Middle East J Dig Dis. April 2023;15(2):121-125

doi 10.34172/mejdd.2023.330 http://mejdd.org

Middle East Journal of Digestive Diseases MEJDD

Original Article

The Effect of Topical Nifedipine versus Diltiazem on the Acute Anal Fissure: A Randomized Clinical Trial

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Abstract

Background: The anal fissure is one of the most common anorectal diseases that is associated with reduced quality of life and productivity loss. We aimed to compare the efficacy of topical nifedipine and diltiazem for the treatment of acute anal fissure (AAF).

Methods: This single-blind randomized clinical trial was conducted at Ziaeian hospital, Tehran**.** Patients with an acute fissure diagnosis were allocated to two groups. Group A applied 3 grams of 0.3% nifedipine cream on the peri-anal area, three times a day, for 8 weeks. Group B also applied the same amount of 2% diltiazem-ointment on the peri-anal area for the same period. The primary outcome was fissure remission in the 8th week of the treatments. The duration of pain relief, the side effect of treatment, and the recurrence rate were also compared between the groups.

Results: After 8 weeks of treatment, a remission rate of 77.4% was shown in the nifedipine group which was significantly higher than the diltiazem group with a remission rate of 54% ($P=0.01$). Applying nifedipine ointment is associated with earlier pain relief compared with diltiazem ($P<0.001$). After 6 months of follow-up, the relapse rate was not statistically different between the nifedipine and diltiazem groups (16.3% versus 21.4%, respectively).

Conclusion: The application of topical nifedipine is associated with shorter pain relief and more remission rate for AAF compared with topical diltiazem. However, both methods were not different in terms of related side effects and AAF recurrence rate.

Keywords: Diltiazem, Nifedipine, Acute anal fissure

Cite this article as: Momayez Sanat Z, Mohammadi Ganjaroudi N, Mansouri M. The effect of topical nifedipine versus diltiazem on the acute anal fissure: a randomized clinical trial. *Middle East J Dig Dis* 2023;15(2):121-125. doi: 10.34172/mejdd.2023.330.

Received: October 20, 2022, **Accepted:** February 9, 2023, **ePublished:** April 30, 2023

Introduction

The anal fissure is one of the most common anorectal diseases that is associated with reduced quality of life and productivity loss. An anal fissure is defined as a tear or open ulcer that develops in the skin of the anal margin.[1,2] Acute anal fissure (AAF) (lasting less than six weeks) is more common than the chronic type. An AAF is usually treated spontaneously or by maintaining a high-fiber diet and staying well hydrated through receiving enough fluids; however, it is associated with pain and bleeding, and in case of ineffective treatment it can lead to recurrence, infection, and abscess.[1,3]

For the treatment of AAF, the main goal is the reduction of the internal anal sphincter (IAS) resting pressure and the improvement of blood flow in the ischemic area. The American Society of Colon and Rectal Surgeons (ASCRS) recommends that non-surgical treatment, especially with a pharmacological agent such as topical glyceryl trinitrate and calcium channel blockers (CCB), should be considered as the first-line therapy.[4,5] Currently, topical treatment with glyceryl trinitrate is widely used for the treatment of anal fissures with a healing rate of up to 80%, although, 20-30% of patients discontinue their treatment[6,7] because of various side effects like headache, postural hypotension, flushing, allergy.[8-10] Also, a high recurrence rate of 50% was reported.[11]

CCBs, like diltiazem and nifedipine, are nitrogen oxide alternative therapeutics that show fewer side effects.[8] CCBs reduce muscle tone by increasing blood flow.[1,12] An updated Cochrane review published in 2012 reported that CCBs (nifedipine and diltiazem) and glyceryl trinitrate have the same effect on fissure healing.[6] However, CCBs have fewer side effects, so some physicians prefer to prescribe CCBs for the treatment of anal fissures.[8] Although all CCBs are from the same drug class, they contain heterogeneous compounds and have different chemical structures, so their potency for blocking calcium channels will be different. Diltiazem potentially inhibits calcium function in the cardiac and vascular smooth muscle cells, while nifedipine is more potent in relaxing peripheral smooth muscle cells.[13] Nifedipine and diltiazem efficacy for the treatment of anal fissures have been evaluated separately in various studies. Kujur and colleagues showed that these two drugs had the same

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effect in the treatment of chronic anal fissures,[14] however, the number of studies focused on the application of these drugs for the treatment of AAFs is limited. Also, nifedipine is not a common treatment for anal fissures in Iran and it is the first study to use nifedipine for the treatment of AAF. Therefore, in the present study, we aimed to compare the effect of topical nifedipine versus diltiazem for the treatment of AAF.

Materials and Methods

Study Design and Ethics

This single-blind randomized clinical trial was conducted in Ziaeian hospital between July 2021 and December 2021. The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (Ethics Approval ID: IR.TUMS.MEDICINE.REC.1399.420) and registered at the Iranian Registry of Clinical Trials website (identifier: IRCT20190414043275N1). Also, written informed consent was taken from each participant.

Participants

The participants were those women and men who were admitted to the Gastroenterology Clinic because of anal pain or rectal bleeding. Patients who were diagnosed with AAF were recruited. Inclusion criteria were age above 18 years and AAF symptoms lasting for less than 6 weeks. An anal fissure is a small tear in the thin, moist tissue (mucosa) that lines the anus. On the other hand, patients with recurrent anal fissures, a history of anal surgery, anorectal malformation, receiving oral therapy or topical medications for anal fissures, and hypersensitivity to diltiazem were excluded from this study.

Random Allocation Concealment and Blinding

In the present study, eligible participants were randomly allocated to two groups of intervention according to a computer-generated list. Since the primary packaging type of each drug was identical; blinding was not possible for participants, but we placed drugs in similar secondary packages, to blind the physician who was responsible for intervention allocation. A special code was defined for each drug box and kept in a sealed envelope. When the participant's eligibility was confirmed by the physician, the clinic's nurse provided the physician with the drug box according to the envelope contents. The outcome investigators (nurses and specialists) were unaware of the type of intervention.

Intervention

Before the intervention, participants' demographic characteristics, anal examination findings, and symptoms (pain) were recorded. Then patients were randomly allocated into two equal groups. The participants of group A were asked to apply 3 g of 0.3% nifedipine cream on the peri-anal area (2-2.5 cm inside the internal sphincter, about a knuckle of the index finger), three times a day, for 8 weeks. In group B, the participants were asked to use the same amount of 2% diltiazem-ointment similar to that of the nifedipine group on the peri-anal area (inside the internal sphincter) for the same period. Also, both groups were advised to intake a high-fiber diet, use 10-15 minutes of warm sitz bath three times per day, and increase water consumption. The participants were followed up for 8 weeks and anal pain and complications associated with treatment were asked about and recorded every week through phone calls. In the 8th week, the anal examination was performed for all participants, and fissure remission was evaluated. Complete remission was defined as a complete epithelialization of the mucosa at the fissure area.

After 6 months of intervention, the fissure relapse (recurrence fissure symptoms) was evaluated through a phone call. If the patient had fissure symptoms such as pain or bleeding, she/he was invited to the clinic for further examinations.

Outcomes

The primary outcome was fissure remission in the 8th week of the treatments. The duration of pain relief, the side effect of treatment, and the recurrence rate were also compared between the two groups.

Sample Size and Statistical Methods

Based on previous studies,[15-17] the rate of anal fissure healing in the diltiazem group was 60% and in the nifedipine group was 85% with a 5% significance level and a power of 80% and anticipated dropout a sample size of 53 patients per group was necessary.

Student's t-test was used to assess the difference between the two groups for pain relief and bleeding. We also used chi-square tests to examine the significant variation in remission rate and side effects between the groups. The level of statistical signification was P value < 0.05. All statistical analyses were carried out using SPSS software version 16.

Results

The study was initiated on 106 participants, 53 participants in the diltiazem and 53 participants in the nifedipine group. Three participants of the diltiazem group did not adhere to the assigned regimen and withdrew from the study. Finally, 50 participants in the diltiazem and 53 participants in the nifedipine group were compared in the final analysis (Figure 1).

The basic characteristics of the participants are shown in Table 1. The mean age (SD) of the participants was 40.67 (± 10.34) and 37.98 (± 11.85) in the nifedipine and diltiazem groups, respectively.

According to the results described in Table 1, there was no significant difference between the two groups regarding age, body mass index (BMI), sex, and smoking ($P > 0.05$). Of the total participants, 80% in the diltiazem group and 73.6% in the nifedipine group reported

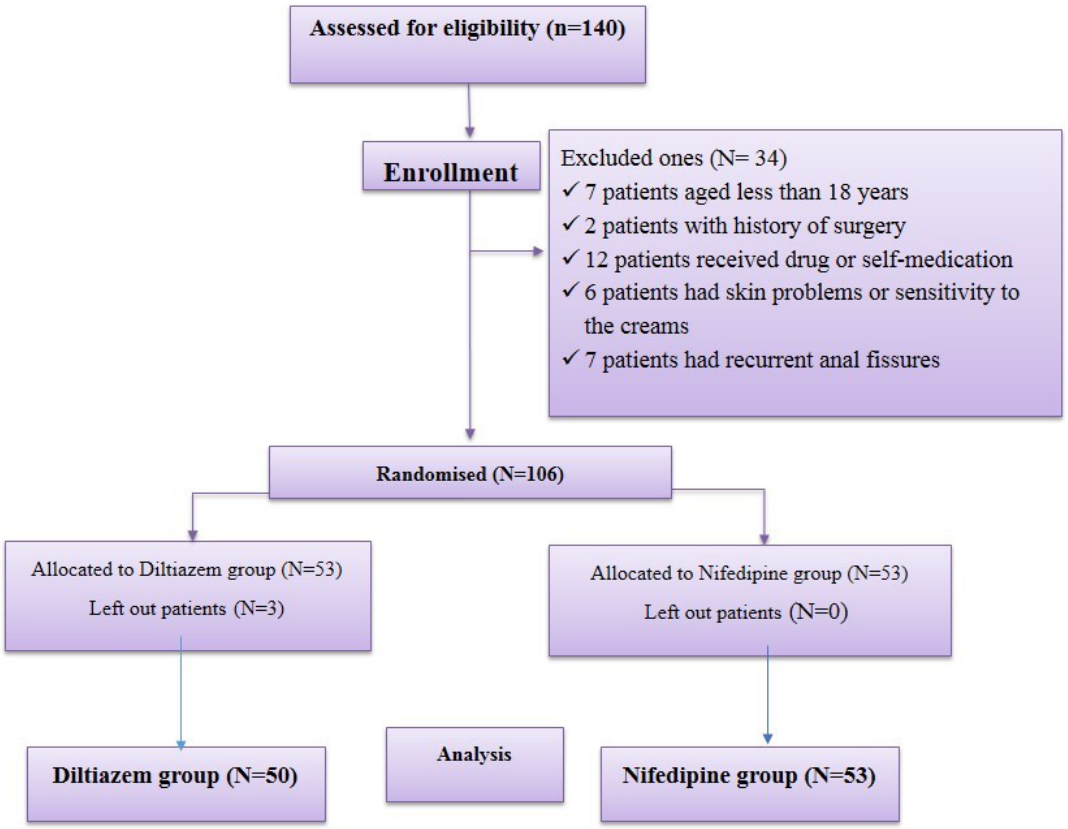

Figure 1. CONSORT diagram

Table 1. Basic characteristics of the participants

Variables	Diltiazem group (n=50)	Nifedipine group (n=53)	*P* value
Gender, No. (%)			
Female	43 (86)	41 (77.4)	0.25
Male	7 (14)	12 (22.6)	
Age (years)	37.98 (11.85)	40.67 (10.34)	0.22
Smoking, No. (%)			0.194
Yes	1 (2)	5 (7.7)	
No	49 (98)	48 (92.3)	
BMI, No. (%)			0.65
Normal	17 (37)	14 (28.6)	
Over Weight	17 (37)	22 (44.9)	
Obese	12 (26.1)	13 (26.5)	
Fissure location, No. (%)			0.10
Anterior	21 (42.9)	27 (54)	
Posterior	24 (49)	23 (46)	
Both	4 (8.2)	0 (0)	
Defecation, No. (%)			0.49
Normal	10 (20)	14 (26.4)	
Diarrhea	0 (0)	0 (0)	
Constipation	40 (80)	39 (73.6)	

constipation. The anal fissure was located in the posterior midline in 24 (49%) and 23 (46%) participants in the diltiazem and nifedipine groups, respectively. The rates of constipation and localization of the anal fissure were not significantly different between the two groups (0.49 and 0.92, respectively) (Table 1).

The remission rate after 8 weeks of treatment and relapse in the 6 months after the intervention is presented in Table 2. After 8 weeks of treatment, a remission rate of 77.4% was shown in the nifedipine group, which was significantly higher than the diltiazem group with a remission rate of 54% ($P=0.01$). The mean time taken for complete pain relief was 7-21 days in the diltiazem group and 4-10 days in the nifedipine group. This shows that applying nifedipine ointments is associated with earlier healing compared with diltiazem ($P<0.001$).

In the nifedipine group, the rate of self-reported complications was recorded as the following: flushing (6.82%), dizziness (6.82%), hypotension (4.55%), headache (4.55%), and heartbeat (2.27%). In the diltiazem group, complications were dizziness (2.44%) and headache (2.44%). The rate of complications was not significant. When it comes to the recurrence of AAF in the participants, a follow-up was carried out after 6 months and the results represented that the relapse rate was not statistically different between nifedipine and diltiazem groups (16.3% versus 21.4% respectively).

Discussion

This study showed that the application of nifedipine was more efficient in terms of pain relief and remission rate compared with diltiazem in patients with AAF. The side effects were rarely reported by the patients in both groups

Table 2. Comparison of remission, relief, and relapse of symptoms between the two groups

Outcomes	Diltiazem group (n=50)	Nifedipine group (n=53)	*P* value
Healing, No. (%)	27 (54)	41 (77.4)	0.01
Side effect, No. (%)	2 (4)	7 (13.2)	0.16
Relapse, No. (%)	6 (21.4)	7 (16.3)	0.75
Time taken for complete pain relief (wk), Median (min-max)	12 (7-21)	6 (4-10)	<0.001

of patients and side effects were not significantly different between the two drugs. The AAF recurrence rate was similar between the two groups in this study.

Although the exact underlying pathophysiology of anal fissure is not clear, it is a widely held view that sphincter hypertonia following a traumatic injury can lead to increased anal canal pressure and subsequent local ischemia of the anal mucosa.[18] Therefore, therapeutic methods are focused on the reduction of IAS resting pressure to ameliorate local blood circulation in the ischemic area. Calcium ions have a fundamental function in the maintenance of basal IAS tone.[19] CCBs inhibit cellular calcium influx through voltage-gated L-type calcium channels in smooth muscle myocytes, thereby they relax smooth muscle and hence enhance blood perfusion. Finally, the boosted blood supply in the anal fissure area facilitates the healing process.[8] Similar to our results, in a study by Kujur and colleagues topical nifedipine or diltiazem was introduced as an effective method for the treatment of AAF. Accordingly, a higher healing rate was reported compared with our results.[14] According to the results of other studies, an acceptable healing rate was reported for the application of topical CCBs such as nifedipine or diltiazem as a first-line treatment method of AAF.[5,20,21] There is a difference between the remission rates reported in the earlier studies. This disagreement could be related to differences in drug concentration, duration of intervention, or the characteristics of the participants.

Few clinical trials have been conducted to compare the effect of nifedipine or diltiazem on AAF.[14] In a study by Antropoli and colleagues, 141 patients received topical 0.2% nifedipine gel, and 142 patients received topical 1% lidocaine and 1% hydrocortisone acetate gel, every 12 hours for three consecutive weeks. The rate of complete remission of AAF in the nifedipine group was 95%, whereas, in the control group, the remission rate was only 50%.[22] Also, Akıncı et al evaluated the AAF treatment and recurrence prevention in 100 participants that randomly received two different treatment methods, 0.2% glyceryl trinitrate verse 0.5% topical nifedipine, for 21 days. Symptomatic relief and the healing rate of the nifedipine group were higher than the glyceryl trinitrate group (56% and 86% versus 22% and 64%, respectively).[18] Katsinelos and colleagues showed that treatment with 5% nifedipine for 8 weeks was associated with an 85.2% healing rate in patients with AAF. Headache was reported in 7.4% of patients.[17]

After medical treatment, anal canal pressure returns to the pre-treatment level, so in medical treatment methods, the recurrence rate is high .[18] In this study, the recurrence rate after 3 months was 16.3% in the nifedipine group and 24.1% in the diltiazem group, which was not statistically different. In the Akıncı et al study, recurrence after 3 months of follow-up in the nifedipine group was 18%.[18] In Wasfy and colleagues' study, after 4 months of follow-up, no recurrence was observed in participants with acute fissures who underwent 8 weeks of diltiazem treatment.[9]

Studies that evaluated nifedipine for fissure treatment, have reported headaches.[23] In another study fissure treatment with topical diltiazem was associated with hypotension in 10%, fibrosis in 15%, skin tag in 15% of participants, and also headache.[9] Based on our results, in the nifedipine group, flushing, dizziness, hypotension, and heartbeat were reported. In the diltiazem group, the side effects were headaches and dizziness.

One of the strengths of our study was that it has been designed as a clinical trial. However, the participants were aware of the kind of treatment which is one of the limitations of this study.

Conclusion

In comparison with previous treatment methods, the application of topical nifedipine and diltiazem could have several advantages including reduction of pain and bleeding, fewer side effects, and a low rate of AAF recurrence. The results of our study showed that topical nifedipine compared with topical diltiazem is associated with a shorter treatment period and more remission rate for the treatment of AAF. Also, topical diltiazem and nifedipine were not different in terms of CCBs related side effects and AAF recurrence rate.

Acknowledgments

The authors wish to thank Tehran University of Medical Sciences for the approval and financial support of this study, as well as all the participants in this study.

Competing Interests

The authors declare no conflict of interest related to this work.

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