

## Outcomes of non-surgical treatment of chronic anal fissure: A comparative study

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Azhy Muhammed Dewana<sup>1</sup> Baderkhan Saeed Ahmed<sup>1</sup> Ahmed Abdulkadir Baban<sup>1</sup> Rawand Musheer Haweizy<sup>1\*</sup>

### Abstract

**Background and objective:** Chronic anal fissure is a common health problem related to high morbidity. The chemical option for treating chronic anal fissures is highly preferred.

**Methods:** A clinical prospective comparative study was carried out in the General Surgery Outpatient Department in Rizgary Teaching Hospital, Erbil, KRG, during the period from January 2019 to December 2021, on a sample of 100 patients randomly recruited patients with chronic anal fissures divided into two groups with 50 participants each: the DTZ group, who received 2% diltiazem ointment, and the GTN group, who used 0.2% glyceryl trinitrate ointment twice daily for 6 consecutive weeks. The aim of the study is to compare the efficacy and effects of topical Diltiazem (DTZ) and topical glyceryl trinitrate (GTN) in the management of chronic anal fissures.

**Results:** There was a highly significant association between fissure healing at the 4th week and patients treated with DTZ ( $P < 0.001$ ). A highly significant association was observed at the 6th week between fissure healing and DTZ treatment ( $P < 0.001$ ), while there was later a highly significant association between fissure healing at the 8th week and patients treated with GTN ( $P < 0.001$ ). A significant association was observed between treatment adverse effects and patients treated with GTN ( $P = 0.05$ ). DTZ was found to be more effective for symptomatic relief than GTN.

**Conclusion:** Both DTZ and GTN are effective in the treatment of chronic anal fissures, but treatment with DTZ is accompanied by faster healing and lower side effects.

**Keywords:** Non-surgical treatment; Chronic anal fissure; Diltiazem.

### Introduction

A chronic anal fissure (CAF) is a tear in the epithelial tissue of the anoderm that has been there for at least 6 weeks. Most fissures occur at the midline, toward the person's back, where raised edges and scarring at the fissure base distinguish it from an acute anal fissure, which would look like a fresh wound.<sup>1</sup> Acute anal fissure usually heals within 6 weeks, otherwise, it becomes chronic, in which phase the ulcer enlarges in size. Females are more frequently affected than males, by a ratio of around 58% to 42%. Most patients are aged in their 30s, but fissure could happen at any age, and is well known as a cause of pain and constipation in children.

The pathogenesis of endodermal fissure is still not completely elucidated, but it is likely to be multifactorial. CAF is presumed to be ischemic ulcers, enhanced by sphincter hypertonia.<sup>2</sup>

The healing process is obstructed by fibrosis, provoked by repeated mechanical injuries and chronic inflammation.<sup>1</sup> The passage of hard faeces, previous anal surgery trauma, and infection may be causative factors.<sup>3</sup> Increased maximum resting anal canal pressure and decreased anal blood flow in the posterior midline are considered causative factors, and the diverse possibilities involved have led to the introduction of several medical approaches.<sup>3,4</sup> Edema around the fissure

<sup>1</sup> Department of Surgery, College of Medicine, Hawler Medical University, Erbil, Iraq.

Correspondence: rawand.haweizy@hmu.edu.krd

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may occur, and could be accompanied by an anal sentinel tag and hypertrophied anal papilla proximal to the fissure.<sup>2</sup>

Atypical fissures, usually in the lateral positions, should raise the possibility of other associated diseases, such as Crohn's disease, tuberculosis, syphilis, AIDS, or malignancy. An anal fissure is most often manifest with unbearable anal bleeding and pain during defecation.<sup>2</sup> Patients in general describe a prior episode of constipation. Digital and anoscope examination may result in excruciating pain and is relatively contraindicated.<sup>4</sup> The surgical dissection of the internal anal sphincter is a common treatment change of CAF; although, it is associated with many co-morbidities and higher recurrence rates (reaching about 30%). Chemical sphincterotomy is applied by using many agents like glyceryl trinitrate (GTN), diltiazem (DTZ), botulinum toxin, nifedipine, and bethanechol, which act by lowering anal sphincter pressure.<sup>5,6</sup> GTN is a nitric oxide donor which contributes to internal anal sphincter relaxation via a non-adrenergic non-cholinergic pathway.<sup>6</sup> The posterior location of many anal fissures is related to the scarcity of posterior arteriolar anastomoses.<sup>7</sup> DTZ (calcium-channel blockers) is a peripheral and coronary vasodilator agent with a limited negative inotropic activity that prevents cardiac conduction, particularly at the sinoatrial and atrioventricular nodes. It causes smooth-muscle relaxation by blocking slow L-type calcium channels, thus preventing the influx of calcium into the smooth muscle cell and decreasing intracellular calcium concentration.<sup>7</sup>

The ischemic nature of CAF due to maximum resting anal sphincter pressure necessitates local, topical treatment, including GTN. DTZ may improve blood perfusion to the affected anoderm, and thus improve healing.<sup>3</sup> Albeit surgical sphincterotomy heals most fissures, it has a high risk of causing permanent or temporary anal incontinence.<sup>4,8</sup>

Patients are encouraged to use medical and conservative treatment, including GTN

and DTZ, with no fear of incontinence.<sup>9</sup> Topical GTN decreases the maximum anal sphincter pressure and heals anal fissures, but the vast majority of patients report headaches as a side effect.<sup>10</sup> The use of calcium channel blocker to lower the anal sphincter pressure has a great impact with fewer side effects, due to the anal sphincter using a calcium-dependent mechanism to preserve its tone.<sup>11</sup>

## Methods

### Study design and settings

The current study design is a clinical prospective study, carried out in the General Surgery Outpatient Department in Rizgary Teaching Hospital, Erbil, during the period between January 2019 to December 2021.

### Study population

The study population comprised all patients referred to the study setting with anal pain and a history of non-healing anal fissures of more than 6-8 weeks.

### Inclusion criteria

Patients aged between 18 to 60 years with the presence of anal fissure for more than 8 weeks that had failed to heal with conservative measures, such as analgesics, laxatives, and a high-fiber diet. Characteristics of chronicity, include indurated edges, sentinel skin tag, and exposed horizontal fibers of the anal sphincter on the floor.

### Exclusion criteria

- Patients with associated piles, fistula, and abscesses.
- Pregnancy and lactation.
- Migraine.

### Sampling

The sample consisted of 100 patients with CAF presented to the study setting, subject to eligibility as per the inclusion and exclusion criteria. 100 eligible patients were randomly allocated into two groups of 50 patients each who received ointment daily over 8 consecutive weeks: one group received 2% DTZ ointment, and the other received 0.2% GTN ointment.

**Data Collection**

Patients’ data were collected directly from them using a prepared questionnaire designed by the researchers, with sections on demographic characteristics (age and gender); symptoms (including pain, bleeding, discharge, and constipation); local findings (posterior midline, anterior midline, or both) and skin tags; fissure healing (at second, fourth, sixth, or eighth weeks); and adverse effects (if found), such as headache, perianal pain, nausea, vomiting, and diarrhoea.

**Patient assessment**

Instruction was given to apply the topical GTN or DTZ with a fingertip-sized portion of ointment applied to the anal verge. All patients were encouraged to keep warm and to have a high-fiber diet with good hydration. They were followed up every fortnight over the course of 8 weeks, and then at 2-month intervals during assessment in each visit to keep an accurate record of healing, pain, and side effects recorded. “Healing” was operationally defined as the total disappearance of the fissure on examination. The term “recurrence” refers to the fissure reappearing at the same anatomical location within a month after a 6-week course of topical application of GTN or DTZ.

**Ethical considerations**

Ethical approval to conduct this study was granted by the Ethical Committee of Hawler Medical University, College of Medicine. All participants were informed in full of the voluntary nature of participation and their right to withdraw at any time without giving a reason, and that all their data would be treated confidentially, with no personally identifying information being reported.

**Statistical analysis**

Patient data were analyzed using Microsoft Excel and the statistical package for social sciences (SPSS, version 23). Outcomes of analysis were arranged in categorical variables. The Chi-square test and Fisher’s exact tests were used for categorical variables. A *P* value of 0.05 or less was regarded as significant.

**Results**

As 100 patients participated in the study, numerical and percentage values are interchangeable when reporting patient data. More patients were male (66%) than female (34%), with a male-to-female ratio of 2:1. Their mean age was 34. 2±2. No significant differences were observed between CAF patients treated with DTZ or GTN in terms of age (*P* = 0.200) or gender (*P* = 0.600) (Table 1).

**Table 1** Study groups’ demographic characteristics.

Variable	Study groups				P-value
	DTZ		GTN		
	No.	%	No.	%	
<b>Age (years)</b>					0.200*
20-29	14	(28.0)	9	(18.0)	
30-39	36	(72.0)	41	(82.0)	
<b>Gender</b>					0.600*
Male	34	(68.0)	32	(64.0)	
Female	16	(32.0)	18	(36.0)	
Total	50	(100.0)	50	(100.0)	

\* Chi-square test

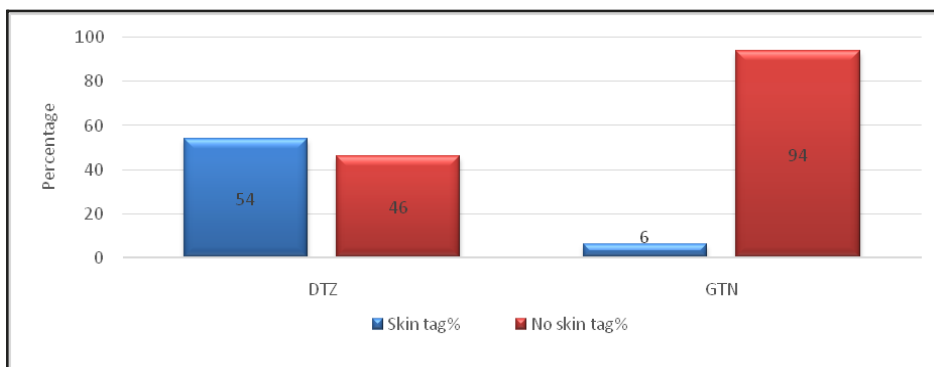
There was a significant association between the pain CAF symptom and patients treated with GTN ( $P = 0.01$ ); 100% of CAF patients treated with GTN had pain symptoms, while 88% of patients treated with DTZ did. A significant association was observed between the bleeding CAF symptom and patients treated with GTN ( $P = 0.02$ ); 88% of CAF patients treated with GTN had a bleeding symptom, while 70% of patients treated with DTZ had it. There was a significant association between discharge/pruritus CAF symptoms and patients treated with DTZ ( $P = 0.005$ ); 70% of CAF patients treated with DTZ had discharge/pruritus symptoms, while 42% of patients treated with GTN had discharge/pruritus symptoms. A significant

association was observed between constipation CAF symptoms and patients treated with GTN ( $P = 0.006$ ); 94% of CAF patients treated with GTN had constipation symptoms, while 74% of patients treated with DTZ had constipation symptoms (Table 2). No significant differences were observed between CAF patients treated with DTZ or GTN regarding posterior midline fissures as all patients had posterior midline fissures. There was a highly significant association between the skin tag finding of CAF and patients treated with DTZ ( $P < 0.001$ ); 54% of CAF patients treated with DTZ had a skin tag, compared to only 6% of patients treated with GTN (Figure 1).

**Table 2** Distribution of CAF symptoms according to study groups.

Variable	Study groups				P
	DTZ		GTN		
	No.	%	No.	%	
<b>Pain</b>					0.010*
Yes	44	(88.0)	50	(100.0)	
No	6	(12.0)	0	-	
<b>Bleeding</b>					0.020**
Yes	35	(70.0)	44	(88.0)	
No	15	(30.0)	6	(12.0)	
<b>Discharge/pruritus</b>					0.005**
Yes	35	(70.0)	21	(42.0)	
No	15	(30.0)	29	(58.0)	
<b>Constipation</b>					0.006**
Yes	37	(74.0)	47	(94.0)	
No	13	(26.0)	3	(6.0)	
<b>Total</b>	50	(100.0)	50	(100.0)	

\* Fisher's exact test, \*\*Chi-square test.



**Figure 1** Distribution of skin tags according to study groups.

No significant differences were observed between CAF patients treated with DTZ or GTN regarding fissure healing at 2<sup>nd</sup> week, as all patients had no fissure healing at this point. There was a highly significant association between fissure healing at the 4<sup>th</sup> week and patients treated with DTZ (26%,  $P < 0.001$ ). A highly significant association was observed between fissure

healing at the 6<sup>th</sup> week and patients treated with DTZ (30%,  $P < 0.001$ ). There was a highly significant association between fissure healing at the 8<sup>th</sup> week and patients treated with GTN ( $P < 0.001$ ); 100% of patients treated with GTN had fissure healing at the 8<sup>th</sup> week, while only 44% of patients treated with DTZ had fissure healing at that time point (Table 3).

**Table 3** Distribution of fissure healing according to study groups.

Variable	Study groups				P
	DTZ		GTN		
	No.	%	No.	%	
<b>Fissure healing in the 2<sup>nd</sup> week</b>					NA**
Yes	(0.0)	(0.0)	0	(0.0)	
No	50	(100.0)	50	(100.0)	
<b>Fissure healing in the 4<sup>th</sup> week</b>					<0.001*
Yes	13	(26.0)	(0.0)	(0.0)	
No	37	(74.0)	50	(100.0)	
<b>Fissure healing in the 6<sup>th</sup> week</b>					<0.001*
Yes	15	(30.0)	(0.0)	(0.0)	
No	35	(70.0)	50	(100.0)	
<b>Fissure healing in the 8<sup>th</sup> week</b>					<0.001*
Yes	22	(44.0)	50	(100.0)	
No	28	(56.0)	(0.0)	(0.0)	
Total	50	(100)	50	(100)	

\* Chi-square test, \*\* Not Applicable.

A significant association was observed between treatment adverse effects and being treated with GTN ( $P = 0.05$ ); 12% of patients treated with GTN had adverse effects, while only 2% of patients treated with DTZ had adverse effects.

No significant differences were observed between CAF patients treated with DTZ or GTN regarding headache ( $P = 0.3$ ).

There was a significant association between adverse perianal pain and patients treated with GTN ( $P = 0.01$ ); 12% of patients treated with GTN had perianal pain. No significant differences were observed between CAF patients treated with DTZ or GTN regarding nausea, vomiting, and diarrhoea, as no patients reported these adverse effects (Table 4).

**Table 4** Distribution of adverse effects according to study groups.

Variable	Study groups				P
	DTZ		GTN		
	No.	%	No.	%	
<b>Adverse effects</b>					0.050* S
Yes	1	(2.0)	6	(12.0)	
No	49	(98.0)	44	(88.0)	
<b>Headache</b>					0.300*
Yes	1	(2.0)	0	-	
No	49	(98.0)	50	(100.0)	
<b>Perianal pain</b>					0.010*
Yes	0	0	6	(12.0)	
No	50	(100.0)	44	(88.0)	
<b>Nausea</b>					NA**
Yes	0	-	0	-	
No	50	(100.0)	50	(100.0)	
<b>Vomiting</b>					NA**
Yes	0	-	0	-	
No	50	(100.0)	50	(100.0)	
<b>Diarrhoea</b>					NA**
Yes	0	-	0	-	
No	50	(100.0)	50	(100.0)	
<b>Total</b>	50	(100.0%)	50	(100.0%)	

\* Fisher's exact test, \*\* Not Applicable.

There was no significant correlation between CAF patients treated with GTN and DTZ regarding symptoms at the 2nd week ( $P = 0.9$ ), nor the 6th and 8th weeks.

A significant association was observed between bleeding symptoms and patients treated with GTN in the fourth week ( $P = 0.4$ ) (Table 5).

**Table 5** Distribution of symptom relief for different follow-up periods according to study groups

Variable	Study groups				P
	DTZ		GTN		
	No.	%	No.	%	
<b>At the 2<sup>nd</sup> week</b>					0.900*
Pain	0	-	0	-	
Discharge	3	(33.3)	0	-	
Constipation	2	(22.3)	9	(75.0)	
Bleeding	4	(44.4)	3	(25.0)	
<b>At the 4<sup>th</sup> week</b>					0.040*
Pain	9	(24.3)	2	(17.4)	
Discharge	11	(29.7)	4	(14.8)	
Constipation	11	(29.7)	10	(37.1)	
Bleeding	6	(16.3)	11	(40.7)	
<b>At the 6<sup>th</sup> week</b>					0.900*
Pain	13	(26.0)	9	(25.0)	
Discharge	9	(18.0)	6	(16.7)	
Constipation	16	(32.0)	11	(30.5)	
Bleeding	12	(24.0)	10	(27.8)	
<b>At the 8<sup>th</sup> week</b>					0.490*
Pain	22	(40.0)	39	(44.9)	
Discharge	12	(21.8)	11	(12.7)	
Constipation	8	(14.5)	17	(19.5)	
Bleeding	13	(23.7)	20	(22.9)	

\* Fisher's exact test.

## Discussion

The treatment of CAF has developed recently from surgical to medical options, because of morbidity and the risk of incontinence resulting from surgery. Chemical sphincterotomy can be done by using different agents. First-line use of medical treatment cures most CAFs economically and conveniently.<sup>12</sup>

This study explored the outcomes of DTZ and GTN ointments' application among 100 CAF patients, with the mean age distribution of  $33.24 \pm 1$  (66% female and 34% male), similar to comparable studies.<sup>11</sup> In the present study, symptoms relief was significantly higher for patients treated with DTZ than among those who received GTN regarding pain ( $P = 0.01$ ), bleeding ( $P = 0.02$ ), discharge/pruritus ( $P = 0.005$ ), and constipation ( $P = 0.006$ ). These findings agree with the results of a study which reported that CAF patients receiving DTZ reported significantly decreased scores for pain, bleeding, itching, and constipation symptoms.<sup>2</sup>

In the current study, most local findings of CAF except for skin tags were equally distributed among patients treated with DTZ or GTN, consistent with a study in India.<sup>13</sup> However, our study revealed a highly significant association between CAF-related skin tags and DTZ treatment ( $P < 0.001$ ), similar to a study in Singapore which recommended the use of DTZ specifically because of its effectiveness for skin tags.<sup>1</sup> However, in our study, all patients treated with GTN were healed by the 8th week compared to only 44% of patients treated with DTZ, but the healing (for those who were healed) was significantly earlier and faster for patients treated with DTZ than for patients treated with GTN ( $P < 0.001$ ). This is consistent with the results of a study in Japan, which reported more effective and rapid healing of CAF using DTZ compared to other chemical agents.<sup>14</sup>

In Iraq, a prospective observational study found that treating CAFs with 2% DTZ ointment enriched with zinc sulfate (2%)

over a 2-month course avoided the surgical treatment option in about half of the patients, with fewer side effects.<sup>15</sup>

In the current study, a significant association was observed between treatment with GTN and adverse effects ( $P = 0.05$ ). A study in India also showed that topical DTZ is better than topical GTN in treating chronic fissures, due to lower side effects.<sup>16</sup> The main side effect accompanying the use of GTN in the present study was significant perianal pain ( $P = 0.01$ ), consistent with a study in Saudi Arabia.<sup>17</sup> Patients commonly decline GTN treatment due to adverse effects like headache, orthostatic hypotension,<sup>18</sup> syncope attacks, and tachyphylaxis.<sup>19</sup> In the current study, only one patient with CAF treated with DTZ reported headache symptoms.

Unfortunately, the effectiveness of GTN is temporary, and the recurrence rate is approximately 35%.<sup>20</sup> While the adverse effects of both GTN and DTZ in the current study were low, they were lower among patients treated with DTZ, similar to a study conducted in Pakistan.<sup>21</sup> The current study found no significant correlation between CAF patients being treated with GTN or DTZ regarding symptoms at the 2nd week ( $P = 0.9$ ), or the 6th and 8th weeks, but a significant association was observed between the bleeding symptom and patients treated with GTN in the fourth week, similar to a study conducted in India.<sup>22</sup>

## Conclusion

Both DTZ and GTN chemical agents are effective for the treatment of CAF, but the former facilitates a faster healing process, with fewer adverse effects and more symptomatic relief. While diltiazem should be recommended as the first line of treatment for CAF, it remains a good substitute in cases where DTZ is unavailable. More research is needed on the effectiveness of DTZ in treating CAFs, particularly for different patient groups.



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**Competing interests**

The authors declare that they have no competing interests.

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