

The Effect of Topical Nifedipine in Treatment of Chronic Anal Fissure

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Abstract- Chronic anal fissure is the most common cause of anal pain associated with internal anal sphincter hypertonia. Reduction of hypertonicity is a special treatment for fissure healing. For this purpose chronic anal fissures were conventionally treated by anal dilatation or by lateral sphincterotomy. However, both of these methods may cause a degree of incontinence in some patients. The uptake of medical therapies that create a reversible chemical sphincterotomy has recently become widespread. The aim of this prospective clinical trial study was to assess the effectiveness of nifedipine in healing anal fissure, a calcium channel blocker that reduces sphincter pressure. A single-blind randomized comparative trial was setup to compare traditional treatment with stool softeners and 2% lidocaine cream against 0.5% nifedipine cream for 4 weeks. 110 patients were included in this study, 60 patients in the nifedipine group and 50 patients in the control group and the therapeutic outcome and side effects were recorded. Healing had occurred in 70% of patients in the nifedipine group and in 12% of patients in the control group after 4 weeks treatment ($P < 0.005$). Recurrence of symptoms occurred in four of healed patients in the nifedipine group and three patients in the control group in two months. The final result of nifedipine application after 12 months follow up was recurrence in 11 patients (26.19%). Mild headache occurred in four patients (6.6%) of the nifedipine group. Patients in the nifedipine group showed significant healing and relief from pain compared with patients in the control group. Recurrence rate with nifedipine use in spite of control of predisposing factors such as constipation was significant. Another finding was low complication rate with this treatment.

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Introduction

Anal fissure is a common ulcer-like lesion in the anoderm. This painful condition affects the anal canal just distal to the dentate line and causes considerable morbidity while affecting the quality of life. The etiology of this disease is in doubt up to now but mucosal ischemia secondary to sphincter spasm is an acceptable etiology (1). Laser Doppler flowmetry has shown that the posterior area of the anoderm is less well perfused than other areas of the anoderm. It has been speculated that increased tone in the internal sphincter muscle further reduces the blood flow, especially at the posterior midline.

Acute anal fissures usually heal spontaneously or by conservative treatment with stool softeners and local anesthetic agents, but chronic anal fissures usually do not respond to such measures and treatment is aimed at reducing the anal internal sphincter pressure with

minimal complications. In some recent studies with long term follow-up, it seems that lateral internal sphincterotomy is a more long-lasting treatment for chronic anal fissure compared with topical agents and does not compromise long-term fecal continence (2). On the other hand there were some reports that traditional surgical techniques such as partial division of the internal sphincter or manual dilatation of the anus can cause the risk of permanent anal incontinence (3-5). This considerable problem has led to a look for alternative therapies for the treatment of anal fissure. Chemical sphincterotomy by local application of agents or oral drugs that reduce the sphincter pressure until the fissure has healed, has gained acceptance in treatment of chronic anal fissure at first line. These agents include local injection of botulinum toxin (6), topical glyceryl trinitrate (GTN) (7,8), bethanechol (9), diltiazem (10), indoramin (11), and nifedipine (12-14). The purpose of the present study was to obtain accurate information on

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the efficacy and safety of topical application of nifedipine cream (0.5%) as an effective therapeutic modality in healing chronic anal fissure.

Patients and Methods

Patients with a definite diagnosis of chronic anal fissure who referred to a single surgical team in a district general hospital, from Feb 2002 to October 2005 were enrolled in this study. Inclusion criteria included patients with chronic anal fissure who had symptoms lasting for more than six weeks and failed to resolve with conservative therapy consisting of stool softeners, high fiber diet and warm sitz bath and their physical examination reveal fibrotic anal ulcer with indurations at the edges, skin tag, and exposure of the horizontal fibers of the internal anal sphincter. Exclusion criteria were any history of reaction to topical agents, associated condition or disease such as cancer, fistula, abscess, Crohn's disease, HIV-related anal ulcer, tuberculosis ulcer, leukemic ulcer, pregnancy, third and fourth-degree hemorrhoids, and patients who did not present for follow up.

The selected patients were randomized in two groups. Sixty five patients were under treatment with 0.5% nifedipine cream and 55 patients with 2% lidocaine cream two times daily for four weeks. The cream application was with the patients' tip of the index finger to just inside and 1 cm² around the anus circumferentially. The patients were encouraged to follow a high-fiber diet and use warm sitz baths. Five Patients (two patients of the nifedipine group and three patients of the control group) who did not show improvement and suffered from severe symptoms after 2 weeks were offered surgical treatment. Five patients (three patients of the nifedipine group and two patients of the control group) were lost to follow up because they did not want to continue their medical treatment. Therefore the real number of patients included in this study was 110 patients (60 patients in the nifedipine group and 50 patients in the control group). Treatment was considered successful if the fissure had healed within 4 weeks. Responding patients were assessed periodically post-treatment. At each follow up visit healing of the fissure was assessed visually and the intensity of pain was assessed from a visual analogue score. Every patient was instructed how to mark daily the level of pain during defecation on charts. These charts were graded from 0 to 10, marked at one end as no pain and at the other end as the worst pain. Pain severity categories were defined. Patients with a score of

3 or less were defined as having mild pain, those with a score of 6 or more were considered to have severe pain and those between them were known as having moderate pain. All of the patients were advised to control their constipation during the treatment and follow up periods.

The healing of the fissure and any side effects were recorded. If healing occurred after the initial 4-week period, the patients were consequently followed up in clinic at 2, 6, and 12 months, or earlier if symptoms had relapsed. In addition, the patients were called by telephone every two months and they were advised to come back if their symptoms recurred. Statistical analysis was done by Statistical Package for Social Science (SPSS) program version 10. The qualitative data were presented in the form of numbered percentage. *Chi-square* test was used as a test of significance for qualitative data. The quantitative data were presented in the form of mean, standard deviation and range. Student's *t*-test was used as a test of significance for quantitative data. $P < 0.05$ was considered statistically significant.

Results

One hundred ten patients with chronic anal fissure were considered in this study. The Nifedipine group included 60 patients, 36 female (60%) and 24 male (40%). Their mean age was 33.71 ± 6.31 ranging from 18 to 60 years. The control group included 50 patients, 30 female (60%) and 20 male (40%). Their mean age was 33.6 ± 6.18 years ranging from 17 to 60 years. There was no significant difference in sex distribution ($P = 1$) or in age ($P = 0.7$) in the two groups (Table 1). The fissures were posterior in 72 patients (65.4%), anterior in 18 patients (16.3%) and both anterior and posterior in 20 patients (18.1%) (Table 2).

Table 1. Gender and age comparison in two groups

Groups	Female	Male	Mean age
nifedipine	36(60%)	24(40%)	33.71±6.31
Control	30(60%)	20(40%)	33.6±6.18

Table 2. Position of anal fissures in two groups

Groups	Anterior	Posterior	Anterior and posterior
nifedipine	42	10	8
control	30	8	12
Total	72(65.4%)	18(16.3%)	20(18.1%)

Table 3. Comparison of two groups after treatment

Groups	Relief of pain	Complete healing
nifedipine	45(75%)	42(60%)
control	10(20%)	6(12%)

At the end of 4 weeks all patients in nifedipine group experienced noticeable improvement in their symptoms of bleeding and pain. They also reported progressive improvement of pain during defecation. Relief of pain was observed in 45 patients (75%) and reduction of pain with moderate scoring in 15 patients of the nifedipine group. Complete healing of the fissure, which was defined as epithelialization of the anal fissure bed, occurred in 42 of 60 (70%) patients. The remaining 18 patients (30%) were not healed at 4 weeks and eight of them who were not ready for surgical therapy, underwent an additional course of nifedipine. Two patients of the last mentioned group experienced complete remission but they were not calculated as responding patients. In the control group, 10 of 50 (20%) patients reported relief of pain and 40 patients complained of moderate score pain; complete healing had occurred in 6 of 50 (12%) patients after 4 weeks treatment, this shows a significant difference between the two studied groups ($P < 0.005$) (Table 3). In nifedipine group there were no significant adverse effects, there was only mild headache in four patients (6.6%), who were treated with acetaminophen. Overall, 54 (95.4%) patients of this group reported no side effects associated with nifedipine cream.

Four of healed patients the nifedipine group and three of healed patients in the control group had recurrence within the first 2 months of follow up. So, the overall healing rate after 2-month follow up was found to be 63.3% for the nifedipine group, and 6% for the control group, with significant difference ($P < 0.001$). In 6 and 12 months follow up, recurrence in the nifedipine group was four (6.6%) and three (5%) patients and one (2%) and no patients in the control group, respectively. Final results after one year showed anal fissure recurrence in 11 patients (26.19%) who received nifedipine cream. Indeed four of the recurrent diseases had new ulcer locations. Six patients of this recurrent group received an additional course of nifedipine 0.7% for 4 weeks and healing of fissure occurred in three of them.

Discussion

Up to now a number of studies have shown that topical ointments containing agents that cause transient

reduction of the internal anal sphincter spasm by provision of exogenous nitrous oxide to the muscle tissue, promote the healing of chronic anal fissures (15, 16). Relaxation of the internal anal sphincter can be measured during smooth muscle relaxant therapy by measurement of the patient's maximal anal resting pressure (MARP) (17). Indeed these agents act as sphincterotomy without the complication of irreversible incontinence. Topical GTN was the most widely used non-surgical treatment for chronic anal fissure. The main adverse effect of topical GTN therapy for anal fissure treatment is that almost 40% of patients using this agent experience headaches. These headaches may decrease compliance and in some patients are so severe to lead to discontinuation of treatment (18). Another known considerable drawback to GTN therapy is high recurrence rate (19). Poor compliance with prescribed treatment often contributes to low outcome.

Calcium channel blockers such as nifedipine and diltiazem had some success in treating anal fissure by both oral and topical use (12, 20). Lower adverse effects (headache, flushing) and a higher rate of healing have been observed after topical application compared with oral use (20, 21). The transport of calcium through the L-type calcium channels are important for the maintenance of internal anal sphincter tone (22), a calcium channel blocker reduces the tone and spontaneous activity of the sphincter by decreasing the intracellular availability of calcium (22-24). Experimental studies designate that nifedipine has local anti-inflammatory effect (25) and produces modulating effect on the microcirculation too (26). A numbers of studies have shown that topical nifedipine with a healing rate of up to 95% has a higher effectiveness compared to diltiazem with a 67% healing rate (12,13,27). The aim of this study was to make obvious the efficacy of nifedipine treatment against placebo. Other points were defined during this study: duration of treatment for healing achievement, recurrence rate and side effects of nifedipine application.

Our study showed that the topical use of 0.5% nifedipine could achieve complete healing in 70% of the patients after 4wk. This finding is lower than a similar study reported by Perrotti *et al.* (13). Perhaps the addition of local anesthetic to local nifedipine has beneficial effect in lowering internal sphincter tone. On the other hand recurrence has been reported in about 42% of patients treated with nifedipine (28) while our study suggests a lower recurrence rate (26.19%).

An interesting finding of our study is the fact that, despite the applied dosage of nifedipine (0.5%) which

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was at least twice as high as in previous studies (12, 13), there was no increase in adverse effects and so compliance was not affected. However, Katsinelos *et al.* in similar study with longer period of treatment showed higher healing rate with higher side effect frequency (29). Only four patients (6.6%) suffered from mild headache, which was relieved by acetaminophen. On the other hand durability of treatment compared with some studies with various topical agents such as GTN (13), diltiazem (30), nifedipine (12, 13) was shorter and frequency of dosing was decreased too.

The reported adverse effects of topical nifedipine treatment with various dosages were unnoticeable so we can suggest higher concentration of nifedipine with shorter course in future studies to achieve higher and faster healing of fissure with at least the same side effect.

One of the obvious failures of nonsurgical treatment in anal fissure is recurrence. During consultation regarding the advantages and disadvantages of surgical vs. chemical sphincterotomy, patients should be aware that some of the patients receiving nifedipine as the primary treatment for anal fissure subsequently required further treatment.

Although this study has a considerable follow-up period and gives encouraging results, the authors suggest more evaluation in further studies over larger number of patients with longer-term follow up.

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