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Original article

Topical Diltiazem versus topical Glyceryl trinitrate (GTN) in the treatment of chronic anal fissure: Prospective study

Rithin Suvarna, Hanumanthappa MB*, Panchami, Guruprasad Rai,

a Associate Professor, Department of Surgery, AJ Institute of Medical sciences, Mangalore - 575003

a Associate Professor, Department of Surgery, AJ Institute of Medical sciences, Mangalore - 575003

a Associate Professor, Department of Physiology, Fr Muller Medical College, Mangalore - 570003

d Resident, Department of Surgery, AJ Institute of Medical Sciences, Mangalore - 575003

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ABSTRACT

Introduction: Anal fissure (AF) is a linear tear in the distal anal canal & is associated with spasm of internal anal sphincter muscle. Acute AF usually heals with simple measures. The usual treatment of chronic fissure is surgical sphincterotomy. However, it may cause permanent anal incontinence. The present study was undertaken to assess the efficacy & safety of topical Diltiazem & topical Glyceryl trinitrate in the management of chronic anal fissure. Also, they were compared with each other. **Materials & methods:** In this prospective comparative study, 200 patients with chronic anal fissure were equally & randomly divided into DTZ group (received 2% diltiazem ointment) & GTN group (received 0.2% Glyceryl trinitrate ointment). The ointment had to be applied to anal verge twice daily for 6 weeks. Assessment was done at 2nd, 4th & 6th weekends for fissure healing, pain relief & side effects. **Results:** Complete fissure healing was observed in 71.87% of patients in DTZ group & 68.23% in GTN group ($P < 0.0001$). Pain response was good & was fairly similar in both the groups. Headache occurred in 5.20% in DTZ & 67% in GTN group ($P < 0.0001$). Recurrence rate was 9.67% in DTZ & 19.56% in GTN group. **Conclusion:** Topical Diltiazem is preferred to topical Glyceryl trinitrate in the treatment of chronic fissure, because it is associated with a few side effects.

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1. Introduction

Anal fissure (AF) is a linear tear in the distal anal canal and is a common painful condition affecting the anal canal [3]. The main pathology appears to be a persistent hypertonia and spasm of the internal anal sphincter which results in mucosal ischemia [10,11,14]. Acute AF usually heals spontaneously or with simple measures such as stool softeners & dietary modification [23]. But chronic AF generally requires sphincterotomy (chemical or surgical sphincterotomy). Surgical sphincterotomy heal most fissures, but it is associated with the risk of permanent anal incontinence [1, 6, 13, 15]. Therefore, various medical therapies (chemical sphincterotomy), including topical diltiazem (DTZ) & topical Glyceryl trinitrate (GTN), have been tried for the treatment of chronic anal fissure without fear of incontinence [10]. Kocher et al in their study reported no significant difference in the fissure healing or improvement of symptoms of chronic anal fissure between the patients receiving DTZ & GTN [9]. They, however,

observed more side-effects (particularly headache) with GTN than with DTZ [9]. In a study, Carapeti et al found fissure healing in 67% of patients treated with GTN, while headache was observed in 72% of cases [5]. In another study conducted by Knight et al, fissure healed in 75% of cases treated with topical diltiazem [1]. The present study was undertaken to assess the efficacy & side effects of topical diltiazem & topical GTN in the management of chronic anal fissure. Also, they were compared with each other.

2. Materials and Methods

This was a prospective comparative study conducted in AJ hospital & research centre, Mangalore from Dec 2009 to Jan 2012. The study was carried out on 200 cases presented with chronic AF after obtaining informed written consent. Clearance from the local ethical committee was obtained for the study. Inclusion criteria were: patients aged between ≥ 18 yrs and ≤ 65 years; presence of chronic anal fissure for more than 8 weeks that had failed to resolve with simple measures such as laxatives & high fibre diet; examination revealed features of chronicity (induration at the edges, external skin tag, and exposure of the horizontal fibers of the internal anal sphincter on the floor). Patients with anal fissure due to other diseases like inflammatory

* Corresponding Author : Dr Hanumanthappa MB

A J Institute of Medical Science
Mangalore
India
E-mail: mb_h@rediffmail.com

bowel disease, tuberculosis, malignancy, sexually transmitted diseases, previous treatment with local ointment or surgery; patients who had associated hemorrhoids, fistula, pregnant/lactating women and patients with significant cardiovascular conditions were excluded. The selected patients received treatment as outpatients. Clinical examination, including digital rectal & proctoscopic examination, was performed on all the subjects. Sigmoidoscopy & colonoscopy were performed as & when necessary. Two groups were made, DTZ group & GTN group. For each group, 100 patients were recruited, randomized by sequential order as follows (DTZ, GTN). DTZ group was treated with 2% diltiazem ointment while GTN group was instructed to use 0.2% glyceryl trinitrate (GTN) ointment twice daily for 6 consecutive weeks. The subjects were instructed to apply the medicine (about a size of pea) to the anal margin using their tip of the index finger. The patients were encouraged to use high fiber diet and warm sitz baths. They were assessed at 2nd, 4th and 6th weekend during the course of the treatment & then bimonthly for a year. At each visit, fissure healing, pain relief, any side effects & recurrence were recorded. The treatment protocol was considered violated if a patient didn't comply with the treatment as advised. Healing of the fissure was assessed visually and the intensity of pain was assessed from a visual analogue score. Healing was defined as complete disappearance of fissure on examination. Every patient was supplied with a pain score chart & was educated how to mark daily the level of pain on it. These charts were graded from 0 to 10, marked at one end 0 (no pain) and at the other end 10 (worst pain). The disease was termed recurrent if the fissure reappeared at the same site one month after 6 weeks course of topical application. Data was collected and was analyzed statistically using SPSS version 17 software. The P values were calculated using chi-square test and were considered significant below 0.0001

3. Results

Table 1: Clinical details of the subjects

Characteristic	DTZ group (N=100)	GTN group (N=100)
Males	44	48
Females	56	52
Age in years (range)	18-65	18-64
Duration of symptoms	8-9 months	8-9 months
Symptoms:		
Pain	94%	97%
Bleeding	87%	86%
Constipation	61%	55%
Co-morbidity:		
Diabetes mellitus	8	12
Local Findings:		
Posterior midline AF	22	17
Anterior midline AF	4	11
Anterior +posterior midline AF	85	79
Sentinel pile	85	83
Sphincter spasm		

Ages of the patients were fairly similar in both the groups (tab 1). In both groups, there was a slight female predominance. Pain was the main presenting symptom followed by bleeding per-rectum (tab 1). Posterior midline was the commonest location (tab 1). Majority of the cases had sphincter spasm. At 2nd, 4th & 6th weekends, cases were assessed for fissure healing, pain alleviation & side effects. 15 cases from GTN group & 4 cases from DTZ group failed to complete the study due to headaches & cooperation problems. Those subjects were not considered in the final statistical analysis.

Table 2: Fissure healing in DTZ group & GTN group

Fissure healing	DTZ group (N=96)	GTN group (N=85)	P value
2nd weekend	6	7	
4th weekend	56	51	
6th weekend	69	58	<0.0001

Complete fissure healing was observed in 71.87% of DTZ group & 68.23% of GTN group in 6 weeks (P <0.0001) (tab 2 & fig 1).

Figure 1: Fissure healing in DTZ group & GTN

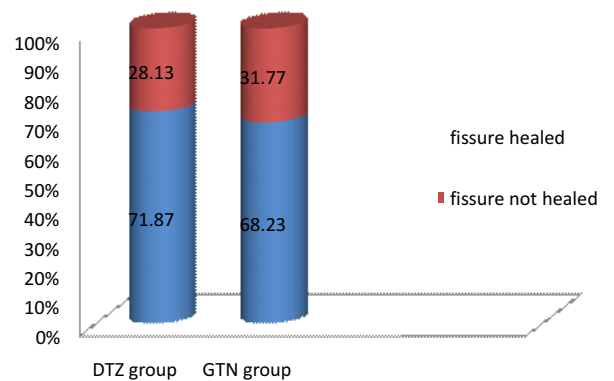
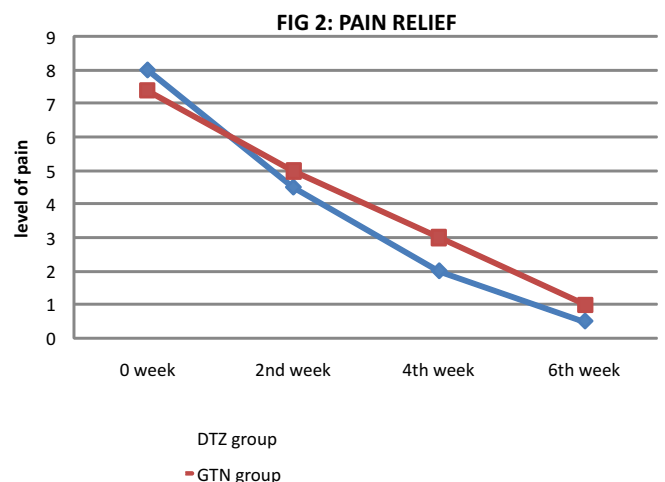


Fig 2: Pain response in DTZ & GTN groups



Side effects of the medicines (Tab 3)

Table 3: Side effects observed in DTZ group & GTN group

Side effect		GTN group (N=85)	P value
1.Headache:		57	<0.0001
Mild (painscore≤3)	4	38	
Moderate (pain score 4-6)	1	13	
Severe (pain score≥7)	0	6	
2.Perianal itching	6	8	

67% of subjects from GTN group developed headache compared with 5.20% in DTZ group (P <0.0001) (tab 3). One patient in DTZ group required analgesic, while 28 cases in GTN group requested for pain killers.

Recurrences:

96 of 100 cases in DTZ group & 85 of 100 from GTN group completed the full 6 weeks course of treatment. However, 7 of 69 fissure healers in diltiazem group & 12 out of 58 fissure healers with GTN application didn't turn up for follow up, while the rest completed the full 1 year follow up.

Table 4: Recurrences in DTZ & GTN group

	DTZ group (N=62)	GTN (N=46)
No of patients with recurrences	6	9

Recurrence rate was observed in 9.67% of cases in DTZ group compared to 19.56% in GTN group.

4. Discussion

Anal fissure is a slit in the lining of the distal anal canal [3] & is the most common cause of severe anal pain [2]. Posterior midline is the commonest site, but anterior midline fissures are not infrequent, especially in females [11, 12]. Constipation & passage of hard stools have been known to be the initiating factors of fissure [2]. In females, it is usually triggered during pregnancy and following childbirth [2]. They can be associated with inflammatory bowel disease & tuberculosis.

The exposed internal sphincter muscle underneath the fissure goes into spasm resulting in severe pain. Besides, the spasm pulls the edges of the fissure apart, which impairs healing of the wound. The typical symptoms of anal fissure are anal pain during defecation associated with the passage of bright red blood per rectum [3]. The pain may be so severe that patients may postpone defecation for days together until it becomes inevitable [2]. This leads to hardening of the stools, which further worsen the condition. The fissures can be either acute or chronic. Acute fissure is of short duration (less than a month) and has fresh mucosal edges [3]. They usually heal spontaneously or with simple measures like high fibre diet, adequate water intake, & warm sitz baths [2,3].

Chronic fissures generally have indurated edges [3]. External skin tag (sentinel pile) is commonly observed [3]. Horizontal fibers of the internal sphincter are usually exposed on the floor of the well developed fissure, which leads to spasm due to irritation [2].

Chronic anal fissures are usually not amicable to the aforementioned simple measures [2]. A definitive therapy has been considered essential to tackle this problem [2]. Various methods of treatment modalities have been described which may be grouped into non-operative and operative measures.

Non-operative methods include Injection of Botulinum toxin [2], oral nifedipine, topical application of glyceril trinitrate (GTN) and topical diltiazem ointment. Topical GTN has been the most extensively used non-surgical treatment for chronic anal fissure [13]. It is a potent nitric oxide donor [4] & it has been believed that nitric oxide is a neurotransmitter mediating the relaxation of the internal sphincter [3]. GTN ointment or patch applied to the anal verge results in the healing of approximately two-thirds of chronic anal fissures [5-7]. But headache and dizziness are its main drawbacks [7]. Besides, tolerance to nitrates is a well documented fact [7]. Another drawback associated with GTN therapy is high recurrence rate [13, 18].

Nifedipine and diltiazem are calcium channel blockers which act by blocking slow L-type calcium channels in smooth muscle causing relaxation [3]. Topical diltiazem has been reported to result in the healing of chronic anal fissure in 60% to 75% of cases [1, 7, 16, 17, 19]. In a study, Carapeti et al reported fissure healing in 67% of patients treated with GTN [5], while headache was observed in 72% of cases. In another study, Knight et al from UK observed 75% of their cases had fissure healed with topical diltiazem [1]. Only 1 of 71 cases had headache [1].

Topical diltiazem also has been tried successfully in the treatment of chronic AF that have failed to respond to GTN [8, 19]. Diltiazem ointment has been known to cause less headache & a few side effects than GTN ointment without a significant difference in healing rates between the two agents [1, 9]. Also, recurrence rate has been known to be lower with topical Diltiazem [9, 19-22].

5. Conclusion

Both Diltiazem ointment (2%) & glyceryl trinitrate ointment (0.2%) are quite effective in the treatment of chronic fissure in ano. However, topical Diltiazem is preferred to topical glyceryl trinitrate as it is better tolerated with a few side effects.

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