

RESEARCH ARTICLE

Value Assessment of Local Treatment (Diltiazem Hydrochloride gel/vs Glycerile Trinitrite ointment) in acute Anal Fissure

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Received: 07th July, 2022; Revised: 13th August, 2022; Accepted: 09th September, 2022; Available Online: 25th September, 2022

ABSTRACT

Background: Anal fissure is a linear tear in the distal anal canal, associated with spasm of internal anal sphincter. Acute anal pain with bleeding on defecation are the main symptoms. Different types of chemical treatment to relax the sphincteric muscles have tried.

Objective: Assess the efficacy, side effects and recurrence rate of 0.2% glycerile trinitrate ointment (GTN) and 2% diltiazim hydrochloride gel (DTZ) in treatment of acute anal fissure.

Methods: A prospective randomized trial of 112 patient with acute anal fissure over 1.5 years period at Al-Kindy Teaching Hospital. The diagnosis was entirely clinical. Setting of inclusion and exclusion criteria, ethical consideration respected. Two groups of patients submitted randomly to either 0.2% GTN ointment or 2% DTZ gel twice daily for 8 weeks. Correct pain score by the patient every day, follow up to the end of week 1, 2, 8 and at 6 months. Scientific signs of healing assessed blinded to the mode of treatment. The collected data was analyzed and compared.

Results: Complete fissure healing was observed in (83.3%) of the DTZ group and (76%) of the GTN group. Pain response was better in DTZ than GTN patients were. Side effects had reported. The recurrence rate was (15%) in DTZ group and (30%) in GTN after 6 months follow up.

Conclusion: Topical Diltiazem is greater than Glyceryl trinitrate in managing acute anal fissure with low side effects and reappearance rate.

Keywords: Diltiazem HCl, Glyceryl trinitrate, Fissure-in-ano, Local treatment.

International Journal of Drug Delivery Technology (2022); DOI: 10.25258/ijddt.12.3.28

How to cite this article: Hassan, HA, Obeid, LM, Aldahash, AAM. Value Assessment of Local Treatment (Diltiazem Hydrochloride gel/vs Glycerile Trinitrite ointment) in acute Anal Fissure. International Journal of Drug Delivery Technology. 2022;12(3):1093-1096.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

An anal fissure is a slash in the anoderm that may end in an ulcer in the long axis of the anal canal. The ulcer typically extend to the circular ring muscle (internal anal sphincter).^{1,2} The fissure is described as acute if it has been present for less than six weeks, or chronic if present for more than 6 weeks.³ Once the fissure develops, the internal anal sphincter goes to spasm, cause further separation of tear, impairing blood supply to the fissure (which impair healing) and causing pain.³⁻⁵ Exposure to faeces also slows healing.³ It affects people of all ages, both genders, and about 50% of people in the age range of 20–50 years expressed fissure symptom at least once in their lifetime.² The classical symptoms are anal pain during or after defecation, the sensation of tearing, ripping or burning can last

for several minutes to hours accompanied by passage of bright blood per rectum. The bleeding separated from the stool and usually scanty.⁶ Anal fissure are usually caused by trauma that affects anal canal, such as after passage of large or hard stool or explosive diarrhea, less commonly fissure are caused by foreign body insertion or anal intercourse.⁴ Anal fissure can also occur in patients with other medical conditions such as crohn's disease.⁴ There are several agents used to reducing anal sphincter spasm like Glyceryl trinitrate (TGN) and Diltiazem hydrochloride (DTZ).^{7,8} The ischemic nature of acute anal fissure due to high resting anal sphincter pressure, so local treatment of agent may improve blood supply to the affected anoderm and thus enhancing healing.⁹ These agents as GTN ointment (0.2%) (relaxing smooth muscle artery) and DTZ

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Table 1: Clinical details of the 2 groups

| Character | DTZ group (n.60) | GTN group (n.52) |
|--------------|------------------|------------------|
| Pain | 57 (95%) | 49 (94.2%) |
| Bleeding | 50 (83.3%) | 44 (84.6%) |
| Constipation | 42 (70%) | 41 (78.8%) |

gel (2%) (act as calcium channel blocker agent) relaxing the internal sphincter thus increases blood supply and encourage fissure healing.¹⁰ This drug (DTZ) was primarily used for treatment of hypertension, main side effects are headache, dizziness, and faintness are noted in several cases. The patient may suffer from severe headache and various allergic reactions such as itching, swelling of lips, throat, or tongue and difficulty in breathing.¹⁰ Study aims to assess the efficacy, side effects and recurrence rate of 0.2% glycerile trinitrate ointment (GTN) and 2% diltiazim hydrochloride gel (DTZ) in treatment of acute anal fissure.

METHOD

A prospective, double-blinded, randomized controlled clinical trial carried out during the period (July 2016-December 2017) in Al-kindy Teaching Hospital, [affiliated with Al-kindy College of Medicine University of Baghdad]. The research sample was 112 patients, referred to the surgery clinic of our hospital, with acute anal pain, diagnosed as an acute fissure, after taking patient history and physical examination (inspection of an ulcer in the anoderm with an absence of a sentinel tag). A format papers filled. Patients with inflammatory bowel disease, perianal fistula, anal cancer, tuberculosis, pregnant, lactating, or wishing to become pregnant, patients with significant cardiovascular conditions, haemorrhoidectomy in the previous year and migraine excepted. Pain of anal with ulcer for 6 weeks and less, and vague sentry acute anal fissure, while pain with a non-healing ulcer > 8 weeks was taken as chronic anal fissure “nonetheless of attendance or nonappearance of the sentry tag”. Patients with earlier management for the fissure were included if the end of treatment was 3 months before inclusion (washout period is more than 3 months). Patients aged between ≥ 18 years and ≤ 65 years are included in the study. Group A take 0.2% Glyceril trinitrate GTN cream and Group B take 2% Diltiazem hydrochloride (DTZ) lotion. A visual analogue scale VAS for pain' scorecard was devised. Compliance is single-minded by subjective examination follow-up decided at the finish of weeks 1, 2, 8 and at 6 months. The primary consequence extent was clinical therapeutic at the 8-weeks follow-up. The secondary consequence quantity was the deterioration of the fissure at 24 weeks (6 months). Patients whose fissures had not cured next management with one interference offered the other or operating management. The collected data was analyzed by SPSS version 20 statistical software. Description of data based on their distribution performed by statistical parameters. The analyzed test applied include t-test, Mann-Whitney u test. The significance level was set at $p < 0.05$.

Table 2: Local finding of anal fissure in the two groups

| Local findings | DTZ group (n.60) | GTN group (n.52) |
|---------------------------------|------------------|------------------|
| Posterior midline acute fissure | 51(85%) | 41(78.8%) |
| Anterior midline acute fissure | 9(15%) | 11(21.2%) |

Table 3: Fissure healing in DTZ group and GTN group.

| Fissure healing duration | GTN (n.52) | DTZ (n.60) | p-value |
|--------------------------|------------|------------|----------|
| 1 weeks | 6 | 4 | |
| 2 weeks | 20 | 32 | |
| 8 weeks | 35(67.3%) | 50(83.3) | < 0.0001 |

Table 4: Side effects in both groups.

| Side effects | GTN group(n.52) | DTZ group(n.60) | p-value |
|--------------|-----------------|-----------------|-----------------|
| Headache | 30(57.6%) | 10(16.6%) | 0.0001 |
| Pruritus | 12(23%) | 7(11.6%) | Not significant |
| Hypotension | 3(5.7%) | 0(0%) | Not significant |
| Total (%) | 45 (86.5%) | 17 (28.3%) | < 0.0001 |

Table 5: Recurrence in DTZ and GTN group after 6 months

| | GTN group(N.30) | DTZ group (N.40) |
|---------------------------------|-----------------|------------------|
| No. of patients with recurrence | 9 (30%) | 6 (15%) |

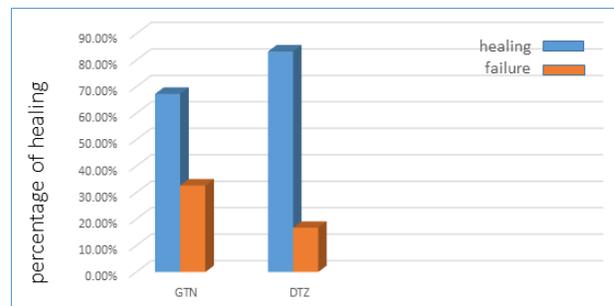


Figure 1: Histogram of fissure healing and failure in GTN and DTZ groups.

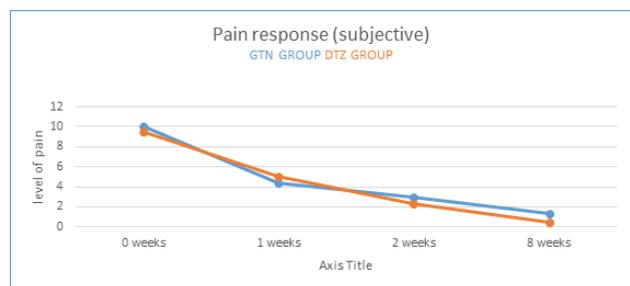


Figure 2: Level of pain in the 2 groups

RESULTS

Out of 130 patients had an anal fissure, about 18 patients were excluded because patients unfit due to associated comorbidities (exclusion criteria) (diabetes mellitus (DM), pregnancy, cardiovascular disease etc.). 112 patients were enrolled in our study, 60 patients (53.5%) were male and 52 patients (46.5%) female. An entire of 112 patients were two groups, group A and group B, age range 18–65 years, with an average 32.3 years. Pain symptom followed by hemorrhage per rectum (Table 1); posterior midline fissure was the most common location (Table 2).

Follow-up after 1, 2, and 8 weeks from start of the treatment reveals complete fissure healing was observed in 35 patients (67.3%) of GTN group and 17 patients (32.7%) show incomplete healing, while 50 patients (83.3%) in DTZ group show complete healing and 10 patients (16.7%) show not complete healing; (p value <0.0001) as shown in Table 3 and Figure 1.

The pain alleviation was better in DTZ group patients as shown in Figure 2.

Regarding the complications that developed following the treatment, 30 patients (57.6%) developed headache in GTN group, while 10 patients (16.6%) developed headache in DTZ group (p -value <0.0001), the other complications (pruritus and hypotension) are not significant as shown in Table 4.

Five patients of 35 fissure healers in GTN group and 10 patients of 50 fissure healers in DTZ. Group did not turn up for follow up, while the rest complete the full 6 months follow up. Table 5.

Recurrence rate observed in 6 (15%) patients in DTZ group compared with 9 (30%) patients in GTN group (p -value <0.05).

DISCUSSION

Over the past years, various hypotheses have been presented regarding the development of anal fissures. Anal trauma to internal sphincter hypertonia and resultant local ischemia, which end in non-healing, have postulated as the contributing factors.⁶ Anal fissure is a slit in the lining of the distal anal canal,⁸ the most common cause of anal pain.⁷ The typical symptoms of anal fissure are anal pain during defecation associated with passage of bright red blood per rectum.⁸ The pain may be so severe that the patient delays defecation for days which leads to the hardening of stools, which worsens the condition. Many treatment options are available for anal fissures including pharmacological and surgical interventions. Whatever the mode of treatment, the principal aim is to decrease the tone of the internal anal sphincter that increases local blood flow, subsequently leading to healing. Pharmacological agents employed include nitrates (isosorbide dinitrate or glyceryl trinitrate), calcium channel blockers (nifedipine, diltiazem), and Botulinum toxin and alpha adrenoreceptor antagonists.⁷ Calcium channel blockers blocking the sluggish L-type channels, causing smooth muscle lessening.⁸ Topical GTN has been widely used as non-surgical treatment for anal fissure.¹¹ It is potent nitric oxide donor¹²

and it had believed that nitric oxide is a neurotransmitter mediating the relaxation of internal sphincter.⁸ The healing rate in the present study is 67.3% of GTN-group and 83.3% of DTZ-group. In the study done by Suvarna *et al.*¹³ the healing rate is comparable to our result regarding GTN-group (68.23%), while DTZ-group was (71.87%). While in a global study done by Pravid J. Gupta,⁷ with large sample of acute anal fissure, 75% was the rate of healing in DTZ-group. The complications in the present study following DTZ is much less than GTN (28.3%, 86.5 resp), A global study by Carapecci *et al.* (14) shows (22%) headache in GTN group, Knight *et al.*¹⁵ showed (1%) headache in DTZ group; in Ahmed J. *et al.*¹⁶ pruritus in GTN group was (8%), while pruritus in DTZ group of Nelson RL17 *et al.* was (16%) while in our study was (11.6%). In the present study, hypotension was (5.7%) in GTN group, while no such event was reported in DTZ-group, A global study by Novell F. *et al.*¹⁰ showed (4%) hypotension in GTN-group, which is comparable to our study. While not reported in the DTZ- group in the study by Nelson R.¹⁸ Most studies on the pharmacological treatment of acute anal fissure show Some variations are there because of the sample size or patients criteria enrolled in the study. Pardhan.¹⁹ stated that the recurrence rate in GTN-group is more than in the DTZ group of patients, (40%, 15% resp.) comparable to the present study after 6 months of follow up treatment.

CONCLUSION

Both (0.2%) GTN ointment and (2%) DTZ gel are quietly effective in treating acute fissure in anus. However, topical DTZ gel is superior to topical GTN ointment, better tolerated with few side effects and recurrence rate.

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