

## The Effect of Asacol (Mesalazine) Suppository on the Healing of Acute Fissures Caused by Diarrhea: A Randomized Controlled Trial

Leila Ghahramani<sup>1</sup>, MD; Seyed Vahid Hosseini<sup>1</sup>, MD; Hajar Khazraei<sup>1\*</sup>, PharmD, MD; Sajad Heshmati Far<sup>1</sup>, MD; Khadije Gorgi<sup>1</sup>, MD

<sup>1</sup>Colorectal Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

### \*Corresponding author:

Hajar Khazraei, PharmD, PhD; Colorectal Research Center, Mohammad Rasolallah Research Tower, Khalili Street, Postal code: 71936-35899, Shiraz, Iran. Tel: +98 71 36281464; Email: hajarkhazraei@gmail.com

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### Abstract

**Background:** An anal fissure is a linear, superficial tear in the squamous epithelium of the anus, specifically in the anoderm distal to the dentate line. Given the well-established anti-inflammatory properties of mesalazine in acute conditions, it helps prevent secondary stricture and reduces the risk of complications such as incontinence that may arise during fissure surgery. This study investigates the effect of Asacol (Mesalazine) suppositories in the treatment of acute anal fissures caused by diarrhea, compared to a placebo.

**Methods:** This double-blind, randomized controlled clinical trial involved 69 patients aged 18 to 65 years who experienced diarrhea followed by acute fissure symptoms lasting less than six weeks. Participants were randomly assigned and blinded into two groups: 34 in the control group and 35 in the treatment group. Both groups applied diltiazem ointment three times daily and took hot water basin baths twice daily. The control group received a placebo, while the treatment group was administered Asacol suppositories. The primary outcome measures were the degree of pain reduction and the speed of recovery.

**Results:** The findings indicated that the recovery rate in the experimental group (80%) was significantly higher than in the control group (38.2%) ( $P < 0.001$ ). The current study also investigated the consumption of coffee and the incidence of anal fissures, revealing that the likelihood of recovery was not associated with tea or coffee consumption. Additionally, patient age showed no significant relationship with the chance of recovery; the mean age of the study population was  $43.49 \pm 15.08$  years.

**Conclusion:** The findings of the current study indicate that Asacol suppositories have a significant effect on the healing of acute anal fissures caused by diarrhea and can be considered a viable treatment option.

**Keywords:** Asacol Suppository, Diarrhea, Acute anal Fissures

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### Introduction

An anal fissure is a wound in the squamous epithelium of the anus, characterized as a linear, superficial tear in the anoderm distal to the dentate line (Figure 1). It is typically caused by the

passage of hard stool (1); however, acute diarrhea, pregnancy, laxative abuse, and other conditions can also contribute to fissure formation. These fissures are thought to result from changes in stool acidity, which lead to mucosal inflammation (2). Anal fissures usually cause pain during defecation (1). In

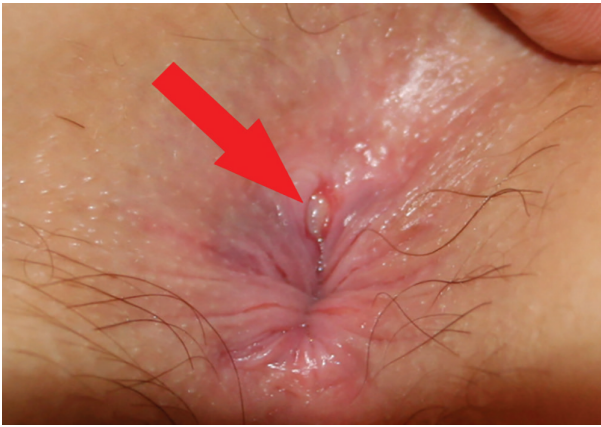


Figure 1: Anal Fissure

nearly 90% of the cases, the fissure is located in the dorsal midline. According to a study by Schouten et al., blood flow in the anoderm at the dorsal midline is lower than in other regions of the anal canal (3).

The remaining 10% of fissures are typically located along the anterior midline. Atypical fissures may be multiple, situated outside the midline, large, and/or irregular in shape. Fissures can result from inflammatory bowel disease (IBD), local or systemic malignancies, sexually transmitted infections, trauma, tuberculosis, or chemotherapy. The etiology and prevention strategies for typical, benign fissures remain incompletely understood. The most significant clinical finding in typical fissure examination is severe spasm of the internal anal sphincter, which appears to cause pain through sphincter ischemia (3). Fissures are classified as acute or chronic based on the duration of initial symptoms: acute fissures persist for less than six weeks, whereas chronic fissures last longer than six weeks (4). Relief of sphincter spasm is associated with pain reduction and fissure healing without recurrence.

The first line of management for acute anal fissure, regardless of the cause (constipation, diarrhea, sexually transmitted diseases, etc.), is medical treatment. Conservative therapy includes various rectal ointments, hydration, sitz baths, and diet modifications (1).

Asacol suppository contains the active ingredient mesalazine, also known as 5-aminosalicylic acid (5-ASA), which is a component of sulphasalazine, a salicylate compound used in the treatment of ulcerative colitis and Crohn's disease. Its anti-inflammatory properties have been proven (5). In one study, local steroid infiltration was shown to be an effective anti-inflammatory treatment for chronic anal fissures (6).

The aim of treatment is to prevent chronic anal fissures. Managing chronic anal fissures with medication is more challenging compared to acute anal fissures and requires greater time, cost, and often surgical intervention. Additionally, both minor and major complications are significant concerns for physicians and patients. Our hypothesis is that acute

anal fissures are primarily caused by changes in stool acidity, which lead to local mucosal inflammation, and that the use of mesalazine may be beneficial.

This study is a randomized controlled clinical trial designed to investigate the effect of Asacol suppositories in the treatment of acute fissures caused by diarrhea, compared to a placebo. The study aims to evaluate the efficacy of Mesalazine in relieving pain, reducing bleeding, alleviating itching associated with acute fissures, and promoting the repair and epithelial healing of fissure surfaces resulting from diarrhea.

## Materials and Methods

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (No. IR.SUMS.MED.REC.1399.095 and registered on ClinicalTrials.gov with the identifier NCT05091775).

### Settings

In this double-blind, randomized controlled clinical trial, 69 female patients aged 18 to 65 years with diarrhea and subsequent acute fissure (symptoms lasting less than six weeks) were randomized and blinded into two groups: 34 in the control group and 35 in the treatment group. Informed consent was obtained from all patients prior to treatment. The CONSORT flow diagram is shown in Figure 2.

Patients were selected consecutively from the patient list. A 1:1 block randomization sequence with randomly varying block sizes of 4, 6, and 8 was generated using a computer-based random number generator. Group assignments were concealed using sequentially numbered, opaque, sealed envelopes, which were opened only after baseline assessment and enrollment.

The patients' medications in both groups were provided in unidentified packages prepared at Shahid Faqihi Hospital. Based on a randomization table of random numbers, patients were assigned to one of the groups and received their respective treatments. The allocation of each patient to Group 1 or Group 2 was conducted by a separate research assistant. Patients in the first group, the control group, were treated with diltiazem gel, approximately the size of a pea, applied topically three times daily, along with hot water baths twice daily and placebo suppositories (manufactured by the Shiraz Faculty of Pharmacy).

Patients in the second group, the treatment group, received topical diltiazem gel three times daily, warm sitz baths twice daily, and one Asacol rectal suppository each night for 14 consecutive days.

**Inclusion Criteria:** Females aged between 18 and 65 years, presenting with an acute fissure and symptoms lasting less than 6 weeks following non-bloody diarrhea.

**Exclusion Criteria:** Patients with recurrent fissures accompanied by skin appendages; a history of long-term constipation; those using immunosuppressive

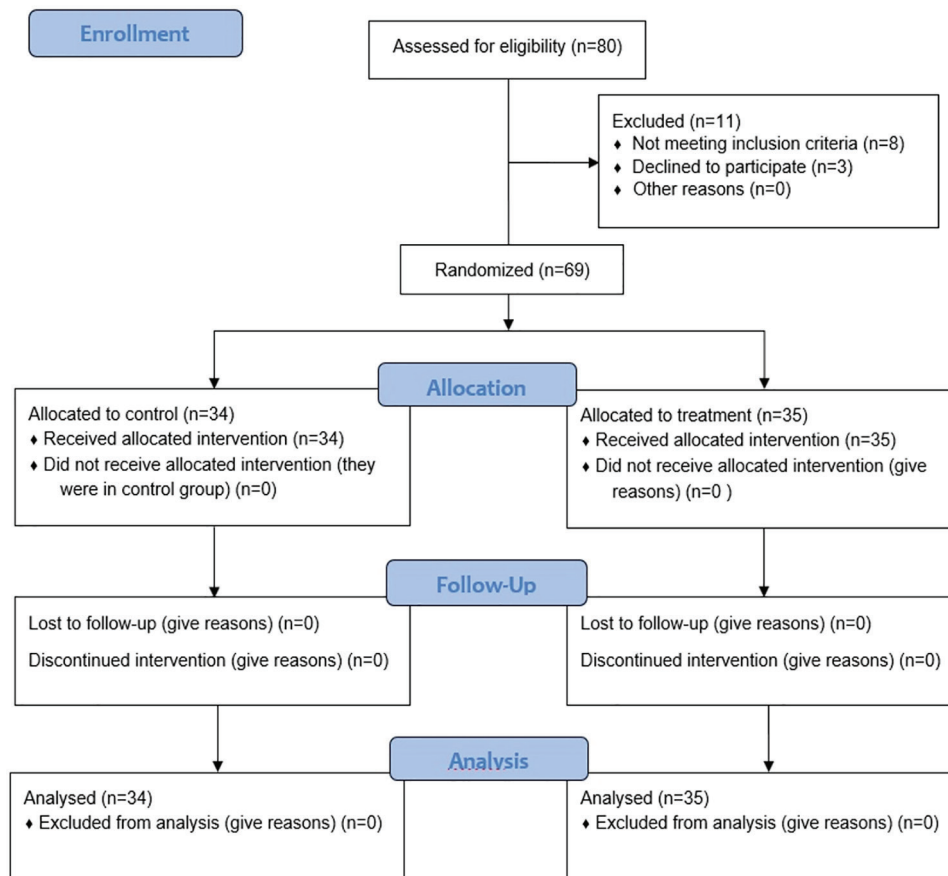


Figure 2: CONSORT Flow Diagram

drugs or corticosteroids; patients suffering from inflammatory bowel diseases such as Crohn's disease and ulcerative colitis; pregnant women; individuals with Grade 3 and 4 hemorrhoids, nerve diseases, or obsessive disorders; those with a previous history of anal surgery; patients with skin diseases such as eczema and psoriasis; those with sexually transmitted infections, tuberculosis, mucosal prolapse, anal fistula, or who have undergone pelvic area radiotherapy were excluded from the study. Additionally, patients allergic to Asacol suppositories or those who did not use them for two weeks were excluded. The presence of a skin tag, indicating chronic fissure, also led to exclusion from the study.

#### Information Collection Tool and Processes

A detailed history and comprehensive examination were conducted for all patients prior to treatment. Patients were interviewed with questions regarding the history related to their condition, including the type, onset time and complaint duration, pain intensity, presence of previous constipation, rectal bleeding, and prior treatments.

For the objective evaluation of pain, a standard method, the Visual Analog Scale (VAS), was used to assess pain during and after defecation, where 0 indicates no pain and 10 represents the maximum possible pain. Patients were examined in the left lateral position to determine the type and location

of the fissure and to rule out other pathologies such as tumors, fistulas, and abscesses.

Patients in each group received daily treatment for two weeks. They were evaluated at the end of the first, second, and sixth weeks. During each visit, a physician conducted interviews to minimize the risk of researcher bias. Treatment adherence and pain levels were recorded using VAS. The primary outcome of the study was the rate of fissure improvement six weeks after treatment, assessed through clinical examination. Healing was defined as complete epithelialization of the fissure site without residual scarring or cracks. Secondary outcomes included reductions in pain and other symptoms. The degree of pain reduction and the speed of recovery were key outcome measures. To eliminate observer bias, a single researcher evaluated all symptoms and measured the improvement rate.

#### Statistical Analysis

In this study, data collected from patients were analyzed using SPSS version 19 software with the Mann-Whitney U test, Independent T-test, and Pearson correlation coefficient. Logistic regression analysis was also performed, and a p-value of less than 0.05 was considered statistically significant.

#### Results

Patients were categorized into two groups. The mean

age (SD) in the control group was 46.24 (16.34) years, while in the experimental group, it was 40.83 (13.45) years. The mean (SD) water consumption (glasses/day) was 1.68 (1.25) in the control group and 4.86 (2.57) in the experimental group. The mean (SD) tea and coffee consumption (glasses/day) was 1.56 (1.24) in the control group and 1.69 (1.41) in the experimental group; this difference was not statistically significant ( $p > 0.05$ ) (Table 1).

As shown in Table 2, the percentage of improvement in the experimental group (80%) was significantly higher than that in the control group (38.2%)

( $P < 0.001$ ).

The patients did not exhibit any infections of human papillomavirus (HPV), tuberculosis (TB), or sexually transmitted diseases. In the control group, two patients reported alcohol use, while in the experimental group, one patient consumed alcohol. Additionally, two patients in the experimental group had a history of smoking.

The logistic regression model analyzing the healing status of anal fissures indicated that none of the variables examined had a significant association with the likelihood of fissure healing (Table 3).

**Table 1:** Patient Characteristics and Demographic Data

Qualitative variable (Number)		Control group n=34	Experimental group n=35
Healthy weight		4	20
Overweight		18	15
Obesity		10	0
Morbid obesity		1	0
Pain	None	9	1
	Mild	16	2
	Moderate	8	4
	Sever	1	28
Itching	None	22	18
	Mild	10	2
	Moderate	1	5
	Sever	1	10
Burning	None	4	9
	Mild	15	5
	Moderate	13	8
	Sever	2	13
Bleeding	None	17	14
	Mild	13	7
	Moderate	3	2
	Sever	1	12
Diarrhea	None	15	18
	<1 week	19	11
	1-3 weeks	0	6
Constipation hx.	Yes	5	14
	No	29	21

**Table 2:** Recovery Status at the Sixth Week of Follow-Up

Qualitative variable		Control group	Experimental group	P-value*	In (common Odds ratio) (95% CI)	Common Language Effect Size %
Recovery status in the sixth week of follow-up (Number, %)	Recovery	13 (38.2 %)	28 (80%)	<0.001	1.866 (0.787-2.945)	76.65% R=0.457
	No recovery	21 (61.8%)	7 (20 %)			

\* $P < 0.05$  as significant level

**Table 3:** The Logistic Regression Model of Anal Fissure Healing Status

Variable	P-value*	Odds ratio (95% ci)
Age	0.556	0.978 (0.907-1.054)
Body mass index	0.989	0.984 (0.108-8.995)
Diarrhea	0.302	4.075 (0.282-58.802)
Constipation	0.179	4.055 (0.527-31.215)
History of radiation therapy	0.676	1.937 (0.087-42.970)
History of chemotherapy	0.683	0.528 (0.025-11.339)
Consumption of tea and coffee	0.679	1.233 (0.457-3.326)

\*  $P < 0.05$  was considered the level of significance.

## Discussion

The present study was conducted to investigate the effect of Asacol suppository on the healing of acute fissures in patients compared to standard treatment. This study is based on the hypothesis that acute fissures caused by diarrhea result from local inflammation in the endodermal area, and that treatment should target this inflammation. Considering the well-established anti-inflammatory properties of mesalazine in acute conditions and its use in treating IBD, this study evaluates whether Asacol suppository can be more effective than standard treatment in alleviating pain, bleeding, and itching associated with acute fissures caused by diarrhea. Alongside other non-surgical methods, this drug treatment may also prevent secondary stricture formation and reduce the risk of complications, such as incontinence, which can occur during fissure surgery.

The findings indicated that the recovery rate in the group treated with Asacol suppository (80%) was significantly higher than that of the control group (38.2%). The control group received diltiazem ointment, which has been shown in some studies to be effective in treating chronic anal fissures. Clinical trials have estimated an effectiveness rate of approximately 29% (7).

In the current study, only 34 individuals were examined as a control group during a 6-week follow-up. The limited sample size reduced the accuracy of measuring the effectiveness of diltiazem treatment, which may explain the differing results obtained. Additionally, the aforementioned studies evaluated the effectiveness of diltiazem on chronic fissures, whereas the current study focused on acute fissures.

In the study by Gupta (2007), the level of pain in patients with anal fissures who used a hot sitz bath did not differ from that of patients who did not use this method. However, the group that used the hot sitz bath reported significantly higher satisfaction and a greater reduction in burning sensation (8).

We did not find any studies regarding the effectiveness of mesalazine suppositories in the treatment of acute anal fissures. However, considering the increased recovery rate observed in the experimental group, this treatment appears to be effective. It is evident that factors influencing the pathophysiology of acute anal fissures can accelerate healing, with local inflammation being a significant contributor. Therefore, mesalazine suppositories, due to their anti-inflammatory properties, were expected to be effective in treating acute anal fissures. Previously, Salari et al. (2016) reported greater effectiveness of egg yolk compared to nitroglycerin in treating acute anal fissures (9). This finding is noteworthy because Shen Q et al. (2013) demonstrated that egg yolk modulates NF- $\kappa$ B levels during the inflammatory process (10), which is a key regulator in the transcription pathway. Similarly, one

of the mechanisms by which mesalazine exerts its effects is through the inhibition of NF- $\kappa$ B activation in inflammation.

In the present study, the patients' age showed no significant relationship with the likelihood of recovery. The average age of the study population was  $43.49 \pm 15.08$  years, consistent with previous studies reporting an average age of approximately 40 years for patients with anal fissure. Patient sex may influence the rate of healing due to the pathophysiology of acute fissure and physiological differences between male and female skin. In this study, pain, burning, and bleeding were the most common symptoms of acute anal fissure. Similarly, previous studies have identified bleeding and pain as the predominant symptoms, which aligns with the current findings.

Constipation and obesity are typically associated with a higher incidence of anal fissures (11). However, in the present study, neither constipation nor body mass showed a significant relationship with the likelihood of anal fissure recovery. Additionally, although diarrhea is considered a contributing factor to anal fissures, it was not significantly associated with the chance of fissure recovery in this study. Previous research has indicated that solid tumors without metastases are significantly related to the incidence of anal fissures (11); therefore, it was expected that patients undergoing malignant treatment would have a higher incidence of fissures. Nevertheless, in the current study, chemotherapy and radiotherapy did not significantly affect the likelihood of recovery from acute anal fissures.

The current study investigated the consumption of coffee and the incidence of anal fissures, finding that the likelihood of recovery was not associated with tea or coffee consumption. It is important to note that previous studies examined the relationship between these factors and the occurrence of anal fissures, whereas present research focused on the relationship between recovery and these factors; therefore, differing results were anticipated.

### Limitations

Although randomization was employed, baseline differences were observed between groups. The intervention group presented with more severe symptoms and lower functional status at baseline, which may have caused the observed improvements to underestimate the true treatment effect. Most patients referred for diarrhea were women, and the attending surgeon was also female (a cultural factor that influenced this selection). Consequently, the study was conducted exclusively on one gender, eliminating the possibility of analyzing gender as a variable. Patient sex could influence healing speed due to the pathophysiology of acute fissures and physiological differences between male and female skin. Furthermore, limitations in previous similar studies prevented comparison of findings

and hindered a more comprehensive understanding. Additionally, this study was conducted during the COVID-19 pandemic, which restricted the sample size. The control group did not attend the 6-week follow-up, further challenging the accuracy of the analysis.

### Suggestions

It is recommended that additional clinical trials with larger sample sizes be conducted to investigate the effects of Asacol suppositories on acute fissure repair and to compare the benefits and risks of this treatment option. Based on the findings of these studies, a decision can be made regarding the inclusion of Asacol suppositories in the management guidelines for anal fissure treatment.

### Conclusion

The findings of the current study indicate that Asacol suppositories have a significant effect on the healing

of acute fissures caused by diarrhea and can be considered a viable treatment option.

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### Authors' Contribution

Leila Ghahramani, Seyed Vahid Hosseini, Hajar Khazraei, Sajad Heshmati Far, and Khadije Gorgi made substantial contributions to the conception and design of the study, data acquisition, and the analysis and interpretation of data. Leila Ghahramani and Hajar Khazraei contributed to drafting the article and revising it critically for important intellectual content. All authors approved the final version for submission.

**Conflict of Interest:** None declared.

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