to the fissure, oral nifedipine, the topical application of glyceryl trinitrate (GTN) and topical diltiazem ointment showing promising results<sup>12</sup>. Previous study have found that combination treatment with Minoxidil and Lignocaine helps in faster healing of anal fissures and provides better symptomatic relief than either drug alone.<sup>15</sup>

In the present study we have divided patients in two groups, A and B for the analysis of the effect of Minoxidil 2% ointment and Diltiazem 2% ointment used as local application respectively on CAF healing, painful symptoms, bleeding per rectum, recurrence rate and side effect profiles were compared with each other.

Bharadwaj et al<sup>11</sup> reported 73% fissure healing rate in 16 week follow up period with Diltiazem 2% ointment. Knight JS et al<sup>13</sup> reported a healing rate of 75% after 8-12 weeks treatment with Diltiazem 2% ointment. Griffin N et al<sup>14</sup> reported a low, 48% healing rate with topical Diltiazem in 8 week follow up. Muthukumarassamy et al<sup>15</sup> using 0.5% Minoxidil ointment, 10 (29.4%) out of 34 patients developed complete fissure healing at 6<sup>th</sup> week follow up. 14 (41.2%) out 34 patients achieved partial healing in at 6<sup>th</sup> week follow up.

In the present study Minoxidil when used as 2% topical application causes significantly higher and faster complete fissure healing rate than Diltiazem 2% and 0.5% Minoxidil as shown in the other studies.

## CONCLUSION

Minoxidil causes faster and higher complete healing rate (74.5%) as compared to Diltiazem ointment (50%) after 6 week follow up. Minoxidil when used as 2% topical ointment is effective in relieving pain in 65.9% patients as compared to 15.9% patients in Diltiazem 2% group. So it is superior to Diltiazem 2% ointment in relieving pain during defecation by reducing spasm of IAS.

Minoxidil gives us significantly lower recurrence rate (6.4%) as compared to the Diltiazem (11.4%). Minoxidil 2% produced side effects like hypertrichosis, headache and perianal dermatitis in comparison to 0.5% Minoxidil that was used in previous study.

The present study of using Minoxidil 2% topical application provides faster and higher healing rate, effectively control BPR and significantly provide pain relief with low recurrence

rate as compared to the Diltiazem 2% for treatment of CAF. So the present study provides Minoxidil 2% topical application is a good alternative in CAF healing in place of Diltiazem 2% with few side effects which could be ignored in regard to benefit of CAF healing.

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**Source of Support:** Nil; **Conflict of Interest:** None

**Submitted:** 01-02-2018; **Accepted:** 11-02-2018; **Published:** 22-02-2018