

Comparison of topical glyceryl trinitrate with diltiazem ointment for treatment of chronic anal fissure.

A randomized clinical trial.



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BACKGROUND: *The aim of this study was to compare the effect of topical glycerol trinitrate ointment (GTN) with topical diltiazem hydrochloride ointment (DTZ) in the treatment of chronic anal fissure.*

METHOD: *Prospectively, 102 patients were treated randomly with either GTN ointment (0.2%) or DTZ ointment (2%) couple of times daily for 12 weeks.*

RESULTS: *Forty-five patients (88.2%) in group DTZ and 36 patients (70.6%) in group GTN had reduction of symptoms. The decrease in the symptoms for group DTZ were significantly more than that for group GTN ($P=0.02$). Mean time of symptom reduction was 2.44 ± 0.30 in group DTZ and 2.50 ± 0.28 weeks in group GTN without significant differences between two groups ($P>0.05$). Complete relieving of symptoms was observed in 72.5%, 54.9% patients in groups DTZ and GTN, respectively. The frequency of complete relieving of symptoms between two groups was not significant ($P>0.05$). Complete remission of anal fissure was occurred in 66.7% patients in group DTZ and 54.9% patients in group GTN, which was no different, significantly. Mean time taken for fissure healing in GTN group was dramatically less than DTZ group ($P=0.001$). Finally, 33.3% of patients in DTZ group and 45.1% of patients in GTN group was operated. The need for operation was not significant between two groups ($P>0.05$).*

CONCLUSION: *Both DTZ and GTN are equally effective and can be the preferred first-line treatment of chronic anal fissure. However, GTN is associated with a higher rate of headache, and it should be replaced by DTZ.*

KEY WORDS: Anal fissure, Lateral sphincterotomy.

Background

Anal fissure is a linear tear in the mucosa of the anal canal normally extending distally from the dentate line to the anal verge. An acute tear in the mucosa is analogous to a 'split lip' of the anus; if this fails to heal it progresses to a chronic anal fissure¹. Although there is no defined time period distinguishing acute from chronic fissures, some authors suggest a chronic fissure should

be present for at least 6–8 week^{2,3}. However, the standard treatment for chronic anal fissure has been lateral sphincterotomy which has a high success rate⁴ but can cause significant short- and long-term morbidity with incontinence rates of up to 30 per cent⁵.

In recent years, various medical therapies have been used for the treatment of chronic anal fissure with a view to reducing the resting anal canal pressure and improving the vascularity of internal sphincter muscle. The agents that have been used are glycerol trinitrate ointment (GTN)^{6,7}, nifedipine^{8,9}, botulinum toxin⁶, bethanechol¹⁰ and diltiazem hydrochloride (DTZ)^{10,11}. GTN ointment produces a temporary 'chemical sphincterotomy', with healing rates of 83–86% in early studies^{12,13} but only 30–46% in more recent publications^{14–17}. Up to 80% of patients¹⁵ develop headaches during treatment

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that reduce compliance¹⁶. Topical Diltiazem 2% reduces anal pressure and is found to be equally effective as that GTN ointment with fewer side effects¹⁷.

In this study, a comparative evaluation of diltiazem and GTN was done to examine the efficacy in the management of chronic anal fissure.

Methods

This prospective, randomized clinical trial was conducted in the St. Zahra Hospital from June 2004 to Oct 2008. All 102 patients were informed regarding the treatment protocol and its probable complications, and informed sanction was obtained from each patient. Inclusion criteria were males and females 18 years and older with chronic anal fissure having at least two of the following three criteria: (1) pain during and after defecation of more than 6 weeks duration, (2) the presence of a sentinel anal tag, and (3) visibility of the horizontal fibers of the internal anal sphincter in the base of lesion. Patients having any of the following features were excluded from the study: 1) acute anal fissure, 2) specific local pathological conditions (Crohn's disease, anal cancer, tuberculosis), 3) presumed or confirmed pregnancy or lactation, 4) allergy to diltiazem or GTN, 5) clinically considerable cardiovascular abnormalities, 6) chronic headaches, 7) associated complications (abscess, fistula).

The 102 consecutive patients who satisfied the selection criteria were divided into 2 groups according to a computer-generated centralized randomization list, namely Group DTZ (Diltiazem), Group GTN (Glycerol trinitrate).

This was a prospective, randomized, double-blind study. The study protocol was approved by the Ethics Committee of our faculty and was carried out in accordance with the principles of the Helsinki Declaration. The methods were explained to the patients and informed consent was obtained from all patients under

study. Patients in Group DTZ were treated with topical diltiazem ointment (2%), while group GTN did use GTN ointment (0.2%). Patients were advised to apply 3 gram of ointment per dose circumferentially 1 cm inside the anus, near the internal anal sphincter, every 12 hours for 12 weeks. Neither group of patients was prescribed stool softeners or bulk laxatives for the duration of treatment. The patients under study were initially followed twice a week to find the relief of pain and, thereafter, once every 2 weeks for the fissure healing. At each visit, the patients were interviewed to assess their pain relief, healing of the fissure, and side effects of treatment, if any. Patients were given daily diary cards, asked to indicate the worst pain experienced each day on linear analog charts with a scale of 0 to 10 (Visual analogue Scale), and were questioned about side effects (Headache, blood pressure changes, anal irritation, allergic reactions) of treatment. Healing was defined as complete skin closure over the fissure, confirmed by anoscopy. Patients who did not heal after 12 weeks, those intolerant to the treatment, and those who did not report any improvement of symptoms within 8 weeks were offered to undergo surgical lateral internal sphincterotomy. Data analysis was conducted with Statistical Package for Social Sciences (SPSS) V13 using Student's t, chi-squared, logistic regression, and correlation tests. A value of $P < 0.05$ was considered significant.

Results

There were 102 patients with mean age of 29.90 years, with a range of 17–61 years. 90.2 percent of fissures occurred in the posterior midline. All the three groups were similar in terms of age, sex distribution, signs and symptoms, and location of fissure and type of symptoms (Table I and Figure 1). Forty-five patients (88.2%) in group DTZ and 36 patients (70.6%) in group GTZ had reduction of symptoms. The decrease in the symptoms for group DTZ were significantly more than that for

TABLE I - Comparison of the features of patients in two groups

Feature	Group DTZ (n=51)	Group GTN (n=51)	P Value
Male: Female (M/F ratio)	0.88	0.82	> 0.05
Age (yr), mean $\pm$ SD (range)	30.23 (28.29 $\pm$ 32.17)	29.56 (27.90 $\pm$ 31.22)	> 0.05
Decrease in symptoms (patients)	45 (88.2 %)	36 (70.6%)	0.02
Mean time taken for decrease in symptoms (weeks)	2.44 $\pm$ 0.30	2.50 $\pm$ 0.28	> 0.05
Complete relieve of symptoms (patients)	37 (72.5%)	28 (54.9%)	0.06
Mean time taken for complete relieve of symptoms (weeks)	5.08 $\pm$ 0.64	4.07 $\pm$ 0.50	0.02
Fissure healing (patients)	34 (66.7%)	28 (54.9%)	0.2
Mean time taken for fissure healing (weeks)	7.58 $\pm$ 2.01	4.85 $\pm$ 1.84	0.001
Surgical operation (patients)	17 (33.3%)	23 (45.1%)	0.2
Mean time of need for surgery (weeks)	9.05 $\pm$ 2.56	5.33 $\pm$ 1.41	0.001
Headache (patients)	0	30 (58.8%)	0.001
Mean time of headache relief (weeks)	0	4.75 $\pm$ 1	0.001

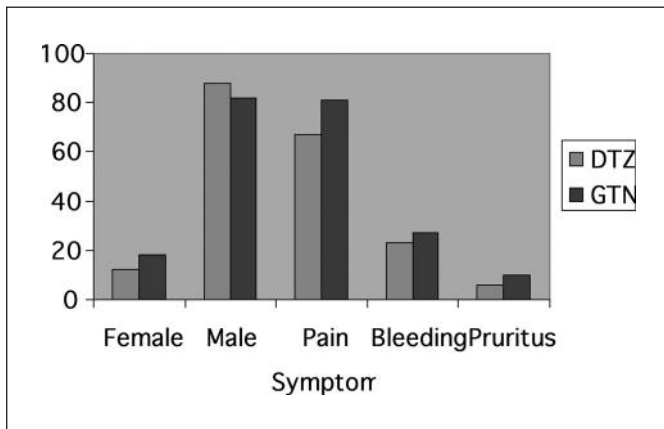


Fig. 1: Demographic data of patients in two groups.

group GTN ($P=0.02$). Mean time of symptom reduction was 2.44 ± 0.30 in group DTZ and 2.50 ± 0.28 weeks in group GTN.

There was no significant difference in time of symptom reduction between two groups ($P>0.05$). Complete relieving of symptoms was observed in 72.5%, 54.9% patients in groups DTZ and GTN, respectively.

The frequency of complete relieving of symptoms between two groups was not significant ($P>0.05$). However, in the DTZ group, mean time taken for complete relieving of symptoms was 5.08 ± 0.64 weeks which was significantly different from time in the GTN group (4.07 ± 0.50) ($p=0.02$). Totally, complete remission of anal fissure was occurred in 66.7% patients in group DTZ and 54.9% patients in group GTN, which was no different, significantly. Mean time taken for fissure healing was 7.58 ± 2.01 weeks in DTZ group and was 4.85 ± 1.84 weeks in GTN Group. Mean time taken for fissure healing in GTN group was dramatically less than DTZ group ($P=0.001$). Finally, 33.3% of patients in DTZ group and 45.1% of patients in GTN group was operated.

The need for operation was not significant between two groups ($P>0.05$). In DTZ group, patients' preference and no response to medical treatments were the indications of surgery in 29.4% and 70.6%, respectively. On the other side in GTN group, the indication of surgery was severe headaches (side effect of treatment) in 60.9%, patients' preference in 34.8% and no relief following medical treatment in 4.3% of patients. Indications of surgery was significantly different in two groups ($P=0.001$).

Except patients' preference, 26.1% patients in DTZ group and 34.9% patients in GTN group were operated and there was no significant difference between two groups ($P>0.05$). The mean time of need for surgery following medical treatment was 9.05 ± 2.56 weeks in DTZ group and 5.33 ± 1.41 weeks in GTN group (except patients who was operated due to severe headaches) and the difference was significant ($P=0.001$).

None of the patients using diltiazem ointment showed headache, while 30 (58.8%) patients using GTN ointment reported headaches. By reason of headache, 14 (28%) patients stop medication and was operated. The headache of remained patients (16 patients) relieved spontaneously. The mean time of headache relief in patients who tolerated the side effect was 4.75 ± 1 week. Two patients treated with DTZ had skin pruritus and no patients treated with GTN showed this side effect. Both groups were free from the other side effects such as dizziness and anal burning.

Discussion

Resolution of symptoms of anal fissure and healing can be attained by invasive interventions or by chemical sphincterotomy. Because of the complications associated with operative lateral internal sphincterotomy and the risk of incontinence, medical alternatives for surgery have thus been tried to obtain. Chemical sphincterotomy is noninvasive, precludes the need for general anesthesia, and could be applied at home by the patient itself.

GTN ointment are metabolically degraded to nitric oxide which relaxes the internal anal sphincter¹². 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^{11,12,19-21,23}.

Diltiazem ointment is found to be effective but with no headache associated. In the present study, a comparative evaluation of DTZ and GTN has been performed to evaluate the efficacy and complications in the management of chronic anal fissure.

In our study, symptoms of 88.2 % patients reduced with DTZ ointment while symptoms of 70.6% patients reduced with GTN ($P=0.02$), but there is no difference in mean time taken for reduction of symptoms between two groups. Lund and Scholefield⁷ found that there is marked pain relief after using GTN ointment and the effects of application are not immediate. Carapeti¹⁰ described the early marked pain relief after using DTZ ointment. The frequency of complete relieving of symptoms between two groups was not significant. However, the time taken for complete relieving of symptoms in GTN group was about 4 weeks after treatment that was significantly less than DTZ group ($P=0.02$). The mean time taken for healing for the DTZ group was 7.58 ± 2.01 weeks and for the GTN group, 4.85 ± 1.84 weeks. This shows that GTN causes early healing in comparison to DTZ ointment. Complete relieving of symptoms was observed in 72.5%, 54.9% patients in groups DTZ and GTN, respectively.

Ultimately, 66.7% of the anal fissures healed with DTZ ointment and 54.9% of fissures healed with GTN ointment. There is no difference in the complete remission of fissure and complete pain relief between two groups.

In a study done by Lund and Scholefield ⁷ 66% of the patients using GTN ointment regularly for 6–8 weeks showed complete healing of the fissure. Carapeti et al. ¹⁰ stated that 67% of the patients healed after 8 weeks of using GTN ointment. In our study, 30 (58.8%) of the patients using GTN ointment had headaches, while none of the patients using diltiazem ointment showed headache. Carapeti et al. ¹⁰ were reported headache in 72%, and this led to discontinuation of the treatment by many patients. In the end, lateral internal sphincterotomy was done in 33.3% of patients in DTZ group and 45.1% of patients in GTN group. The need for operation was not significant between two groups.

On the basis of above findings, we concluded that DTZ ointment (2%) and GTN ointment (0.2%) are both effective treatment modalities for chronic anal fissure. GTN caused early relief in symptoms and fissure in comparison to DTZ. From other point of view, DTZ ointment was found to be superior due to absence of headache in comparison to GTN ointment. Both DTZ and GTN are equally effective and can be the preferred first-line treatment of chronic anal fissure. However, GTN is associated with a higher rate of side effects (headache), and it should be replaced by DTZ.

Riassunto

PREMESSA: Lo scopo di questo studio è stato quello di paragonare gli effetti topici di una pomata a base di trinitrato di glicerolo (GTN) con quelli di una pomata di idrocloruro di diltiazem (DTZ) per il trattamento di una ragade anale cronica.

METODO: 102 pazienti sono stati trattati a random ed in maniera prospettica rispettivamente o con una pomata GTN (0.2%) oppure con una pomata DTZ (2%) due volte al giorno per 12 settimane.

RISULTATI: Quarantacinque pazienti (88.2%) del gruppo DTZ e 36 pazienti (70.6%) del gruppo GTN sono andati incontro alla riduzione dei sintomi. La diminuzione della sintomatologia nel gruppo DTZ è stata significativamente maggiore rispetto al gruppo GTN ($P=0.02$). Il tempo medio della riduzione dei sintomi è stata di 2.44 ± 0.30 settimane nel gruppo DTZ e 2.50 ± 0.28 settimane nel gruppo GTN senza differenze significative tra i due gruppi ($P>0.05$). È stata osservata una completa remissione dei sintomi nel 72.5% e nel 54.9% dei pazienti rispettivamente nel gruppo DTZ e nel gruppo GTN. L'incidenza della completa remissione dei sintomi tra i due gruppi non è risultata significativa ($P>0.05$). La remissione completa della ragade anale si è ottenuta nel 66.7% dei pazienti del gruppo DTZ e nel 54.9% dei pazienti del gruppo GTN, senza significativa differenza. Il tempo medio intercorso per la guarigione della ragade nel gruppo GTN è stato decisamente inferiore di quello del gruppo DTZ ($P=0.001$). Infine 33.3% dei pazienti del gruppo DTZ e 45.1% dei pazienti del

gruppo GTN sono stati sottoposti ad intervento chirurgico. La necessità di intervenire chirurgicamente non è stata significativamente differente tra i due gruppi ($P>0.05$).

CONCLUSIONI: Sia il DTZ che il GTN sono egualmente efficaci e possono rappresentare il trattamento di primo approccio nel trattamento della ragade anale cronica. Comunque il GTN si associa ad una maggiore comparsa di cefalea, ed allora deve essere sostituito con il DTZ.

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