

ORIGINAL ARTICLE

OUTCOME OF 0.2% GLYCERYLTRINITRATE CREAM VERSUS 2% DILTIAZEM CREAM IN THE TREATMENT OF CHRONIC ANAL FISSURE

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Background: Anal fissure is a linear tear in the distal anal canal resulting from persistent hypertonia and spasm of the internal sphincter which results in mucosal ischemia. We have conducted a study in order to compare the outcome of 0.2% glyceryl trinitrate cream versus 2% diltiazem cream in the treatment of chronic anal fissure **Methods:** This randomized controlled trial (RCT) was carried out in the Department of Surgical “B” unit, at Ayub Teaching Hospital, Abbottabad, Pakistan from 15th June 2012 to 15th May 2015. One hundred and eighty-four patients who visited the outpatient department for the treatment of chronic anal fissure were included in the study. They were divided into two groups with 92 patients in each group. Patients in group “A” included those patients receiving topical glyceryl trinitrate and group “B” patients were those receiving topical diltiazem cream. **Results:** Out of 184 patients 66.3% were males, 33.7% were females. Mean age of the patients was 43.84±7.976 and mean duration of symptoms was 10.55±2.524. Overall outcome in terms of healing was 71.2%, among which 80.4% were from diltiazem group while 62% in glyceryl trinitrate group. Complete relief of pain was observed in 67.9%, 26.1% complained of mild pain and 5.4% complained of moderate pain. Only one patient in glyceryl trinitrate group complained with severe pain with no healing after one month of follow up. No statistical association was found between healing outcome and gender as well as age of the patients ($p>0.05$) although an association was found between healing outcome and duration of symptoms ($p<0.05$). **Conclusion:** This study shows that diltiazem has better outcome in terms of healing of chronic anal fissure and reductions in symptoms, i.e., pain compared with glyceryl trinitrate.

Keywords: Chronic anal fissure; Diltiazem; Glyceryl trinitrate; Cream; Chemical sphincterotomy

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INTRODUCTION

Anal fissure is a common condition affecting all age groups particularly young individuals.¹ It is a linear tear in the distal anal canal resulting from persistent hypertonia and spasm of the internal sphincter which results in mucosal ischemia.² It results in pain during defecation and per rectal bleeding. Various therapies have been used for the treatment of anal fissure with a view to reduce the resting anal canal pressure and improving the vascularity of internal sphincter muscle.³ Surgical treatment of chronic anal fissure is with lateral internal sphincterotomy.⁴

The exact aetiology of anal fissures is unknown, but the initiating factor is thought to be trauma resulting from the passage of a particularly hard or painful bowel movement. Microtrauma of the anus by constant saddle vibration in professional mountain bikers can lead to chronic inflammation and a resultant AF.⁵ There is also a suspicion that the water stream from bidet-toilets may be a cause of anterior fissure-in-ano.⁶ 3–11% of anal fissures are associated with childbirth and typically this type of aetiology predisposes to fissure localization in the anterior anal commissure.⁷ Links between sexual abuse and AF have been considered.⁸ Low-fibre diets, such as those lacking in raw fruits and vegetables, are

associated with the development of anal fissures. No occupations are associated with a higher risk for the development of anal fissures. Prior anal surgery is a predisposing factor because scarring from the surgery may cause either stenosis or tethering of the anal canal, which makes it more susceptible to trauma from hard stool.⁹ The most common location for primary AF is the posterior anal midline. Only 10% of females and 1% of males have a fissure located in the anterior midline.¹⁰⁻¹²

The most commonly observed abnormalities are hypertonicity and hypertrophy of the internal anal sphincter, leading to elevated anal canal and sphincter resting pressures.¹³ Topical glyceryltrinitrate cream a nitric oxide donor compound has been shown to cause relaxation of anal sphincter and thus effective in the treatment of anal fissure.² Diltiazem can lower the anal sphincter pressure by its calcium channel blocking effect and is therefore useful in the treatment of anal fissure.¹⁴ Analysis of the available literature shows that by far, medical manipulation of the internal sphincter should be the first-line treatment in Anal Fissure. A surgical therapy is called for if the medical therapy fails or there is a recurrence.²

Topical diltiazem also has been tried successfully in the treatment of chronic anal fissure.¹⁵ Topical glyceryltrinitrate cream has been the most extensively used non-surgical treatment for chronic anal fissure.¹⁴ A randomized controlled trial conducted in Iran in which complete relief of symptoms in diltiazem ointment group was 72.5% and glyceryltrinitrate cream group was 54.9%.¹⁶

This study is designed to determine the outcome of diltiazem cream versus glyceryltrinitrate cream in the treatment of chronic anal fissure. Although surgery is the gold standard for the treatment of chronic anal fissure, but to reduce the workload on hospitals and keeping in view the financial constraints of the patient, medical therapy is considered as first line therapy in our society. However, glyceryltrinitrate cream is associated with headache and a higher rate of other side effects on the other hand systemic absorption of diltiazem is very low as compared to glyceryltrinitrate and hence the chance of systemic adverse effects is comparatively low. Therefore, replacing glyceryltrinitrate with diltiazem will benefit the patients in effective pain management, good healing results and low risk of headache along with other adverse effects.

MATERIAL AND METHODS

It was a Randomized Controlled Trial (RCT), carried out in the Department of Surgical "B" unit, at Ayub Teaching Hospital, Abbottabad, Pakistan from 15th June 2012 to 15th May 2015. All patients between age 16–60 years of either sex with chronic anal fissure of greater than 6 weeks were included in the study, while the patients with co-morbid conditions like diabetes, anemia and malnourishments were excluded. A total of 184 patients who visited the outpatient department and satisfy inclusion criteria were included in study. These patients were divided into two groups of 92 each. Patients who received topical glyceryltrinitrate cream were placed in group A and those receiving topical diltiazem cream were placed in group-B.

An approval from the hospital's ethical and research committee was obtained prior to the commencement of the study. All patients meeting the inclusion and exclusion criteria examined on outpatient department were included in the study. The patients were assured that his/her confidentiality will be maintained and informed consent obtained after the purpose and benefits of the study had been explained to them. Demographic characteristics like name, age, gender, address and phone number of all patients was recorded. A detailed medical history was obtained from the patients and complete general physical and systemic examination was carried out. Patients were allocated into two groups through

blocked randomization. Patients in group "A" included those patients receiving topical glyceryltrinitrate and group B patients were those receiving topical diltiazem cream. First patient was decided after a coin toss and after that alternate patients were included in either group. Wound size was measured and pain graded by the same surgeon on arrival of the patient. Follow up was carried out after one month on which time healing of fissure, pain relief and headache complaint were graded by the same surgeon. Information was recorded on a pre-designed *pro forma* (attached). Exclusion criteria were followed strictly to control confounders and bias in the study results.

Data was analysed using SPSS version 19. Mean±SD was calculated for continuous variables like age and duration of symptoms and disease. Frequencies and percentages were calculated for categorical variables like gender and outcomes i.e. healing and pain. Age, gender and duration of disease were stratified to see the effects of modifiers. To compare the outcome of both the drugs chi-square test was used keeping *p*-value of ≤0.05 as significant. Post-stratification chi-square test was also applied to compare the stratas.

RESULTS

Mean age of study population was 43.84±7.976 years. The youngest study participant was 16 years old and the age of oldest study participant was 60 years. Similarly, the mean duration of disease was 10.55±2.524 weeks. Shortest duration of disease was 6 weeks and the longest duration of disease was 16 weeks.

Among the study population, 122 (66.3%) of the patients were males and 62 (33.7 %) were females. Healing occurred in 131 (71.2%) patients and almost one third, i.e., 53 (28.8%) of the patients did not respond to treatment. Of these 125 (67.9%) patients had complete relief of pain, 48(26.1%) complained of mild pain, 10 (5.4%) complained of moderate pain and 1 (0.5%) patient complained of severe pain after treatment. While the detail of pain of both drugs, i.e., diltiazem and GTN is shown in table-1.

When chi-square test was applied to determine the significance of the difference between Group A and Group B with regard to the outcome in terms of healing, a *p*-value = 0.006 (value 7.659, df 1) was obtained which was highly significant detail shown in table-2.

Age of the patient was stratified into four age groups such that patients aged 30 years and younger in group one, 31–40 in group 2, 41–50 in group 3 and 51–60 in group 4. The highest rate of healing was observed in group 1 shown in table-3

below. When chi-square test was applied to determine the significance of the difference among age groups with regard to the outcome in terms of healing, a p -value=0.752 (value 1.204, df 3) was obtained which was not significant ($p>0.05$).

Duration of disease was categorized into three groups such that group one consisted of 6-9 weeks, group two 10-13 weeks and group three consisted of duration of disease from 14 weeks and above, detail of wound healing and duration is given in table:5 below. When chi-square test was applied

to determine the significance of duration of disease with regard to the outcome in terms of healing, a p -value=0.049 (value 6.050, df 2) was obtained which was significant ($p<0.05$).

Gender of the patient and outcome was cross-tabulated in table-4, by applying chi-square test a p =0.752 (value 1.204 df 3) was obtained which was not significant ($p>0.05$).

Details of wound healing and duration of disease is shown in table-5

Table-1: Pain relief after treatment

	No pain	Mild	Moderate	Severe
GTN	58 (63%)	26 (28.3%)	7 (7.6%)	1 (1.1%)
Diltiazem	67 (72.8%)	22 (23.9%)	3 (3.3%)	0 (0%)

Table-2: Cross-tabulation of groups of patients and healing of wound

Wound Healing	GTN		Diltiazim		<i>p-Value</i>
	Yes	No	Yes	No	
Count	57	35	74	18	0.006
%within the Group	62.0%	38.0%	80.4%	19.6%	
Total count in Group	92		92		

Table 3: Cross-tabulation of age groups of patients and healing of wound:

Age in years	Wound healing	
	Yes	No
30 and below	3 (75%)	1 (25%)
31-40	56 (74.7%)	19 (25.3%)
41-50	48 (70.6%)	20 (29.4%)
51-60	24 (64.9%)	13 (35.1%)
Total	131 (71.2%)	53 (78.8%)

Table-4: Wound healing* Gender of patient Cross tabulation

Wound Healing	Yes		No	
	M	F	M	F
Count	91	40	31	22
% within Gender of patient	74.6%	64.5%	25.4%	35.5%
Total Count	131		53	
Total %	71.2		28.8%	

Table-5: Cross-tabulation between wound healing and duration of disease:

Duration of healing in weeks	Wound healing	Percent
6-9	50	38.17
10-13	59	45.04
14 and above	22	16.79
Total	131	100

DISCUSSION

In the modern world, the treatment of chronic anal fissure has moved from surgical to medical modalities because of disability and the risk of incontinence associated with surgery and other complications.¹⁶ Chemical sphincterotomy can be done using a variety of agents. A first line use of medical therapy cures most chronic anal fissures economically and conveniently.^{3,17} Chemical sphincterotomy is non-invasive, avoids the need for general anesthesia, and could be applied at home by the patient itself. Glyceryltrinitrate remains the standard chemical sphincterotomy against which

other newer treatments are compared.¹⁸ It has been studied most widely with effective healing in most of the cases, but headache is a major side effect with its use, which may lead to a discontinuation of the treatment. On the other hand, topical diltiazem is associated with fewer side-effects, probably because of minimal systemic absorption.^{19-21,17}

The mean age of patients in our study population was 43.847.97 which shows that the occurrence of chronic anal fissure is predominantly confined to the middle-aged group. Although our study included patients from age 30-60 for the convenience of better patient compliance for follow up and communication, this figure can be biased. Out

of 184 patients about two quarter (66.3%) was males and a quarter (33.7%) was females which can be attributed to the conservative approach and cultural limitations of females in the local set up especially for Perianal diseases.

Although there is an extensive debate in the literature over the exact duration of anal fissure to describe it as chronic anal fissure, many studies suggest that anal fissure with symptoms beyond six weeks can be labelled as chronic. In our study, we included patients with symptoms from six weeks and above.^{38,39,22,18}

Chronicity of the symptoms and outcome of treatment were compared which showed significant correlation ($p < 0.05$). Patients with symptoms from 6–9 weeks responded with 76.9% treatment outcome compared with 10–13 weeks of symptoms history which resulted in 63.4% healing outcome. These findings need to be evaluated further because if the chronicity of symptoms has any effect on the outcome in other studies as well then, these findings can guide towards treatment strategies to improve outcomes. A longer duration of symptoms may guide towards a more vigorous treatment and hence higher doses for more chronic anal fissures.

In our study, symptoms of 72.8% of patients completely relieved with DTZ ointment while symptoms of 63% patients relieved with GTN however, not significant statistically ($p > 0.05$). These results were comparable with the study carried out by Sanei *et al* which showed complete relief of symptoms was observed in 72.5 patients in DTZ group and 54.9% in GTN group but it was not statistically significant ($p > 0.05$).¹⁶ Among these patients 88.2% of the patients in DTZ group and 70.6% patients in GTN group showed reduction in symptom ($p = 0.02$). Complete remission of anal fissure was observed in 80.4% patients in DTZ group and 62% in GTN group which was higher compared to 66.7% in DTZ group and 54.9% in GTN group.¹⁶ Although these findings are comparable but duration of treatment and follow up was different between the two groups which can significantly alter the outcome.²³ Although another author suggests that duration of treatment more than six weeks have no significant effect on the outcome.²⁴ In our study patients were followed after one month whereas duration of treatment and follow up was one and half month in the study carried by Sanei *et al*¹⁶

There was significant difference in the complete remission of fissure ($p < 0.05$). These findings were almost consistent with those of Lund²⁵ and Scholefield²⁶ which showed that 66% of the patients using GTN ointment regularly for 6–8 weeks had complete healing of the fissure. Carapeti *et al*²⁷ stated that 67% of the patients healed after 8 weeks

of using GTN ointment. Tomar and Saxena found no significant difference in both groups in term of relief in pain, bleeding and fissure healing except the higher incidence of headache in glyceryltrinitrate group in contrast to our findings. Tolerability of diltiazem and patient satisfaction was higher. The lack of significant difference may be attributed to the sample size which was 25 in each group.²⁰

However, study carried out by Hashmi and Siddiqui included 50 and 47 patients in GTN and DTZ group respectively. It showed statistically significant difference for DTZ group in terms of wound healing and side effects mainly the headaches ($p = 0.02$ and 0.003 respectively) which was similar to our study outcome.³

Another randomized clinical trial conducted at Aga Khan University Hospital, Karachi comprised 60 adult patients supported the effectiveness of diltiazem. Patients, who used diltiazem reported more symptomatic relief than glyceryltrinitrate ($p < 0.01$). Side effects were found more in glyceryltrinitrate than diltiazem ($p < 0.01$).²¹

CONCLUSION

This study shows that diltiazem has better outcome in terms of healing of chronic anal fissure and reductions in symptoms, i.e., pain compared with glyceryl trinitrate. Moreover topical 2% diltiazem appeared to be well tolerated and proving to be the preferred first-line method of chemical sphincterotomy for chronic anal fissures. Long-term follow-up is needed to assess the risk of fissure recurrence after initial healing with diltiazem. Diltiazem has fewer side effects, a better healing response and low recurrence rates however, glyceryltrinitrate is associated with a higher rate of side effects though headache can be managed with analgesics, and overall satisfaction rate is higher with diltiazem.

AUTHORS' CONTRIBUTION

MSK: Conception and design & final approval and guarantor of the article. IA: Collection and assembly of data. JZ: Analysis and interpretation of the data, Statistical expertise. SA: Drafting of the article. AK: Critical revision of the article for important intellectual content.

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