Topical Diltiazem vs. topical Glyceril trinitrate in the treatment of chronic anal fissure : A prospective, randomized, double-blind trial

Shahram Ala[1], Majid Saeedi[2], Roja Hadianamrei[3], Ali Ghorbanian[3]

(1) Department of Clinical Pharmacy, (2) Department of Pharmaceutics, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran ; (3) Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.

Abstract

Background and study aims : **Chemical sphincterotomy is a new way for the treatment of chronic anal fissure which avoids the risk of faecal incontinence associated with traditional surgical methods. The aim of this study was to compare topical Diltiazem with topical Glyceril trinitrate in the treatment of chronic anal fissure.**

Patients and methods : **61 patients (10 Male, 51 Female) between 16-81 years of age with chronic anal fissure were included in this prospective, randomized, double-blind trial. The patients were randomly allocated to either Diltiazem gel (2%) or Glyceril trinitrate ointment (0.2%) and were asked to use the treatment twice daily for 8 weeks. Each patient was reviewed every two weeks ; pain scores, healing and side effects were assessed.**

Results : **Healing occurred in 33 of 36 (91.66%) patients treated with Diltiazem after 6 weeks and 15 of 25 (60%) patients treated with Glyceril trinitrate after 8 weeks which shows a significant difference in favour of Diltiazem ($P < 0.001$). The rest of the patients were either non-compliant or did not heal and underwent surgery. Headache occurred in all of the patients treated with Glyceril trinitrate but none of the patients treated with Diltiazem developed headache. The frequency of other side-effects was also less in patients treated with Diltiazem ($P < 0.001$).**

Conclusions : **Diltiazem gel was found to be superior to Glyceril trinitrate ointment due to significantly higher healing rate and fewer side-effects.** (Acta gastroenterol. belg., **2012**, 75, **438-442**).

Key words : Diltiazem, topical, chronic anal fissure, glyceril trinitrate, chemical sphincterotomy.

Introduction

Anal fissure is a common painful anorectal condition characterized by severe post defecation anal pain, rectal bleeding and anal discharge (1). Most of the acute anal fissures heal spontaneously ; however a proportion become chronic. The most common approach for treating chronic anal fissure is surgical sphincterotomy which has a high success rate (4) but is associated with the risk of permanent anal incontinence in some patients (3,5) generating enthusiasm for therapies that do not involve sphincter division or paralyzing stretch.

Chemical sphincterotomy is an alternative therapy which avoids the risk of anal incontinence associated with surgical treatments (6). Various therapeutic agents such as nitrates, botulinum toxin, calcium channel blockers and cholinomimetics have been proposed to achieve reversible chemical sphincterotomy (7).

Glyceril trinitrate (GTN) is probably the most commonly used pharmacological treatment for chronic anal fissure and is now a well-established first-line treatment. However, the drawback of GTN is that more than 50% of the patients treated with GTN experience headache as a side effect, which leads to discontinuation of treatment in some cases and reduced compliance in others. In addition, the recurrence of fissure in patients treated with GTN is rather high (8-13).

Diltiazem (DTZ) has been shown to lower resting anal pressure (RAP) by relaxing the internal anal sphincter and therefore has found to effectively heal chronic anal fissures. Topical preparations of DTZ have been shown to be more effective than oral preparations with fewer or no side effects (14-16). There is a large amount of published data showing the beneficial effect of GTN in the treatment of anal fissure but few data on DTZ.

The objective of this study was to compare topical DTZ gel and topical GTN ointment for the treatment of chronic anal fissure. The specific questions that this study aimed to answer were :

1) Which one of the two pharmacotherapies is more effective in the treatment of chronic anal fissure in the study population ?
2) Are there minimal or no side effects of DTZ compared with GTN ?

Materials and Methods

Materials

The following chemicals were used as received from the suppliers : Methyl and propyl paraben, glycerin, ethanol (Merck, Germany), HPMC (Colorcon, UK). Diltiazem was gently provided by Darupakhsh Co. (Tehran, Iran). Glyceril trinitrate ointment (0.2%) produced by Cadila co. was used in this study.

Preparation of Diltiazem gel

Diltiazem gel was prepared from the materials listed in table 1 by following procedure : appropriate amount

Correspondence to : Roja Hadianamrei, Pharm. D., Faculty of Pharmacy, Mazandaran University of Medical Sciences, 18th kilometer Farahabad road, 48175861 Sari, Iran. E-mail : hadian.r@gmail.com

Submission date : 14/01/2012
Acceptance date : 06/07/2012

Table 1. — **Type and amount (w/w %) of materials used for preparation of Diltiazem gel**

HPMC	Diltiazem	Methyl paraben	Propyl paraben	Glycerin	Distilled water
3%	2%	0.18%	0.02%	10%	84.8%

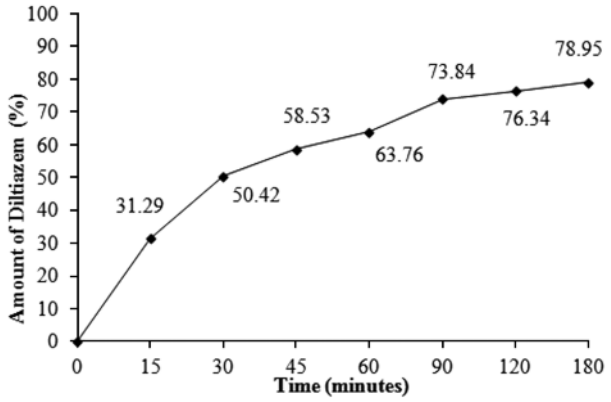

Fig. 1. — Release profile of Diltiazem from the gel

of HPMC was dispersed in preserved water (methyl paraben 0.18% and propyl paraben 0.02%) and glycerin in a flask covered with parafilm overnight. Diltiazem solution (2%) was added to the above gel and stirred with a double bladed mixer (Ika-werk, Germany) at 500 rpm for 30 minutes.

The release profile of Diltiazem from the gel was determined in-vitro by the following method : a plate containing 2 g of Diltiazem gel was placed in a 250 ml vessel ; 100 ml of distilled water was added to the vessel and stirred simultaneously at 50 rpm. The vessel was occluded to evade the volume changes due to evaporation and the temperature was set at 30-35°C. Aliquots were taken from the receptor compartment at specific time points and the Diltiazem content was assayed spectrophotometerically at 236 nm. Fig. 1 shows the release profile of Diltiazem from the gel.

The final formulation was controlled microbiologically based on USP 24.the physical stability of the formulation was evaluated at 4°C, 25°C and 40°C.

Patient selection

61 outpatients (10 Male, 51 Female) between 16-81 years of age with chronic anal fissure referring to Imam Khomeini and Bouali Sina hospitals, Sary, Iran under the care of two colorectal surgeons were enrolled in the study. Chronic anal fissure was defined by the presence of at least two of the following conditions : (1) Pain on defecation for more than 2-3 months which has failed to resolve with stool softeners and local anaesthetics. (2) Presence of a sentinel anal tag and (3) Exposure of the horizontal fibers of the internal anal sphincter (15,17).

Patients having any of the following conditions were excluded from the study : Acute anal fissure, Inflammatory bowel disease, colorectal cancer, tuberculosis, pregnancy, lactation, unreliable contraception in female patients, significant cardiovascular diseases, patients with a history of allergic reactions to Diltiazem or Glyceril trinitrate and patients already taking Calcium channel blockers, Beta adrenergic antagonists, Nitrates or anaelgesics (6,16). Patients having pain despite the use of GTN were entered the study after a washout period of at least two weeks (6).

The study has been approved by the research ethics committee of Mazandaran University of Medical Sciences and has been performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. In addition, written informed consent was obtained from all of the patients prior to their enrollment in the study.

Randomised Trial

All patients were randomly divided into two groups following simple randomization procedure using a computer generated list of random numbers. Group A (36 patients) received Diltiazem gel (2%) and group B (25 patients) received Glyceril trinitrate ointment (0.2%). Patients were asked to apply 2 cm of Diltiazem gel (equal to 8 mg Diltiazem) or 2 cm of Glyceril trinitrate ointment (equal to 6 mg Glyceril trinitrate) on the perianal skin, but not actually inside the anus and gently massage for 1 minute twice daily for eight weeks. The patients were allocated to either Diltiazem or Glyceril trinitrate by an individual who was not aware of the content of the tubes and was not involved in the subsequent trial process. Neither the patients nor the researchers were aware of the randomization codes A and B until the end of the trial. Patients underwent clinical examination and visual inspection of the fissure prior to the treatment course and were reviewed every two weeks. Pain relief, healing of the fissure and side-effects of the treatment including headache, nausea/vomiting, constipation, incontinence, rashes and dermatitis were assessed. Healing was defined as resolution of symptoms (anal pain and bleeding) and absence of fissure on examination (15). The severity of pain was assessed using Visual analogue scale (VAS) scored from 0 (no pain) to 10 (unendurable pain).

Statistical analysis

Statistical analysis of the data was performed using biomedical software SPSS (SPSS for windows, version 15, SPSS Inc, Chicago, IL). Comparative evaluation of the groups was performed using χ^2 test for qualitative data and paired t-test for quantitative data and the amounts of $p < 0.05$ were considered to indicate a statistically significant difference.

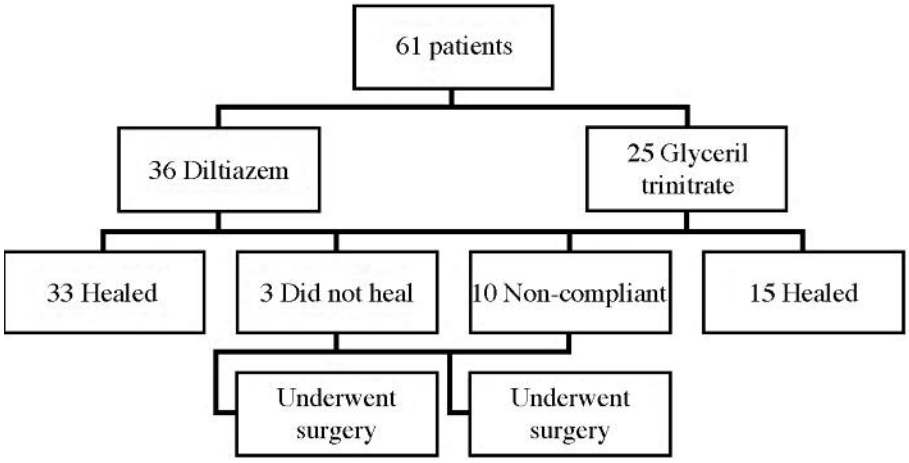

Fig. 2 — Outcomes of treatment with Diltiazem gel (2%) and Glyceril trinitrate ointment (0.2%)

Results

Fig. 1 shows the release profile of Diltiazem from the gel. Drug release started almost immediately and after 180 minutes 78.95 ± 0.38% of the drug was released from the gel.

The formulation was physically stable at 4°C, 25°C and 40°C for 6 months and it passed the microbiological control successfully.

Treatment outcomes are summarized in Fig. 2. In group A (patients treated with Diltiazem gel) healing was observed in 33 of 36 (91.66%) patients after 6 weeks. 19.5% of the patients in group A were found to be healed at first examination after 2 weeks of treatment, 52.8% healed after 4 weeks and 19.36% healed after 6 weeks which makes up a total healing rate of 91.66% within 6 weeks. Three other patients did not heal and were subsequently treated by surgery. In group B (patients treated with Glyceril trinitrate ointment) healing occurred in 15 of 25 (60%) patients after 8 weeks. 10 other patients were non-compliant and discontinued treatment after 4 weeks mainly due to headache. No healing was observed in this group earlier than 4 weeks (Fig. 3).

The decrease in mean pain score was significantly higher for group A at the second week compared with group B ($P < 0.001$) but at the fourth and sixth weeks, the mean pain score was almost equal for the two groups ; by the eighth week, no pain was observed in any patients of either group (Table 2). Headache was noted in all patients in group B but no patient in group A experienced headache. The frequency of constipation and pruritus was also higher in group B compared with group A ($P < 0.001$) (Table 3). Except for pruritus, which was present in 2 patients in group A and 3 patients in group B, no other side-effects were present at the beginning of the trial.

Discussion

Anal fissure is a very common problem across the world causing considerable morbidity, therefore appropriate treatment is mandatory. Currently, chronic anal fissure is treated by chemical or surgical sphincterotomy. Traditional surgical treatments are associated with the risk of faecal incontinence, therefore pharmacological agents that relax the anal smooth muscle, to accomplish reversibly what occurs in surgery, have been used to obtain fissure healing (1-5).

Among the various pharmacotherapies for chronic anal fissure, Glyceril trinitrate (GTN) is the most extensively studied and still remains the standard for chemical sphincterotomy against which other treatments have to be compared (8-12). Within controlled clinical trials, healing of chronic anal fissure with GTN has been achieved in 46-83% of patients (8,10-12). GTN may have an initial high healing rate ; however, there is a high percentage of recurrence and significant side effects, most notably headache, which may lead to discontinuation of the treatment (11-13).

Topical Diltiazem (DTZ) has been found to be effective in the treatment of chronic anal fissure without causing headache. In a study conducted by Carapeti *et al.* (14), it was found that DTZ gel with concentrations of 1% and above can produce a dose dependent reduction of the maximum resting anal pressure (MRAP) up to a maximal effect. 2% DTZ gel produced a maximal effect of 28% reduction in the MRAP with no systemic or local side effects.

Jonas *et al.* (16) compared topical and oral preparations of DTZ in the management of chronic anal fissure and demonstrated that both oral and topical preparations of DTZ were effective in treating chronic anal fissure but topical DTZ appeared to be more effective than the oral

Table 2. — **Mean pain scores (VAS) of the patients during the trial**

Time (weeks)	0	2	4	6	8
Group A	5.51	2.09	2.04	0	0
Group B	5.53	4.12	2.62	0.6	0

Table 3. — **Frequencies of adverse effects in patients**

Adverse effect	Headache	Constipation	Nausea/Vomiting	Pruritus	Dermatitis	Rash
Group A	0	2	0	3	0	0
Group B	25	12	0	10	0	0

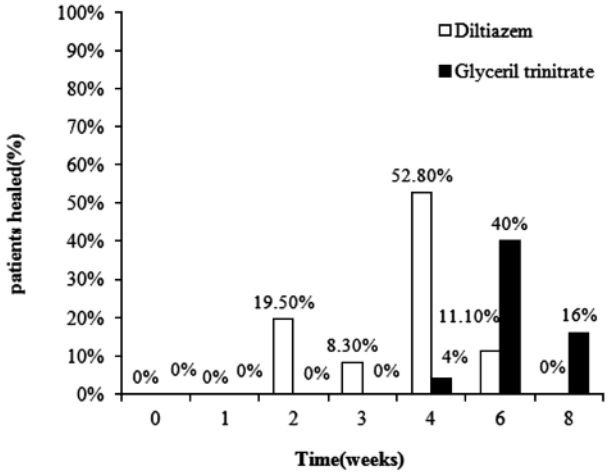

Fig. 3 — Percentage of patients healed with Diltiazem gel (2%) and Glyceril trinitrate ointment (0.2%) at different time intervals.

preparation (65% vs. 38% healing rate). In another study, they reported 49% healing rate in patients with chronic anal fissure resistant to GTN following treatment with DTZ gel (6). Das gupta *et al.* (17) reported 48% healing rate in patients treated with DTZ gel with no considerable side effects. In a similar study by Knight *et al.* (15) 89% healing rate was reported for DTZ ointment with dermatitis in 6% of the patients and headache in only one patient.

In the present study a comparative evaluation of DTZ gel (2%) and GTN ointment (0.2%) was performed to assess the effectiveness and complications of these two pharmacotherapies in the management of chronic anal fissure.

As the results show, 91.6% healing was achieved in group A (patients treated with DTZ gel) which is close to the healing rate reported for DTZ by Knight *et al.* (15). On the other hand, the healing rate in group B (patients treated with GTN ointment) was 60%, which is very close to the results of previous studies by Lund and Scholefield (8), Kennedy *et al.* (10) and Carapeti *et al.* (12) who have reported 60-70% healing rate in patients treated with GTN ointment. A comparison between the two groups shows that DTZ has been more effective than GTN in treating chronic anal fissure in the studied population (paired t-test, $p < 0.007$).

Our results show that in group A healing started almost immediately and a considerable pain reduction was observed in all of the patients in this group at first visit after 2 weeks. Furthermore, no pain was recorded in any patients from this group who were responsive and compliant to treatment after 6 weeks. In contrast, in group B no healing was achieved before 6 weeks. There was a marked pain relief following treatment with GTN, but the effects were not immediate and started after 4 weeks. These results suggest an earlier initiation of action for DTZ compared with GTN and support the results obtained by Lund and Scholefield (8) and Carapeti *et al.* (12). It could be inferred from all these data that DTZ gel has caused earlier healing with a higher healing rate compared with GTN ointment.

Side effects, most notably headache, were not significant in group A, while in group B all of the patients have experienced varied degrees of headache ; The incidence of constipation and pruritus was also higher in this group ($P < 0.001$) (Table 2) which supports the results of previous studies (12-15,17).

It could be concluded from all the above mentioned data that Diltiazem gel (2%) has been more effective than Glyceril trinitrate ointment (0.2%) in the treatment of chronic anal fissure and has been associated with fewer side effects. Hence, it could be regarded as a suitable substitute for Glyceril trinitrate in the treatment of chronic anal fissure.

Acknowledgements

The authors gratefully acknowledge Dr. Ommolbanin Hojjati and Dr. Fariborz Eshghi for their cooperation in patient selection.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. GOLIGHER J.C. Surgery of the anus, rectum and colon. 3rd edn. London : Balliere Tindall, 1975.
2. PITT J., BOULOS P.B. Chemical sphincterotomy for anal fissure. *Colorectal. Dis.*, 1999, **1** : 2-8.
3. KHUBCHANDANI I.T., REED J.F. Sequelae of internal sphincterotomy for chronic anal fissure in ano. *Br. J. Surg.*, 1989, **76** : 431-434.
4. OH C., DIVINO C.M., STEINHAGEN R.M. Anal fissure 20-year experience. *Dis. Col. Rectum*, 1995, **38** : 378-382.
5. GARCIA-AGUILAR J., BELMONTE C., WONG D., LOWRY A.C., MADOFF R.D. Open versus closed sphincterotomy for chronic anal fissure : long term results. *Dis. Colon Rectum*, 1996, **39** : 440-443.
6. JONAS M., SPEAKE W., SCHOLEFIELD J.H. Diltiazem heals Glyceril trinitrate- resistant chronic anal fissures. A prospective study. *Dis. Colon Rectum*, 2002, **45** : 1091-1095.
7. DHAWAN S., CHOPRA S. Nonsurgical approaches for the treatment of anal fissures. *Am. J. Gastroenterol.*, 2007, **102** : 1312-1321.
8. LUND J.N., SCHOLEFIELD J.H. A randomized, prospective, double-blind, placebo-controlled trial of Glyceril trinitrate ointment in treatment of anal fissure. *Lancet*, 1997, **349** : 11-14.
9. LUND J.N., ARMITAGE N.C., SCHOLEFIELD J.H. Use of Glyceril trinitrate ointment in the treatment of anal fissure. *Brit. J. Surg.*, 1996, **83** : 776-777.
10. KENNEDY M.L., SOWTER S., NGUYEN H., LUBOWSKI D.Z. Glyceril trinitrate for chronic anal fissure. Results of a placebo-controlled trial and long-term follow-up. *Dis. Colon Rectum*, 1999, **42** : 100-106.
11. ALTOMARE D.F., RINALDI M., MILITO G. *et al.* Glyceril trinitrate for chronic anal fissure-healing or headache ? Results of a multicenter, randomized, placebo-controlled, double-blind trial. *Dis. Colon Rectum*, 2000, **43** : 174-179.
12. CARAPETI E.A., KAMM M.A., MC DONALD P.J., CHADWICK S.J., MELVILLE D., PHILLIPS R.S.K. Randomized controlled trial shows that Glyceril trinitrate heals anal fissures, higher doses are not more effective and there is a high recurrence rate. *Gut*, 1999, **44** : 727-730.
13. PITT J., WILLIAMS S., DAWSON P.M. Reasons for failure of Glyceril trinitrate treatment o chronic anal fissure in-ano : A multivariate analysis. *Dis. Colon Rectum*, 2001, **44** : 864-867.
14. CARAPETI E.A., KAMM M.A., PHILLIPS R.S.K. Topical Diltiazem and Bethanechol decrease anal sphincter pressure and heal anal fissures without side effects. *Gut*, 1999, **45** : 719-722.
15. KNIGHT J.S., BIRKS M., FAROUK R. Topical Diltiazem ointment in the treatment of chronic anal fissure. *Brit. J. Surg.*, 2001, **88** : 553-556.
16. MARION J., NEAL K.R., ABERCOMBIE J.F., SCHOLEFIELD J.H. A randomised trial of oral vs. topical Diltiazem for chronic anal fissures. *Dis. Colon Rectum*, 2001, **44** : 1074-1078.
17. DAS GUPTA R., FRANKLIN I., PITT J., DAWSON P.M. Successful treatment of chronic anal fissure with Diltiazem gel. *Colorectal Dis.*, 2001, **4** : 20-22.