

A Double-Blind Randomized Trial Comparing the Effectiveness and Safety of Nifedipine and Isosorbide Dinitrate in Chronic Anal Fissure

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Abstract

Background: Chronic anal fissure is a common disease that is accompanied with pain and bleeding during defecation. Various surgical and non-surgical methods have been offered for the treatment of this condition.

Objective: The aim of this randomised clinical study was to compare the effectiveness and safety of nifedipine and isosorbide dinitrate (ISDN) in the treatment of chronic anal fissure.

Methods: This double-blind clinical trial study was performed on patients aged 20 to 60 years old in 2012 to 2013. The samples with a primary diagnosis of chronic anal fissure were enrolled from the patients admitted to public treatment at the educational Imam Ali Clinic, Shahrekord, Iran by researchers and general surgery specialists. The patients were randomised into two groups: nifedipine 0.3% (n = 35) or ISDN 0.2% (n = 35) applied three times a day for three weeks. The patients were examined on the 7th, 14th, and 21st days of treatment, and the symptoms including bleeding, pain, and healing status, as well as the side effects of the drugs, were assessed. Pain was evaluated using a visual analogue scale (VAS).

Results: After 21 days of follow-up, complete healing was achieved in 77.1% (n = 27) of patients in the nifedipine group and 51.4% (n = 18) in the ISDN group (P = 0.05). The mean VAS of the pain on day 21 was 0.91 (SD 0.01) in the ISDN group and 0.45±0.78 in the nifedipine group, with a statistically significant difference (P = 0.038). The bleeding was similar in the two groups (P = 0.498).

Conclusion: In view of the findings on healing status and pain in the patients, nifedipine may be significantly more effective in the treatment of chronic anal fissure than ISDN.

Keywords: chronic, anal fissure, nifedipine, isosorbide dinitrate

Introduction

Anal fissure is the most painful and common problem of the anorectal region. The main symptom of anal fissure is pain during or after bowel movements. The pain is usually sharp or cutting and intensifies during bowel movement. Painful bowel movements are often associated with bleeding. Bleeding is bright red, and the amount is usually insignificant and not mixed with the stool but is observed on toilet paper (1,2). Anal fissure is chronic if there is a history of anal pain during defecation for at least 2 months with sphincter fibres at the base of the lesion (3). The

management is medical or surgical. The success rate of surgery is 90%, with an anal incontinence rate of 1–10%. Because of the complications of surgery, medical treatment preferred (4,5). Several drugs, such as glyceryl trinitrate, botulinum toxin, isosorbide dinitrate (ISDN), L-arginine, and calcium-channel blockers, have been used to reversibly reduce the internal anal sphincter tone until the fissure heals (7,8). Pharmacologic treatment is aimed to reduce the sphincter tonicity and to reversibly enhance the blood supply to the involved area (9). Nifedipine, a dihydropyridine, is a calcium antagonist that is currently available for oral administration for the

treatment of cardiovascular disorders and leads to smooth muscle relaxation and vasodilation. Topical nifedipine has recently been demonstrated to decline anal resting pressure, relieve pain, and heal acute anal fissures and acute thrombosed haemorrhoids (10,11). Similarly, topical ISDN has been shown to contribute to lowering the anal resting pressure and healing anal fissures (12). The success rates of topical calcium blockers are comparable to those of nitrates (13). The efficacy of topical ISDN and nifedipine for chronic anal fissure treatment has been previously demonstrated (14,15). The purpose of the present study is to compare the effectiveness and safety of nifedipine and isosorbide dinitrate in chronic anal fissure. The primary endpoint was fissure healing. Recovery of symptoms including bleeding, pain and the side effects of the drugs comprise the secondary endpoints.

Materials/Subjects and Methods

Patients and methods

This double-blind clinical trial study was performed from 2012 to 2013 on patients aged 20 to 60 years old. Subjects were enrolled by convenience sampling from patients with a primary diagnosis of chronic anal fissure who were admitted to public treatment at the educational Imam Ali Clinic, Shahrekord, Iran by the researcher and by a general surgery specialist.

In the present study, patients with more than a six weeks history of the disease were enrolled. Exclusion criteria were anal infection or cancer, diabetes, atopic fissure along with chronic intensive inflammation, immune deficiency, receiving oral immunosuppressive drugs or corticosteroids, cardiac disease and not being able to complete participation in the study.

Ethics

Informed consent was obtained from all patients, and their data were kept confidential. The research protocol was approved by the Ethics Committee of Shahrekord University of Medical Sciences (ethics code: 91-8-38).

Patients' assignment

The patients enrolled in the study were randomly assigned to two groups: the first group received local nifedipine 0.3% ointment three times a day, and the second group received local

ISDN 0.2% ointment three times a day. Patients in the two groups were asked to take 1–2 g of the ointments by the tip of the middle finger and apply it to the anal canal. The two groups were matched for age and gender. In this study, the drugs were encoded by an individual not included in the research team, and neither the researcher nor the patients had information about the medicine taken by each patient.

The ointment was provided by a pharmacist in tubes with a similar shape and size. For all patients, a diet containing fibre and a 15 minutes warm bath three times a day were recommended.

Clinical follow-up

During the initial visit, patients met with the general surgeon. Additionally, on the 7th, 14th, and 21st days after the first examination, the patients were assessed for symptoms including bleeding, pain, healing status and side effects due to the ointments, including severe headache, severe vertigo while standing, and nausea. In this study, the patients were followed up for a maximum of three weeks.

Definition of outcome parameters

Outcome definitions

Bleeding was classified as severe, moderate, mild, and no bleeding. If bleeding was consistently observed during bowel movements, it was classified as severe; if bleeding was occasionally observed along with bowel movements, as moderate; and if no blood was observed in the underwear, as mild. Longitudinal anal sore healing was recorded in terms of complete, relative and no healing (15). The healing was complete if the anodermal area was without bleeding and inflammation. Relative healing described decreased inflammation with a pale wound with or without muscle display at the bottom of the wound. No healing described a deep wound with inflamed and swollen edges similar to or worse than the wound at the onset of the treatment. Pain was assessed by a visual analogue scale (VAS). The patients were asked to score the pain prior to and after three weeks of treatment. In the VAS, a 10 cm long straight line, called a visual evaluation scale, is used for ranking pain intensity. On this straight line, "0" represents no pain and "10" represents unbearable pain. Effectiveness is defined as reducing bleeding and pain as well as increasing in patient's healing. Therefore, safety is defined as no observable side effects resulting from the use of the drugs. At a

power of 80% with a significance level of $P < 0.05$, and given a maximum failure rate of 10%, 36 patients were included in each group.

Data analysis

One-way repeated measures ANOVA with a Greenhouse Geisser correction was used to assess the changes in the pain score in each group. Student's t test was used to test for significant differences in the pain score between the two groups at different intervals, and a chi-square test was used to assess the differences in bleeding, complications and healing status between the two groups. Quantitative data were used to compare the mean pain score between the nifedipine group and the ISDN group. Statistical analysis was conducted using SPSS 17, and a P value < 0.05 (2-tailed) was considered significant.

Results

Of the 80 patients who were eligible for the study, 8 did not consent to participate. Of the remaining 72 patients, 36 were randomly assigned to the nifedipine group, and 36 to the ISDN group; however, 1 patient from the nifedipine

group and 1 from the ISDN group were excluded during follow-up due to a withdrawal of consent. Therefore, the final analysis included 35 patients in the nifedipine group and 35 patients in the ISDN group. In the nifedipine group, there were 16 women and 19 men; in the ISDN group, 15 women and 20 men. There was no significant difference in gender between the two groups ($P = 0.81$). The age range of the patients was 21 – 34 years with a mean of 33.31 (SD 6.91) in the nifedipine group and 25 – 44 years with mean of 34.25±5.83 in ISDN group. Based on an independent t test, there was no significant difference in age between the two groups ($P = 0.54$).

Outcomes

Bleeding

As shown in table 1, before the treatment, bleeding was medium in 7 participants and mild in 12 participants in the nifedipine group. In the ISDN group, bleeding was medium in 11 participants and mild in 14 participants. According to the chi-square test, there was no significant difference in bleeding between the two groups ($P = 0.474$). A week after treatment, no bleeding was reported

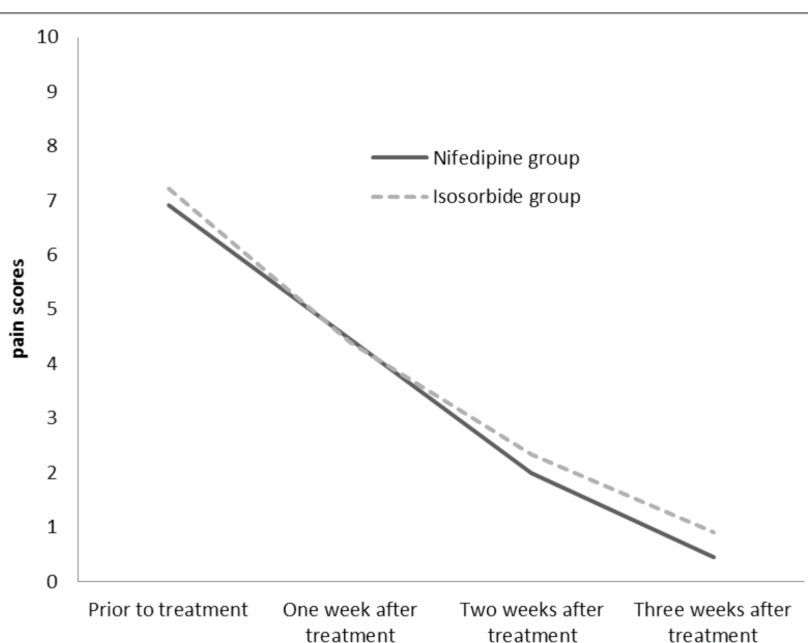


Figure 1: Mean pain score, prior to and one to three weeks after treatment in nifedipine and isosorbide dinitrate groups. Although pain variation variation was not significantly different between the two groups ($P = 0.539$), the participants in both groups exhibited a significant relief of pain ($P < 0.001$).

Table 1: Comparison of bleeding, healing status, and complications between the two groups during treatment intervention

<i>P</i> †	Isosorbide group		Nifedipine group			
	%	No	%	No		
One week after treatment						
0.017*	11.4	4	2.9	1	Severe	Bleeding
	14.3	5	5.7	2	Moderate	
	17.2	6	51.4	18	Mild	
	57.1	20	40	14	No	
0.320	42.9	15	31.4	11	No	Healing status
	57.1	20	48.6	24	Relative	
	0	0	0	0	Complete	
0.001*	82.9	29	22.9	8	Severe headache	Complications
0.150	5.7	2	0	0	Vertigo	
0.001*	37.1	13	5.7	2	Nausea	
Two weeks after treatment						
0.149	5.7	2	0	0	Severe	Bleeding
	11.4	4	2.9	1	Moderate	
	11.4	4	5.7	2	Mild	
0.166	20	7	11.4	4	No	Healing status
	68.6	24	60	21	Relative	
	11.4	4	28.6	10	Complete	
0.001*	42.9	15	5.7	2	Severe headache	Complications
-	0	0	0	0	Vertigo	
0.550	5.7	2	2.9	1	Nausea	
Three weeks after treatment						
0.498	0	0	0	0	Severe	Bleeding
	0	1	2.9	0	Moderate	
	2.9	2	5.7	1	Mild	
0.050	14.3	5	5.7	2	No	Healing status
	34.3	12	17.1	6	Relative	
	51.4	18	77.1	27	Complete	
0.150	5.7	2	0	0	Severe headache	Complications
-	0	0	0	0	Vertigo	
0.310	2.9	1	0	0	Nausea	

**P* < 0.05 significant

† χ^2 test

in 14 participants in the nifedipine group and in 20 participants in the ISDN group; this difference between the groups was significant ($P = 0.017$). At two and three weeks after treatment, 91.4% and 97.1% in nifedipine group and 71.4%, and 91.4% in the ISDN group, respectively, were reported to have no bleeding ($P = 0.149$, and $P = 0.498$).

Pain

Based on table 2, before the treatment, the mean VAS was 7.22 in nifedipine group and 6.91 in the ISDN group; based on an independent t test, there was no significant difference between the two groups ($P = 0.162$). Three weeks after treatment, the mean VAS was significantly less in the nifedipine group than in the ISDN group ($P = 0.038$). The average pain scores prior to and 1– 3 weeks after treatment are shown in figure 1.

Based on analysis by factorial repeated measures ANOVA, there was no significant difference in pain score between the two groups ($P = 0.539$). One-way repeated measures ANOVA showed significant decreases in the pain score in the nifedipine group [$F(2.012,68.4) = 883.06, P < 0.001$] as well as the ISDN group [$F(1.87,63.62) = 428.91, P < 0.001$] across the four time-points.

Healing status

Results for healing status are shown in table 1. One week after treatment, 11 participants in the nifedipine group reported no healing and 22 participants reported relative healing. In the ISDN group, 15 participants reported no healing and 20 reported relative healing ($P = 0.32$). At two and three weeks after treatment, complete healing was reported by less patients in the ISDN group than in the nifedipine group ($P = 0.166$ and $P = 0.05$, respectively).

Consequences of medicines

The consequences of the medicines are shown in table 1. One week after treatment, eight participants in the nifedipine group reported severe headache and 2 participants reported nausea. In the ISDN group, 29 patients had a severe headache, 2 patients reported vertigo while standing, and 13 patients reported nausea. Severe headache and nausea were significantly less in the nifedipine group than in the ISDN group ($P = 0.001$). Two weeks after treatment, only severe headache was significantly less in the nifedipine group ($P = 0.001$). Three weeks after treatment, no consequences were reported in the nifedipine group, but two patients with severe headache and one with nausea were reported in ISDN group.

Discussion

Based on our findings, after 21 days of follow-up, of all the patients with anal fissure treated with ISDN and nifedipine, the nifedipine-treated patients had significantly less VAS pain as compared to the ISDN-treated patients. Additionally, for healing status in the nifedipine group, the participants had complete and relative healing, with a significant difference from the ISDN group. By replicating the observations in each group, the pain decrease was similar, and after follow-up, pain was significantly relieved in both groups. Our study results demonstrated that topical nifedipine is more efficacious than ISDN. A numbers of studies have shown that topical nifedipine with a healing rate of up to 95% has a higher effectiveness compared to diltiazem, which has a 67% healing rate (16,17).

Table 2: Mean and SD of VAS of pain in the two groups during treatment intervention

P^\dagger	Three weeks after treatment		Two weeks after treatment		One week after treatment		Prior to treatment		VAS of pain
	SD	Mean	SD	Mean	SD	Mean	SD	Mean	
0.539	Nifedipine group								
	0.78	0.45	0.97	2	0.85	4.45	1.11	7.22	VAS of pain
	Isosorbide group								
	0.01	0.91	1.16	2.34	0.73	4.40	0.70	6.91	VAS of pain
	0.038 *		0.185		0.765		0.162		P^\ddagger

* $P < 0.05$ significant
 † Factorial repeated-measures
 ‡ t test

Today, the treatment of chronic anal fissure has become challenging because of irreversible damage and deformation of the internal anal sphincter. Additionally, given that most patients with anal fissure are young and worried about non-voluntary faeces excretion and the consequences after surgery, the use of alternative medicines for treating patients with anal fissure has been of recent concern (18).

Calcium channel blockers such as nifedipine have been successfully used for treating anal fissure (19). The transport of calcium through the L-type calcium channels is important for maintaining internal anal sphincter tone. The healing that results from nifedipine is due to not only the effect on the decrease in anal pressure through suppressing calcium flow into the sarcoplasm but also its anti-inflammatory effects. Studies have shown that nifedipine has an adjusting effect on microcirculation and a local anti-inflammatory effect alongside loosening of the internal sphincter of the anus (20). The most common dosage is 0.2%, which is applied topically 2–3 times daily for 6–8 weeks.

In a study conducted by Golfam et al. (15), 110 individuals were studied, out of whom 60 were treated with nifedipine and 50 were controls (conventional treatment). In the nifedipine group, 70% of patients achieved recovery, and in controls, 12% recovery was observed after four weeks. In the Golfam et al. study, recovery and healing of the pain in the nifedipine group was significantly different from that of the control group.

In the present study, severe headache and vomiting in occurred in 5.7% and 2.9%, respectively, of the patients in the ISDN group, while no side effects were reported in the nifedipine group. Thus, it can be assumed that nifedipine consumption is safer than ISDN. Headache is an important adverse event of nitrate treatment and occurs in up to 50% of the patients, who are frequently treated with simple analgesics. It is usually mild and leads to discontinuation of treatment in less than 10% of patients. A positive correlation between nitrate dose and headache has been demonstrated (6). In a study by Berkel et al., after nine weeks of treatment with ISDN, 11 out of 33 patients improved, and 18 out of 27 were treated in a Botox poison group. After one year of ISDN treatment, a 50% recurrence was observed relative to the Botox poison group (21). The reported success rate of ISDN is 50 – 85% (22–24). Regional applications of ISDN have reduced anal pressure, increased the anodermal blood flow, and made the healing of the fissure

possible (25). However, drug doses and durations of treatment varied in the previously reported series (25–27). Kirkil et al. (26), reported that treatment with 5% and 10% topical ISDN three times a day provided a success rate of 53.3% and 26.7%, respectively, on the 20th day. Parellada (27), on the other hand, reported a success rate of 67% with a five weeks 0.2% ISDN treatment and a success rate of 89% with a 10 weeks treatment, which is higher than the success rate of treatment with ISDN in the present study, probably because of our failure to follow the patents for a longer period of time. Three weeks of follow-up may be too early to assess the efficacy of treatment.

Many studies, including the present study, have shown that the first step in the treatment of chronic anal fissure should be medical treatment. In cases of lack of response to the treatment, non-acceptance by the patient or repetitive recurrence, it should be treated surgically.

One of the strengths of the present study was double-blinding, which was particularly important, especially for pain scores, to avoid potential bias related to the drugs used.

Our study does have some limitations, such as the small sample size of the two groups and failure to assess other side effects, such as blood pressure. In addition, follow-up of the patients was conducted by the same researcher who prescribed the treatment and hence was not blind to the patients' treatment assignment. Factors that could potentially affect wound healing (e.g., smoking) were not taken into consideration. Despite these limitations, our study adds useful data regarding the treatment of anal fissure, though further studies are needed.

Conclusion

In this study, nifedipine performed better than ISDN as a treatment for chronic anal fissures and was more effective for the relief of anal fissure pain and the healing rate. In addition, the relatively low occurrence of adverse effects presents an advantage of the nifedipine topical application. However, studies with larger sample sizes and longer follow-up (for example, 5 weeks) could yield findings of a higher efficacy of ISDN.

Further investigations with long-term follow-up and a standard assay including evaluation of blood pressure and other adverse effects due to topical application of nifedipine and ISDN are needed for the precise assessment of their therapeutic efficacy. Therefore, studies with larger sample sizes might more clearly demonstrate

whether there are differences in adverse events and treatment efficacy between nifedipine and ISDN.

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Conflict of Interest

None

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