

Efficacy of Acyclovir in the Treatment of Non-HSV Anal Fissure

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INTRODUCTION

Background: An anal fissure is a common anorectal disease of adults among both genders. Among STDs, infection with the herpes simplex virus (HSV) is the second most common cause of anal fissures. The treatment of choice in mild HSV is topical acyclovir ointment, and in severe cases, oral acyclovir is prescribed. The objective of this study was to evaluate the efficacy of acyclovir in the treatment of anal fissures in non-HSV patients. **Methods:** In this clinical trial, all the patients diagnosed with anal fissures referred to surgery clinics from October 2021 – to March 2022 were included. Patients were divided into experimental (diltiazem and acyclovir) and control groups (diltiazem-ointment only). We followed up with the patients for one month, and the efficacy of the treatment (symptom relief and recurrence) and patient satisfaction were evaluated by a checklist. **Results:** A total of 120 patients were enrolled. Seventy-five patients were men (75%). The most common symptom was painful defecation reported by all patients, followed by bleeding, constipation, pruritus, and diarrhea. No statistically significant difference was found regarding improvement, recurrence, and no improvement between the two groups (P-value> 0.05). Forty-nine patients in the first group (40.8%) and 43 patients from the second group (35.8%) were satisfied with the treatment, but no statistical difference was found (P-value=0.195). **Conclusion:** Adding acyclovir to the management protocols of anal fissure makes no significant difference compared to using diltiazem alone.

Keywords: Anal Fissure, Acyclovir, Anal Fissure Treatment, Diltiazem

INTRODUCTION

An anal fissure is a common anorectal disease of adults among both genders. It is a linear tear in the anal canal region, distal to the dentate line [1-3]. Clinical symptoms of anal fissure consist of bleeding, itching, and pain during and after the defecation [4]. Anal fissures are classified as acute and chronic diseases. Acute anal fissures (lasting less than four weeks) heal most of the time spontaneously. However, some become chronic (lasting more than four weeks) [5].

The pathogenesis of fissures is still unknown, but it seems like the spasm of the anal canal sphincter causes local ischemia in the anal canal region,

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resulting in the delay in the healing process of fissures [6-7]. As the posterior midline region has fewer blood supplies anatomically, most of the fissures are located in this region. Fissures in the lateral areas are most commonly caused by trauma or underlying diseases such as Crohn's disease, tuberculosis, immune deficiency disorders, sexually transmitted diseases (STDs), chemotherapy, and local or systemic malignancies [8].

There are a variety of treatments for fissures aiming to reduce the spasm and hypertonia of the internal anal canal sphincter. First-line treatments are conservative treatments such as increasing the nutritional fiber intake, daily water consumption, cal hygiene, stool softeners, topical analgesic, and anal application of ointments such as glyceryl nitrates and calcium channel blockers (CCBs). These ointments work by improving blood flow to the region and inducing relaxation of the sphincter. CCBs have fewer side effects and therefore are preferred to glyceryl nitrates. However, injection of botulinum toxin (BTX) and lateral internal sphincterotomy (LIS) are the main treatments for recurrent anal fissures [9-11]. When the fissure is in an uncommon region caused by an underlying disease, treatment of the underlying condition should also be considered to prevent future recurrences [12].

Among STDs, infection with the herpes simplex virus (HSV) is the second most common cause of anal fissures. Anorectal diseases of STDs present with lateral anal fissures, proctitis, anus inflammation, etc. Moreover, HSV infections cause constipation and sacral region paresthesia due to the involvement of the autonomic system. Anal infection is more common in HSV-2 than in HSV-1. The treatment of choice in mild HSV is topical acyclovir ointment, and in severe cases, oral acyclovir is prescribed [13-15].

It is known that the healing process will be delayed in any lesion accompanied by ischemia or infection. Considering that anal fissure is a common problem in society, the objective of this study was to evaluate the efficacy of acyclovir in treating anal fissure in non-HSV patients.

METHODS

In this randomized clinical trial, patients referred to surgery clinics of Imam Reza hospital, affiliated with Tabriz University of Medical Sciences, from October 2021 – to March 2022 were included. According to the declaration of Helsinki, the research protocol was reviewed and approved by the local ethics committee with the registration number ICR20200906048636N1.

Inclusion criteria included established diagnosis of anal fissure by a surgeon, age above 18 years, no history of recent herpes simplex virus (HSV) infection or any other sexually

transmitted diseases (STD), and patients' informed consent. Exclusion criteria were a history of recent STD, history of hemorrhoids, or any other conditions affecting the perianal area.

All the patients diagnosed with anal fissure and fulfilling the inclusion criteria who were referred to our clinics during the study period were included. A researcher-made checklist was presented to all participants. Data regarding age, sex, anatomical location of the fissure, pain scoring based on the Visual Analog Scale (VAS) [1] before, two, and four weeks after treatment, amount of bleeding, pruritus, and constipation or diarrhea were documented. VAS is a visual pain measurement scale that extends from a zero score for no pain to a ten score for the worst pain possible, allowing the patient to choose one's score based on the severity of the pain.

Randomization was performed using the rand list version 2.00, and patients were divided into experimental and control groups. For the patients in the first group, we prescribed diltiazem hydrochloride 2% topical ointment twice daily and acyclovir topical ointment every three hours for one week, and typical anti-fissure treatment (diltiazem-ointment only, twice daily) was prescribed for the control group.

We followed up with the patients in weekly appointments for one month. The participants' level of satisfaction from the treatment and symptom relief was asked following two weeks and one month of anti-fissure treatment. Improvement was described as total symptom relief.

STATISTICAL ANALYSIS

The data were analyzed using SPSS software version 22.0 (SPSS INC., IBM Corporation, Chicago, IL). The Kolmogorov-Smirnov test was used to evaluate normality. Qualitative data were reported as frequency (percentage). Quantitative data were presented as mean \pm standard deviation (SD). A chi-squared test was used to examine the relationship between qualitative data. An independent t-test and Mann-Whitney U test investigated the relationship between quantitative data. A P-value less than 0.05 was considered to establish a statistically significant association. Regression analyses were used to estimate the relationship between risk factors and patients' mortality.

RESULTS

A total of 120 patients were enrolled, and 60 patients were included in the experimental group. Table 1 represents the essential characteristics of the patients.

Seventy-five patients were men (75%), and 45 were women. No significant difference was found regarding the mean age between the two groups, with a P-value equal to 0.45. The

most common symptom was painful defecation reported by all patients, followed by bleeding, constipation, pruritus, and diarrhea. No statistical difference was found between the two groups (P-value >0.05).

Table 1: Demographic characteristics and primary symptoms of the patients.

Variable		Experimental group	Control group	P-value
Sex*	Male	35 (58.3%)	40 (66.7%)	0.893
	Female	25 (41.6%)	20 (33.3%)	0.451
Age†		35.4 ±3.5	33.2 ±4.1	0.450
Painful defecation*		60 (100%)	60 (100%)	1.000
Bleeding*		40 (66.7%)	49 (81.7%)	0.610
Constipation*		27 (45.0%)	36 (60.0%)	0.100
Diarrhea*		7 (11.7%)	10 (16.7%)	0.432
Pruritus*		27 (45.0%)	22 (36.7%)	0.353
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† Data are shown as mean ± standard deviation.

*Data are shown as numbers (percent).

Table 2: VAS pain scoring and treatment results.

Variable		Experimental group	Control group	P-value
VAS scoring*	Before Tx	4.34 ±0.86	4.56± 0.95	0.230
	2-weeks following Tx	2.39 ±0.74	2.54± 0.89	0.302
	4-weeks following Tx	1.86 ±0.76	2.04 ±0.75	0.235
Improvement after 2-weeks*		20 (33.3%)	17 (28.3%)	0.553
Improvement after 4-weeks*		34 (56.7%)	30 (50.0%)	0.464
Recurrence/No improvement after 4-weeks*		6 (10.0%)	13 (21.7%)	0.080

*Data are shown as numbers (percent).

Table 2 shows the VAS scoring of the patients before, two-, and four weeks following treatment. We found no statistically significant difference between the two groups regarding pain scoring.

In two weeks of follow-ups, complete symptom relief was reported by 37 patients, of which 17 were from the experimental group and 20 from the control group (P-value= 0.553), and there was no statistically significant difference (Table 2). Also, no statistically significant difference was found regarding improvement, recurrence, and no improvement between the two groups (P-value> 0.05, table 2). At the end of the study period, patients of the experimental and control groups reported a mean of 90 and 78.3% improvement in symptoms, respectively, which was not different statistically (P-value= 0.08).

Furthermore, 49 patients in the first group (40.8%) and 43 patients from the second group (35.8%) were satisfied with the treatment, but no statistical difference was found (P-value=0.195).

DISCUSSION

In this study, we evaluated the efficacy of acyclovir treatment in non-HSV anal fissures. Acute anal fissure has the same incidence rate in males and females [17]. In contrast to the previous studies, in the current study, the study subjects

were predominantly male. This was because the surgeon doing the clinical examinations and treatment procedures was male. Culture in our country encourages patients with perineal diseases to be treated and examined by the same gender. An acute anal fissure is mainly seen between 20 to 40 years of age. In our study, most of the patients were 30 to 40 years old, following the previous studies [17,18].

According to the literature, typical symptoms of patients with acute anal fissure are bleeding and pain around the anus [19]. The pain is usually sharp and is worsened by defecation. Bleeding might occur during painful defecation. Bleeding is in small amounts and bright red [20]. Karapolat et al. studied the efficacy of local antibiotics in the treatment of acute anal fissures. In this study, one hundred patients were randomly divided into two groups. Patients of the first group received 5% lidocaine pomade and patients of the second group received metronidazole cream along with the 5% lidocaine pomade. In this study, the most common chief complaint of the patients was bleeding and pain during the defecation, which was the same as our study [21]. Romero et al. and Coskun et al. also reported pain during and after defecation, bleeding, and constipation as the most common symptoms of the patients [19,22].

Nevins et al. compared healing and recurrence rates of chronic anal fissure in patients treated with topical diltiazem and

topical glyceryl trinitrate in a meta-analysis of randomized controlled trials. They reported 73.1% efficacy for topical diltiazem [23]. In a similar study, Venkatesh et al. 100 patients with anal fissures were studied. In their research, improvement in symptoms was reported at 80%, eight weeks after the treatment with topical diltiazem [24]. In our study, four weeks after treatment, 78.3% improvement was seen in the group receiving topical diltiazem and 90% in the group receiving acyclovir along with the diltiazem. Concluding that, the results of our study followed the previous studies.

As using topical diltiazem alone did not show improvements in symptoms of approximately 20% of the patients, we may conclude that considering other pathophysiologies that lead to anal fissure will improve the healing process. Inflammation and local infection are some of the essential pathophysiologies that should be considered. As reported in previous studies, conditions in the anoderm are one of the leading causes of acute anal fissures [25]. Even a local infection in the subcutaneous region of an anal fissure may progress subclinically and lead to a chronic anal fissure. It is a known fact that the healing process will be delayed in any lesion accompanied by ischemia or infection. In a study done by Garg, patients with anal fissures received oral ciprofloxacin and ornidazole for five days. Symptoms of the patients were significantly improved in their study [26]. Another study added local ornidazole to the treatment and the previous medical regimen for three months. The second study achieved a 90% improvement in the patients' symptoms [27].

In the current study, we used acyclovir to evaluate patients' symptoms and healing rate. According to our results, compared to the patients receiving diltiazem-ointment alone, patients receiving diltiazem and acyclovir had less pain. Furthermore, improvement of symptoms was more significant in the diltiazem and acyclovir group in 4 weeks. Considering that the difference in pain and improvement of symptoms was not significant statistically, we concluded that acyclovir does not have enough efficacy in increasing the improvement of symptoms of anal fissure.

This study was limited by its small sample size and was conducted in a single center. We suggest that more evaluations with prospective studies and larger and multi-center sample sizes should be done.

CONCLUSION

According to the results of our study, adding acyclovir to the management protocols of anal fissure makes no significant difference in relieving pain and symptoms of patients compared to using diltiazem alone.

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