ORIGINAL ARTICLE

Diltiazem vs. Glyceryl Tri-Nitrate for symptomatic relief in anal fissure: a randomised clnical study

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Abstract

Objective: To further resolve the clinical equipoise on the choice of chemical sphincterotomy agent for early symptomatic relief of anal fissure by comparing the effectiveness of 2% Diltiazem gel with 0.2% Glyceryl TriNitrate.

Methods: The randomized clinical trial was conducted at Aga Khan University Hospital, Karachi, from February 1, to July 30, 2008, and comprised 60 adult patients with anal fissure who were equally randomised to either Diltiazem or Glyceryl TriNitrate after taking informed consent. The creams were applied locally; the former twice daily, and the latter three times a day for a period of two weeks. The rest of the treatment was standard. Patients were followed up in clinic by the principal investigator at two weeks for primary outcome i.e. self-reported symptomatic relief on Visual Analogue Scale, and secondary outcomes i.e. side effects and the overall cost of treatment.

Results: Of the total, 31 (52%) patients were males and the overall mean age was 37±11 years. Patients, who used Diltiazem reported more symptomatic relief than Glyceryl TriNitrate ($p<0.01$). Side effects were found more in Glyceryl TriNitrate than Diltiazem ($p<0.01$), and most common side effect in the former group was headache in 12(40%) patients. Cost of the treatment was not significantly different between both treatment arms ($p<0.28$).

Conclusion: Chemical sphincterotomy with topical 2% Diltiazem gel is an effective first-line treatment for early symptomatic relief of anal fissures, owing to negligible side effects.

Keywords: Fissure in ano, Topical Diltiazem, Topical Glyceryl TriNitrate, Chemical sphincterotomy, Visual analogue score. (JPMA 64: 510; 2014)

Introduction

Anal fissure is a superficial linear tear in the anoderm, most commonly caused by passage of a large, hard stool.[1] This tear is distal to the dentate line. It is associated with the spasm of the internal anal sphincter except in post-partum conditions. The aim of the treatment should be to facilitate the healing of the fissure, by reducing the resting tone of the muscle and increasing blood supply.

Glyceryl TriNitrate (GTN) has been used for several years; the nitricoxide lowers the resting tone and increases the blood flow.[2] Diltiazem on the other hand has been derived from the benzothiozapine group; it dilates blood vessels and increases tissue perfusion. It acts as a calcium channel pump blocker and lowers the resting tone of the muscle.[2] There have been several recent studies that have shown that Diltiazem is very effective in treating patients with anal fissures that have not responded to GTN.[3] Diltiazem has also shown to reduce the number of patients requiring surgery.

Since this is a common condition in our part of world, it warrants a cost-efficient as well as effective treatment. One local study reported superiority of lateral sphincterotomy to Diltiazem;[4] but, its cost supercedes the cost of Diltiazem. In another study, Diltiazem was found to be equally effective in terms of healing and lesser side effects than GTN.[5] However, the symptomatic relief was not compared, which is the most common complaint even with medical management. So, to further strengthen evidence, the current study was undertaken to compare the effectiveness of 2% Diltiazem gel with 0.2% GTN for symptomatic relief of anal fissures. We hypothesised that 2% Diltiazem is superior to 0.2% GTN.

Patients and Methods

The randomised clinical trial was conducted at the surgical clinics of Aga Khan University Hospital, Karachi, from February 1 to July 30, 2008. The study was approved by the institutional ethical review committee. Patients with age of more than 14 years and diagnosis of fissure in ano by a consultant general

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surgeon were included, while patients living outside the city, unable to consent or with other pathologies i.e. abscess, fistula, malignancy, were excluded. Informed consent was obtained from all the eligible patients.

The study population was randomised to either Diltiazim or GTN group. In order to avoid selection bias, simple randomisation was done by dividing clinics, where Diltiazem was allocated to all patients attending the clinic on that day and similarly to GTN on the other day. The creams were applied locally; GTN was used three times a day and Diltiazem was used twice daily for a period of two weeks. Both the creams were locally prepared at the institution's central pharmacy. Besides, all the patients were instructed by the principal investigator to take high-fibre diet, increase fluid intake and use isphagol husk.

Data was recorded on a proforma that included sociodemogrphic, lifestyle and outcome variables. A visual analogue scale (VAS) from 1 to 10 was used to determine the difference between pre- and post-treatment pain that was explained to the patient at the initial clinic visit. Reduction in pain (pre-treatment minus post-treatment score) was categorised as fair (1-3), good (4-6) and Excellent ($\geq$7). Primary outcome was self-reported symptomatic relief at two-week follow-up in clinic. To avoid missing data, patients who did not turn back to the clinic at two weeks were followed up via telephone. Secondary outcomes were side effects and the overall cost of treatment. In order to avoid information bias, randomisation and intervention allocation was done by the primary investigator and the follow-up in clinic was done by another resident who was unaware of the treatment allocation.

Data was analysed by using SPSS 16. Continuous variables i.e. duration of discomfort after defecation (in min), time period of pain/ discomfort (in days) and cost were presented as mean ± standard deviation. Categorical variables like relief after using treatment were presented as frequency and percentages. Chi square test was used to compare symptomatic relief (reduction in pain) i.e. fair, good and excellent and adverse effects in both treatment groups. Cost was compared between the groups by student's t-test. P-value of $\leq$0.05 was considered significant.

Results

Total 60 patients were randomized into two equal groups, and all the participants completed the study. Overall, 31 (52%) patients were males and the mean age was 37±11 years. Baseline characteristics of

Table-1: Baseline characteristics of patients.

Variable	Value
Age	37±11 years
Gender	
Male	31 (52%)
Females	29 (48%)
Profession	
House wife	24 (40%)
Indoor office job	21 (35%)
Outdoor job	8 (13.3%)
Labourer	4 (6.6%)
Unemployed	3 (3.3%)
Level of Discomfort	
Mild	5 (8.3%)
Moderate	50 (83.3%)
Severe	5(8.3%)
Effect on social life	33 (55%)
Straining while defection	
No	3 (5%)
Seldom	16 (26.6%)
Often	32 (53.3%)
Always	9 (15%)
Duration of pain after defecation	
0.5 hour	11(19%)
0.5-2 hours	14 (23%)
2-6 hours	25 (41%)
>6 hours	10 (17%)
Number of meals per day	
Two	44 (73.3%)
Three	12 (20%)
Four	4 (6.6%)
Quantity of fiber	
Low	44 (73%)
High	16 (27%)
Quantity of fluid	
Less than one	13 (22%)
1-2 Liters	34 (58%)
3 or more Liters	12 (20%)
Previous treatment	39 (65%)

Table-2: Comparison of outcome variables between Diltiazem and GTN group.

Variable	Diltiazem (n=30)	GTN (n=30)	p-value
Early Symptomatic relief			
No	1 (3.2%)	2 %6.4%)	
Fair	6 (20%)	12 (40%)	
Good	8 (26.6%)	11 (36.6%)	0.01
Excellent	15 (50%)	5 (16.6%)	
Side Effects			
Headache	0	12	
Nause/vomiting	1	1	0.01
Local irritation	2	1	
Cost of treatment (Rupees)	1464±425	1302±705	0.28

GTN: Glyceryl TriNitrate.

patients were noted (Table-1). The median period of suffering was 60 days and about 39 (65%) patients had received prior treatment. Most of the patients 44 (73.3%) reported to have two meals a day, low fluid 47 (78%) and fibre intake 44 (73%). Discomfort caused by anal fissure affected social lives of 32 (53.3%) patients.

Patients, who used Diltiazem reported more symptomatic relief than GTN, with excellent relief in 15 (50%) compared to 5 (16.6%) (p=0.01) (Table-2). Side effects were found more in GTN than Diltiazem and most common side effect in the GTN group was headache in 12 (40%). Despite the side effects, all the patients completed the two-week treatment. Cost of the treatment was comparable between both treatment arms and was not statistically significant (p=0.28%).

Discussion

The randomised clinical study, conducted at a tertiary care hospital of a low-income country, reported higher early symptomatic relief by Diltiazem in anal fissure compared to GTN with significantly less side effects and comparable cost.

Chronic anal fissure may be treated by chemical or surgical sphincterotomy at present. Lateral sphincterotomy results in healing for up to 95% patients. However, there remains a significant risk of incontinence.[6] A recent Cochrane review explored the issue and concluded that surgical therapy was superior to all chemical sphincterotomy agents in the achievement of long-term healing. However, the surgical therapy was associated with risk of incontinence unlike chemical sphincterotomy agents.[7] Apart from the risk of incontinence, the procedure is costly and also carries surgery-related risks. These factors preclude surgery from being the first-line therapy, particularly in low-income countries. So, particularly in such situations, surgery should be a second line therapy reserved for fissures resistant to chemical sphincterotomy.

GTN has remained the standard for chemical sphincterotomy against which other newer treatments have been compared. With GTN, healing has been reported in 45-80 per cent of the patients.[6,8-11] However, significant side effects such as headaches, tachyphylaxsis and occasional loss of flatus control have been reported. Research for a new agent for chemical sphincterotomy will, therefore, have to answer three questions, i.e. does it work? Is it safe? For how long does their effect last?

Our study addressed first two questions. In our study, excellent symptomatic relief at two weeks was reported by 50% on Topical Diltiazem and good to fair relief in further 46.6% patients. This clearly indicated that Diltiazem significantly reduced patient discomfort and facilitated healing of fissure in up to 96% of the patients. Similar results have been reported by other studies. A recent systemic review published during the conduct of our trial reported that healing rate with Diltiazem was equal to GTN, but with fewer side effects and recurrences.[12] Therefore, it recommended Diltiazem to be preferred over GTN. Diltiazem has shown equal efficacy to other chemical sphincterotomy agents i.e. Botulinium toxin.[13]

Diltiazem is associated with fewer side effects as compared to GTN.[14] Most commonly reported side effect of GTN is headache, which at times becomes too notorious to continue with it. Hence this becomes one of the reasons for discontinuation and reported low efficacy of GTN in anal fissures.

This study has some limitations. Firstly, simple randomisation technique was used, which technically is predictable. Secondly, the clinic-based randomisation may affect the results due to different practices, thresholds and prescription variations of different surgeons. Thirdly, it provides only short-term i.e. two-week follow-up of only subjective symptomatic relief. Although there is no validated scale to assess the healing of fissures, but objective examination can provide surrogate information regarding healing.

Conclusion

Chemical sphinterotomy with topical 2% Diltiazem ointment is an effective first-line treatment for early symptomatic relief of anal fissures. The current study reports its superiority over GTN owing to negligible side effects and better symptomatic relief.

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