ORIGINAL ARTICLE

Sphincter-Preserving Therapy with Topical 2% Diltiazem for Chronic Anal Fissure: Our Experience

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Abstract:

Background: Chronic anal fissure is a common problem across the world treated largely by surgical methods. Studies have demonstrated the efficacy of topical agents like Glyceryl Trinitrate (GTN) in anal fissure but it has been shown to have side effects like headache and dizziness. There is a need for a pharmacological therapy for fissure which has fewer side effects. Hence, this study was taken up to assess the efficacy and adverse effects of topical 2% Diltiazem (DTZ) gel. *Aim & Objectives:* To assess the efficacy and side effect of topical treatment with 2% DTZ gel in patient with chronic anal fissure. *Material and Methods:* Consecutive fifty adult patients with symptomatic chronic anal fissure attending the surgery clinic were enrolled in the study form February 2014-July 2014 and they were treated with regular topical application of 2% DTZ cream. Patients were followed up at regular intervals for symptomatic relief and healing of fissure. *Results:* In our study post-defecatory pain, bleeding and irritation were significantly reduced after 2week of therapy and a primary healing rate of 86% (43 out of 50) at 6thweek of therapy. The primary side-effects of 2% DTZ gel appeared to be perianal dermatitis and pruritis ani in 14% cases. *Conclusion:* Topical 2% DTZ gel is an effective agent in the treatment of chronic anal fissure. The need for hospital stay is abolished; psychological and financial burden on the patient is reduced. With a healing rate close to 90%, topical DTZ can be easily advised as the first line of treatment of chronic anal fissure.

Keywords: Chronic Fissure, Diltiazem, Topical Treatment, Chemical Sphincterotomy

Introduction:

A chronic anal fissure is a non-healing linear tear in the distal anal mucosa below the dentate line. An anal fissure is likely to be non-healing if the fissure persists beyond 4 week. A chronic fissure can be identified by the presence of indurated edges, visible internal sphincter fibres at the base of the fissure, a sentinel polyp at the distal end of the fissure or a fibroepithelial polyp at the apex. A chronic fissure classically occurs at the posterior midline position (6 o'clock position), with the anterior midline position occurring in 10% of females and 1% of males. Chronic anal fissures are associated with hypertonia of the anal canal [1] and a reduction in mucosal blood flow, with microcirculatory disturbance and a poor healing tendency [2]. Knowledge of the ischemic nature of anal fissures and the high complication rate of surgical treatment were the basis in the search for nonsurgical treatment options.

The discovery of agents, that produce reversible relaxation of anal sphincters, has brought a paradigm shift in the medical management of anal fissure. Out of such agents, Glyceryl Trinitrate (GTN) and Diltiazem (DTZ) are the forerunners [3]. These drugs have become the first line

treatment for anal fissure, reserving the surgery for failures or recurrences. These agents heal the fissure so effectively that the pharmacological treatment of anal fissure has been termed as 'Chemical sphincterotomy' [4]. Topical GTN acts by releasing nitric oxide, a neuro-transmitter which mediates the relaxation of internal anal sphincter. This relaxation of sphincter facilitates the optimal healing of fissure [5]. Approximately two-third of patients using GTN ointment or patch develop headache as a side effect, which may be severe enough to warrant cessation of treatment [6]. Topical DTZ on the other hand blocks L-type calcium channels thus preventing the influx of calcium into the smooth muscle cell, decreasing intracellular calcium concentration, thus hindering the smooth muscle contraction. In addition to relaxation of the smooth muscles of internal sphincter, they also dilate the blood vessels of the anoderm, leading to an increased blood flow resulting in a faster recovery [7]. The present study comprises of 2% DTZ gel application in the treatment of chronic fissure in ano with respect to both efficacy and complications.

Materials and Methods:

This study was designed as a prospective study. The consecutive fifty adult patients with symptomatic chronic anal fissure attending the surgery clinic of Acharya Vinoba Bhave Hospital were enrolled in the study from February-July 2014. 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 DTZ (5) clinically considerable cardiovascular abnormalities, (6) chronic headaches, (7) associated complications (abscess, fistula). The methods were explained to the patients and informed consent was obtained from all patients under study. The study protocol was approved by the Ethics Committee of Jawaharlal Nehru Medical College, Wardha.

Patients were advised to squeeze 2 cm of the DTZ gel onto a finger and to apply this one cm inside the anus and to the anal margin. Each patient was given a 6 week course of the DTZ gel for twice-daily application, as close to every twelve hour as possible. Objective changes were assessed by the inspection of the anus to determine the extent of fissure healing (recorded as "healed" or "persistent") at baseline and second, fourth and sixth weeks. Anoscopy was performed at baseline and on sixth week. Healing of chronic anal fissure was defined at anoscopy when epithelialization or formation of a scar was achieved at week 6 of therapy. Patients scored the severity of their symptoms of pain, bleeding, or perineal irritation at baseline and second, fourth and sixth weeks on Numeral Rating Scales (NRS) (range: 0-10); it was explained that 0 represented no symptoms and 10 the worst imaginable. Side effects such as itching, headache, and dizziness were recorded at every visit. The

dose of DTZ used in this study was chosen on the basis of dose-response studies reported in the literature, in which concentrations of DTZ gel greater than 2% had no additional effect on anal pressure. At the completion of the trial, patients who did not heal were given the option of either an additional course of topical DTZ gel or surgical treatment.

Statisticalanalysis

Data are presented as mean (range) unless otherwise indicated. The symptom scores of pain, bleeding or irritations at baseline were the independent variables. Wilcoxon signed-rank test (paired difference test) was used to compare baseline and follow-up paired data. SPSS 19 for Windows statistical software was used for all data analyses. A value of $P < 0.05$ was considered significant.

Results:

Fifty consecutive patients who fulfilled inclusion and exclusion criteria were recruited. There was slight female preponderance with 1.4:1 ratio, and the mean age was 38.96 ± 13.93, (range of 18-65year). Patients had experienced symptoms for a mean of 5.5 ± 1.87 month (3-8 month) at the time of inclusion in the study; pain and bleeding were most common symptom. Most common location of fissure was posterior midline (76%), sentinel tag and sphincter spasm were present in majority of cases (80%, 94% respectively) (Table 1).

The first application of DTZ was uneventful in all patients, out of fifty patients, 43(86%) were healed primarily with DTZ within 6 weeks. The remaining seven patients did not respond to DTZ. Two refused surgical treatment. Remaining five patients were offered sphincterotomy. Two patients were again treated with DTZ gel and one was healed subsequently, the remaining one patient underwent sphincterotomy. Seven of forty three patients whose anal fissures healed primarily subsequently underwent excision for sentinel tag. (Table 2)

Pain, bleeding and irritation were significantly reduced ($P<0.05$, $P<0.001$) after 2 week of treatment, and progressively thereafter. (Table 3)

Seven patients (14%) reported Perianal itching; three patients developed mild headache. No other side effects were reported. Overall, the compliance rate was 100% (Table 4).

Table 1: Clinical Profile of Cases with Chronic Fissure in Anoscopy

Features	Number
Sex	
Male	21(42%)
Female	29(58%)
Age in years : range	18-65
Mean ± SD	38.96 ± 13.93
Duration of symptom: range	3-8 months
Mean ± SD	5.5±1.87 months
Symptoms	
Pain	48(96%)
Bleeding	42(84%)
Discharge/itching	06(12%)
Constipation	29(58%)
Local findings	
Posterior midline fissure	38(76%)
Anterior midline fissure	06(12%)
Anterior fissure+ Posterior midline fissure	04(8%)
Multiple fissure	02(4%)
Sentinel tag	40(80%)
Sphincter spasm	47(94%)

Table 2: Healing Rate of Fissure during Treatment

Fissure healing	Number (%)
At second week	00(00)
At fourth week	31(62)
At sixth week	43(86)

Table 3: Numerical Rating Scales Before and At Review Visits during Treatment

Parameters	Pretreatment	Second week	Fourth week	Sixth week
Pain	6.8(0-10)	4(0-8) [b]	2(0-9) [b]	1.3(0-5) [b]
Bleeding	2.8(0-10)	1(0-7) [a]	0(0-5) [b]	0(0-3) [b]
Irritation	3(0-10)	1(0-8) [b]	0(0-7) [b]	0(0-5) [b]

Values are median (range). [a] P < 0.05, [b] P < 0.001 vs pretreatment values

Table 4: Adverse Effect of Drug during Treatment

Side effect	Number (%)
Headache	03(6%)
Perianal dermatitis/pruritis ani	07(14%)
Vertigo	00
Palpitations	00

Discussion:

Fissure-in-ano is a common problem across all parts of the world, causing considerable morbidity and affecting the quality of life of the patients. This necessitates the prompt treatment of the condition with suitable, cost-effective methods. Endoanal ultrasound combined with anal manometry has established a cohort of patients with an anal fissure at increased risk of fecal incontinence following a lateral sphincterotomy. These include women with an obstetric history [9], patients who have undergone previous anal surgical procedures [10,11], and older patients with a short anal sphincter [12]. Chemical sphincterotomy, a medical line of treatment, is now being been accepted as the first line of treatment for chronic anal fissures at various centers. Previous studies have found that DTZ is efficacious in the treatment of chronic anal fissure. Studies showed that oral intake and topical applications of DTZ reduced the anal pressure significantly [13].

In the present study, the mean age of presentation was 38.96 years which is in accordance to previous studies [14-16], with female preponderance (1.4:1) [16,17]. However there are studies which show that male and female are equally affected [18,19]. Anal fissures cause significant pain with defecation and associated minor fresh red bleeding, typically seen on the toilet paper or streaking the surface of the stool. Anal fissures are most commonly seen in the posterior midline, although 10–20% in women

and 1–10% in men are located in the anterior midline [20].

In a study conducted by Tsunoda *et al* (2012), 21 out of 30(70%) were healed primarily with DTZ within six week. Pain, bleeding and irritation were significantly reduced after 1 week, four patient complained perianal itching, one patient discontinued treatment due to delayed onset of headache, overall median compliance rate was 100%(67%-100%).their study also showed that successful treatment can lead to improvements not only in bodily pain, but also in mental health, vitality and general health on the SF-36 (Short-Forum 36 Health Survey) scale.

In another study by Farouk *et al* [1] 2014 out of 612 patients, fissure in only one hundred forty-one patients (23%) either did not heal with topical DTZ ointment or relapsed after stopping treatment. Thirty patients (5%) developed a contact dermatitis as a result of using the cream, and ninety-two patients (15%) complained of pruritis ani during or shortly after completion of their treatment. Similar high healing rate (80%) were demonstrated in other studies [7,15,21].

In a study reported by Jonas *et al* [22], 2002 the efficacy of DTZ for fissures that failed to heal with GTN was evaluated. Consecutive patients (n=39, median age 42 year) with persistent chronic anal fissure despite treatment with GTN ointment (0.2%) underwent anal manometry before and at1 h after application of DTZ gel (700 mg of 2%) to the distal anal canal. The gel was applied twice daily for 8 weeks. Topical DTZ gel lowered maximal anal pressure by 20% and fissures healed in 49% of patients within 8 weeks. Hence, the authors concluded that topical DTZ (2%) was effective treatment for GTN-resistant chronic anal fissure. Similarly Behnam *et al* [23] 2009 compared the effect of topical GTN ointment with topical DTZ ointment in the treatment of chronic anal fissure found both DTZ and GTN were equally effective and could be the preferred first-line treatment of chronic anal fissure. However, GTN was associated with a higher rate of headache, and it could be replaced by DTZ.

In our study post-defecatory pain, bleeding and irritation were significantly reduced after 2 week of therapy and a primary healing rate of 86% (43 out of 50) at 6 week of therapy. The primary side-effects of DTZ 2% ointment appear to be perianal dermatitis and pruritis ani in 14% cases. Overall compliance was 100%. The follow up period available after successful treatment with DTZ gel was short and therefore no long term conclusions could be drawn.

Conclusion:

Topical 2% DTZ appears to be a well tolerated method of chemical sphincterotomy leads to successful treatment of chronic anal fissure and can successfully preserve the integrity of the anal sphincter muscle for the majority of patients but long-term follow-up is needed to assess the risk of recurrent fissure and quality of life after initial healing with DTZ.

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