Randomised Prospective Controlled Trial of Topical 2 % Diltiazem Versus Lateral Internal Sphincterotomy for the Treatment of Chronic Fissure in Ano

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Abstract Fissure in ano is a very common disorder of the anorectal region. Internal sphincter hypertonia with decreased relaxation coupled with mucosal ischemia of posterior anal canal are the major pathologies in chronic anal fissure (CAF). Though lateral internal sphincterotomy (LIS) remains the gold standard of treatment for the disease, it is accompanied by the potential complication of incontinence to both flatus and faecal matter. The aim of our study was to explore the role of topical diltiazem as an effective and a safe alternative to sphincterotomy for chronic anal fissure. Ninety patients with CAF were randomly assigned to group A and group B, with 45 patients each. Group A patients received 2 % diltiazem topical application, twice daily, and group B patients underwent LIS. All the patients were reviewed at first, fourth and sixth week after initiation of treatment. Visual analogue scores for pain and healing of fissure by visual inspection were recorded and compared. In group A, 71 % had complete healing of fissure at 6 weeks, with fair amount of pain relief (mean VAS—3.38), and in group B, 96 % showed healing of fissure, with excellent pain relief (mean VAS—1.87). Headache and flushing were noted in two patients in group A while no patients in group B developed incontinence. We conclude that LIS is more effective than topical diltiazem in the treatment of CAF. Topical diltiazem may be employed as an initial conservative treatment option before considering the surgical alternative.

Keywords Fissure in ano · Lateral sphincterotomy · Pain score · Topical diltiazem

Introduction

Fissure in ano is a very common disorder of the anorectal region, producing anal pain during and for 1–2 h after the act of defaecation. Chronic fissures, by definition, are those that persist beyond 6 weeks. The pathogenesis is not fully clear [1], though reduced consumption of dietary fibre and constipation may be important risk factors [2]. Another hypothesis, supported by both anatomical and anal manometry studies, is that the relative ischemia of the posterior midline anal canal leads to poor healing of the fissure [3].

The American Society of Colon and Rectal Surgeons (ASCRS) recommend conservative management with stool softeners, high fibre diet and sitz bath as the initial line of management [4]. A Cochrane review of anal fissure treatment had shown that topical and injected therapies are only marginally effective to placebo therapy and recommended lateral internal sphincterotomy (LIS) as the gold standard for chronic anal fissure (CAF) [5]. The main drawback of LIS is the potential complication of incontinence to flatus or faecal matter. This is the reason for trying alternative pharmacologic agents (chemical sphincterotomy) in the treatment of CAF. An evidence-based summary regarding the role of topical diltiazem had been recently issued by the National Institute for Health and Care Excellence (NICE, UK) organisation in UK [6].

The aim of this randomised study was to compare the efficacy of topical 2 % diltiazem with the traditional LIS in the treatment of CAF.

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Patients and Methods

This prospective randomised trial was conducted in the Department of General Surgery, Mahatma Gandhi Medical College and Research Institute, SBV University, Puducherry, India, from Oct 2010 to Jan 2012. Ninety patients with CAF (visible sphincter fibres at base, sentinel pile or induration) were randomised to group A and group B (45 patients in each group) by using computer-generated random numbers. All patients with clinically diagnosed fissure in ano, aged between 15 and 70 years, symptomatic for more than 6 weeks and had failed conservative measures were included in the study. Patients with haemorrhoids, fistula, other anal pathologies or previous anal surgeries, cardiac patients and pregnant women were excluded from the study. The proposed procedures were explained in detail and informed consent obtained. The study protocol was approved by the Institutional Ethics Committee. Group A patients received treatment with 2 % diltiazem topical application, twice daily for 6 weeks, and group B patients underwent LIS under spinal/general anaesthesia. All the patients were followed up and reviewed at 1st, 4th and 6th week after intervention. Outcomes measured were healing of fissure (indicated by intact anal epithelium lining), pain relief by visual analogue scale (VAS) and any adverse effects. Specific questions were asked regarding incontinence in the surgical group. The data was analysed by using chi-square and student *t* tests.

Results

Of the 90 patients included in this study, there were 53 male and 37 female patients. Mean age of the patients was 36.3 in group A and 35.8 in group B. The mean duration of symptoms was 5.46 months. Painful defaecation was the major complaint in both the groups. Bleeding and constipation were other common symptoms (Table 1). Other symptoms like pruritus ani and mucus discharge were less common.

At the time of presentation, the mean VAS score was 6.18 (standard deviation (SD) of 1.25) for group A and 6.31 (SD 1.28) for group B patients. The mean VAS score of the patients

Table 1 Clinical profile of the study groups

Clinical features	Group A (n=45)	Group B (n=45)
Age in years: range, mean	19–59, 36.3	19–60, 35.8
Male	27 (60)	26 (58)
Female	18 (40)	19 (42)
Pain	43 (96)	45 (100)
Bleeding	20 (44)	22 (49)
Constipation	28 (62)	33 (73)

Figures in parentheses represent percentage

Table 2 Comparison of visual analogue scale—mean pain score of two groups of patients studied

Visual analogue scale	Group A	Group B	P value
At presentation	6.18±1.25	6.31±1.28	0.0318
1 week	3.93±2.31	3.47±1.95	0.0503
4 weeks	3.58±2.19	1.93±1.12	<0.001
6 weeks	3.38±2.10	1.87±1.08	<0.001

in group A at 1st week of review was 3.93 (SD 2.31) while that of patients in group B was 3.47 (SD 1.95). At the end of 4th week, the corresponding mean VAS scores were 3.58 (SD 2.19) and 1.93 (SD 1.12). The mean VAS score for patients in group A at the end of 6th week was 3.38 (SD 2.10), and group B patients had almost complete pain relief with a mean score of 1.87 (SD 1.08) (Table 2). At the end of 6th week, healing of fissure was noted in 43 (96 %) patients in group B and in 32 (71 %) patients in group A (Table 3). With regard to complications, flushing and headache were noted in two patients of group A. In group B, two patients developed anal wound sepsis in the form of submucosal abscess. There were no complaints of faecal or flatus incontinence in this group.

Discussion

Anal fissure is a very common and painful disorder of the anal canal, and its ideal management remains controversial. Clinical symptoms persisting beyond 6 weeks lead to CAF. The basic underlying pathology is hypertonia of the internal sphincter, raised resting anal canal pressure and the associated ischemia of the anoderm over the posterior midline of anal canal [3, 7–9]. Conservative management yields only temporary relief in the majority of cases. Pharmacologic manipulation is directed towards reducing the sphincter spasm by the usage of NO donors (glyceryl trinitrate (GTN)), calcium channel blockers (diltiazem) and botulinum toxin injection. Many recent reports and guidelines have reported the variable effectiveness of chemical sphincterotomy using topical GTN and calcium channel blockers [10, 11].

The role of botulinum injection in the treatment of anal fissure remains controversial. A recent review has found sufficient evidence to state that this modality is ineffective, with

Table 3 Healing of fissure

Follow-up	Group A (n=45)	Group B (n=45)
1st week	0	0
4th week	26 (58 %)	33 (73 %)
6th week	32 (71 %)	43 (96 %)

drawbacks of high cost and being invasive [12]. This therapy also suffers from significant adverse effects like faecal incontinence, haematomas, infections and recurrence [13].

Data from randomised controlled trials have revealed that LIS is much superior to GTN in the treatment of CAF [14, 15]. A systematic review by Nelson found that GTN was significantly associated with persistence and poor healing of fissure when compared to LIS [12]. Moreover, the major limitations with GTN are headaches in 20–30 % and pruritus ani in up to 10 % of cases [15, 16]. Griffin et al. had reported that topical 2 % diltiazem is an effective option in patients who had failed GTN therapy [17]. Many studies including a meta-analysis have consistently shown that adverse effects with topical diltiazem are very rare and insignificant when compared to GTN [11, 18, 19].

Overall, the male to female ratio in our study was 3.2:2. This may be due to the facts that male patients seek medical help early, the conservative attitude of female patients and the issue of embarrassment associated with physical examination for perianal disorders. The mean age of the total study group was 35.76 years, and this age group is found to have a higher predilection for CAF.

At 4th week of review, pain scores reduced significantly in the sphincterotomy group when compared to the diltiazem group (1.93 vs. 3.58, $p < 0.001$). Pain relief continued to improve at 6 weeks for the surgical group while the diltiazem group fared only slightly better (1.87 vs. 3.38). Other studies have also quoted similar degree of pain relief for topical diltiazem [18, 20]. Chemical sphincterotomy with diltiazem achieves healing rates in the range of 47 to 89 % in the treatment of CAF [20–22]. A recent meta-analysis of 15 trials ($n = 779$) compared healing rates for medical therapy with rates for operative intervention. The patients in the former group had a higher risk of persistence or recurrence of anal fissure when compared to the surgical group (OR 0.11, 95 % CI 0.06 to 0.23) [11].

Our study has shown a healing rate of 71 % at 6 weeks for topical diltiazem and a much superior rate for LIS (96 %). The healing rate for LIS as reported in other studies range from 92 to 100 % [5, 23, 24].

In group A, one patient had headache and another reported flushing. However, patients continued the therapy as these were infrequent and responded well to analgesics. Two patients in group B developed perianal abscess and were treated with incision and drainage.

Conclusions

LIS is more effective than topical diltiazem in the treatment of CAF. Patients unfit for surgery or refusing LIS can be offered a trial of diltiazem. We conclude that LIS provides rapid pain relief and healing of fissure, and it offers an effective treatment

choice. However, topical diltiazem is safe, easy to use with minimal adverse effects and may be considered as the first option. The major limitations are temporary benefits and higher relapse rates. LIS may be considered for patients who fail to respond or relapse with medical treatment.

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Conflict of Interest None.

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