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Original Research Article

Topical diltiazem versus topical glyceryl trinitrate in the treatment of chronic anal fissure: a prospective comparative study

Venkatesh S., Srinivas B. Kulkarni*, Kruthi S. R.

Department of General Surgery, Rajarajeswari Medical College and Hospital, Bengaluru, Karnataka, India

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***Correspondence:**
Dr. Srinivas B. Kulkarni,
E-mail: drsrinivasbk2000@gmail.com

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ABSTRACT

Background: Acute anal fissure (AAF) heals spontaneously with conservative line of treatment. Chronic anal fissure (CAF) needs either traditional surgical lateral sphicterotomy or chemical sphincterotomy with topical agents. The present study aims at the effectiveness of topical diltiazem (DTZ) cream over topical glyceryl trinitrate (GTN) ointment in the treatment of chronic anal fissure.
Methods: A total of 100 patients with CAF were included in this comparative prospective study conducted in Rajarajeswari Medical College and Hospital Bengaluru from July 2017 to December 2018. Eligible patients were randomly assigned to one of the two treatment groups of 50 patients each and were advised to apply 2% DTZ cream or 0.2% GTN ointment by fingertip to the anal verge twice daily for 8 weeks. The results were analysed and compared on two weekly intervals to know the effectiveness of treatment. P value of <0.05 is considered to be significant.
Results: Complete healing of the fissure occurred in 80% of the patients in DTZ group against 76% in the GTN group by the end of 6 weeks (p>0.05, statistically not significant). Mild headache was experienced by 14% of the patients in the DTZ group, while 46% of the cases in the GTN group reported about the same (p<0.05 statistically significant).
Conclusions: Topical 2% DTZ appeared to be well tolerated and effective preferred first-line method of chemical sphincterotomy with less side effects for chronic anal fissure.

Keywords: Anal fissure, Acute anal fissure, Chronic anal fissure, Chemical sphincterotomy, Glyceryl trinitrate, Diltiazem hydrochloride

INTRODUCTION

Anal fissure (AF) is a linear tear in the anal canal, which is distal to the dentate line [1] and it causes considerable morbidity.[2] Acute anal fissure is significantly more common than the chronic form. Anal fissure is common, occurring mostly between the second and fourth decades of life with a lifetime incidence of 11%, and the frequency is approximately equal between men and women.[3,4]

An acute anal fissure (AAF) usually heals spontaneously or with the use of simple measures like high fiber diet with adequate water intake.[5] Chronic anal fissure (CAF) is associated with persistent hypertonia and spasm of the internal anal sphincter.[6] Surgical division of the internal anal sphincter is the traditional treatment of chronic anal fissures, but this causes significant short and long-term morbidity with incontinence rates of up to 30%.[7]

Chemical sphincterotomy is attempted using a variety of agents. The agents used for the same are glyceryl

trinitrate (GTN), botulinum toxin, nifedipine, diltiazem hydrochloride (DTZ) and bethanechol.[8,9]

Topical GTN lowers the anal sphincter pressure and heals anal fissures, but a majority of patients experience headache.[10] The internal anal sphincter has a calcium dependent mechanism to maintain its tone. It is, therefore, possible to lower anal sphincter pressure using calcium channel blocker such as DTZ with fewer side effects.[11-14]

METHODS

This study was conducted in surgery outpatient department of Rajarajeswari Medical College and Hospital Bengaluru from July 2017 to December 2018 for a period of 18 months. 100 patients with CAF were included in this comparative prospective clinical study after clearance from the ethical committee of the college.

A written informed consent was taken from the patients and they were given an option to pull out from the study at any point of time, if they wished to do so. All patients underwent a detailed pretreatment evaluation that included history, general physical examination, clinical inspection of the fissure.

CAF was defined as anal symptoms lasting for more than 8-12 weeks, with horizontal muscle fibers showing at the fissure base and/or the presence of a sentinel tag.

Patients with AF secondary to other diseases like inflammatory bowel disease, malignancy, sexually transmitted diseases, previous treatment with local ointment or surgery; patients who needed anal surgery for any concurrent disease like hemorrhoids, pregnant women and patients with significant cardiovascular conditions were excluded from the study.

Eligible patients were randomly assigned to one of the two treatment groups of 50 patients each. Patients were advised to apply a pea size (approx. 250 mg) quantity of 2% DTZ cream or 0.2% GTN ointment by fingertip to the anal verge twice daily for 8 weeks.

Patients were followed up for 8 weeks on a two weekly basis and those who did not respond to the treatment were offered lateral internal sphicterotomy.

Pain, healing and side-effects were rerecorded. The severity of pain was assessed using visual analogue scale. Side-effects such as headache, nausea, vomiting, diarrhea, perianal itching were analyzed statistically.

Statistical evaluation

The study data were analyzed to evaluate the effect of topical DTZ cream over topical GTN ointment in the treatment of CAF. SPSS software and Microsoft Excel software are used in this analysis. Chi-square test is used to evaluate the results and p value of <0.05 is considered to be significant

RESULTS

100 patients with CAF were included in this study. 50 patients were randomly assigned to receive 2% DTZ cream and 50 patients 0.2% GTN ointment. All the patients in both the groups completed the full 6 weeks course of the treatment.

In this study, the ages of the patients were similar in both the groups with mean age of 38yrs in DTZ group and 36yrs in GTN group. Of which 48% were men and 52% were women in DTZ group where as 54% were men and 46% were women in GTN group.

Pain was the main presenting symptom in both the groups accounting to 94% and 98% in DTZ group and GTN group respectively. Apart from pain; bleeding, discharge, pruritis and constipation were other symptoms which made patients to visit surgical outpatient department. The incidence of symptoms is as follows pain>>bleeding>> discharge/pruritis>>constipation.

Table 1: Patient demography, symptoms and local findings.

Variables	DTZ (n=50)	GTN (n=50)
	N (%)	N (%)
Demography		
Male	24 (48)	27 (54)
Female	26 (52)	23 (46)
Mean age (in years)	38	36
Symptoms		
Pain	47 (94)	49 (98)
Bleeding	40 (80)	42 (84)
Discharge/pruritis	34 (68)	33 (66)
Constipation	26 (52)	31 (62)
Local findings		
Posterior midline fissure	40 (80)	43 (86)
Anterior midline fissure	7 (14)	5 (10)
Both ant and post fissure	3 (6)	2 (4)
Skin tag	35 (70)	37 (74)
Sphincter spasm	46 (92)	47 (94)

DTZ- 2% Ditiazem Hydrochloride, GTN – Glyceryl trinitrate.

The data for categorical variables are given in numbers with percentages in brackets.

Posterior midline fissure was the commonest location and in most of the cases, 80% in DTZ group and 86% in GTN group. Skin tag noted at the base of the fissure in 70% of DTZ group and 74% of GTN group. Sphincter spasm was a prominent finding in both the groups, 92% and 94% in DTZ group and GTN group respectively (Table 1).

At the end of the 2nd, 4th and the 6th weeks, both the groups variable parameters were evaluated and compared. The parameters considered for comparison were fissure healing, pain response, bleeding response, discharge and peri-anal itching and side effects - headache, perianal itching and GI symptoms.

Complete healing of the fissure occurred in 80% of the patients in DTZ group against 76% in the GTN group by the end of 6 weeks (p>0.05, statistically not significant).

Table 2: Fissure healing.

Fissure healing	DTZ (n=50)	GTN (n=50)
	N (%)	N (%)
At 2nd week end	1 (2)	2 (4)
At 4th week end	32 (64)	30 (60)
At 6th week end	40 (80)	38 (76)

The pain relief is significant in both the groups which is comparable and which is attained by the end of 4th week. There was a significant reduction in bleeding, discharge and perianal pruritis in both the groups by the end of 6th week (Table 2).

Table 3: Adverse effects of medicine.

Side effect	DTZ (n=50)	GTN (n=50)
	N (%)	N (%)
Headaches	7 (14)	23 (46)
Perianal itching	3 (6)	2 (4)
Nausea, vomiting and diarrhea	7 (14)	8 (16)

DTZ- 2% Ditiazem hydrochloride, GTN – Glyceryl trinitrate.

Mild headache was experienced by 14% of the patients in the DTZ group, while 46% of the cases in the GTN group reported about it (p<0.05 statistically significant). All of them responded to paracetamol. Perianal itching was another side effect which was reported by 6% of the cases from the DTZ group as compared to 4% in the GTN group. The pruritis was mild and it didn't require any treatment. GI symptoms such as nausea, vomiting and diarrhea were experienced by 14% of DTZ group as compared to 16% of GTN group (p>0.05 statistically not significant) (Table 3).

DISCUSSION

The treatment of chronic anal fissure has shifted in the recent years from surgical to medical modalities because of disability and the risk of incontinence associated with surgery. Chemical sphincterotomy can be done using a variety of agents. A first line use of medical therapy cures most CAF economically and conveniently.[15] Topical GTN remains the standard chemical sphincterotomy agent against which other newer treatments are compared. Controlled clinical trials have shown varied results of healing ranging from 45-80% with topical GTN.[16,17] However, side-effects such as headaches and dizziness are common with GTN, which may limit their application and reduce patient compliance.[16]

This study has shown same rates of healing for both topical GTN and DTZ with no significant difference between them. Side-effects are less with DTZ, a finding also reported by other studies.[11-14]

Studies also showed that topical DTZ is an effective and safe treatment for CAF in patients who have failed topical GTN and need for sphincterotomy can be avoided in upto 70% of cases.[13,18,19] It was found that the combined effect of GTN and DTZ was greater than the effect of either agent alone.

Nifedipine and DTZ are calcium channel blockers which act by blocking the slow L-type calcium channels in the smooth muscle, thus causing relaxation.[1] A number of studies have reported fissure healing in 60% to 75% of the cases with topical diltiazem.[6,19] Carapeti et al, and Knight et al, observed a fissure healing rate of 67% and 73% respectively in their studies.[1,6]

The topical DTZ cream causes less headache and fewer side effects than the GTN ointment, without a significant difference in the healing rates between the two agents.[6] Also, the recurrence rate has been known to be lower with topical diltiazem.[14,18]

Surgery can be used for failures of pharmacological treatment or fissures that recur frequently after cessation of local treatment.

CONCLUSION

To conclude, CAF healing was found in 80% of the cases who received topical DTZ. The duration of the treatment was quite long with topical agents hence causing less patient compliance. Topical 2% DTZ appeared to be well tolerated and effective preferred first-line method of chemical sphincterotomy with less side effects.

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