

Effects of *Aloe vera* cream on chronic anal fissure pain, wound healing and hemorrhaging upon defecation: a prospective double blind clinical trial

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Abstract. – *Aloe vera* is a medicinal plant that promotes wound healing in burn injuries. A prospective clinical trial was conducted to evaluate the effects of a topical cream containing 0.5% *Aloe vera* juice powder in the treatment of chronic anal fissures. The aloe cream was applied by the patients to the wound site 3 times per day for 6 weeks following the instructions of a physician. Pain was assessed with a visual analog scale before treatment and at the end of each week of treatment. Wound healing and the amount and severity of bleeding were examined and evaluated before and at the end of each week of treatment. There were statistically significant differences in chronic anal fissure pain, hemorrhaging upon defecation and wound healing before and at the end of the first week of treatment also in comparison with control group ($p < 0.0001$). In this study, a topical cream containing aloe vera juice was an effective treatment for chronic anal fissures. This is a promising result indicating that further comparative studies are justified.

Key Words:

Aloe vera, Anal fissures, Wound healing, Pain, Hemorrhage.

Introduction

Anal fissures are a common painful condition of the anal region that are characterized by pain upon defecation, anal bleeding, and anal sphincter spasms. An estimate of the incidence of this condition is difficult because many patients with acute fissures do not seek medical advice. The etiology of this condition is uncertain, but mucosal ischemia secondary to sphincter hypertonia is one possible etiology. Acute anal fissures are arbitrarily designated as those presenting with

symptoms for less than six weeks in duration¹. These fissures frequently respond well to conservative treatment with stool softeners and attention to local hygiene. Most anal fissures heal spontaneously. However, a small proportion of acute fissures do not heal and become chronic fissures (traditionally defined as symptoms lasting more than six weeks in duration)². Once patients have had symptoms for this period, they usually do not respond to conservative measures and have traditionally needed to be treated by surgery, which includes either a partial division of the internal sphincter (sphincterotomy) or manual dilatation of the anus. Surgical treatment for this condition has been associated with the side-effect of incontinence in up to 30% of patients^{3,4}. Therefore, a non-surgical method for the treatment of chronic anal fissures is highly desirable. Over the past few years, a number of clinical studies have shown that topical application of ointments containing glyceryl trinitrate (GTN) promote the healing of chronic anal fissures⁵⁻¹⁶. These agents cause transient relaxation of the internal anal sphincter by inducing the release of exogenous nitric oxide to the muscle tissue¹⁷. This treatment is sometimes termed a “chemical sphincterotomy,” and it is not accompanied by the risk of irreversible incontinence. Relaxation of the internal anal sphincter can be assessed during GTN therapy by measuring the patient’s maximal anal resting pressure (MARP)¹⁸. The major side effect of topical GTN therapy for anal fissures is that up to 40% of patients using this treatment experience headaches. These headaches may reduce compliance and, in some cases, are severe enough to lead to the discontin-

uation of treatment. Therefore, many patients seek a natural and safe topical drug alternative for the treatment of anal fissures.

Aloe vera (L.) Burm. f. belongs to the Xanthorrhoeaceae plant family and has long been used as a traditional medicine. It is one of the most recognizable herbs in the world, and the medicinal part of this plant is the succulent leaf. *Aloe vera* juice is obtained by breaking or slicing a leaf and is the principal part of the plant that is used in herbal medicine. *Aloe vera* gel is often processed into a juice and juice powder exhibits healing properties for the skin and contains many important nutrients, including amino acids, B vitamins, and other compounds that support general health. It also has pharmacological properties that have been shown to provide antioxidant, wound healing, antibacterial, antifungal, and immunomodulatory effects¹⁹. The healing of burn wounds is one of the main indications for *Aloe vera* gel use in both animal and human clinical studies²⁰. Recently, it has been shown that *Aloe vera* cream can facilitate wound healing in post-hemorrhoidectomy patients²¹. In addition, another study demonstrated that an aloe cream reduced the healing time in patients with burn injuries compared to silver cream²².

To investigate the potential use of *Aloe vera* for wound healing, this study evaluated the effects of a topical cream containing 0.5% *Aloe vera* juice powder on chronic anal fissure pain, hemorrhaging upon defecation and the healing of fissure wounds.

Patients and Methods

This observational clinical trial study was registered by the Iranian Registry of Clinical Trials under code IRCT138801151786N1. After obtaining approval from the Ethical Committee at Mazandaran University of Medical Sciences, this clinical trial was carried out at Imam Teaching Hospital, which is affiliated with the Mazandaran University of Medical Sciences, Sari, Iran. This study was a double blind, prospective clinical trial that compared the effects of aloe cream on chronic anal fissures before and after treatment. Patients were eligible for entry into the study if they were between the ages of 20-70 years. Patient had to have been admitted to the surgery ward of Imam Hospital due to chronic anal fissure pain and hemorrhaging after defecation. All patients who were enrolled in this study were di-

agnosed by same surgeon based on the presentation of typical chronic anal fissures (idiopathic type). The diagnosis criteria were the following: posterior or anterior wounds at the midline of the anorectum area with skin tags, smooth muscle filaments positioned at the base of the wound and sphincter hypertrophy. The exclusion criteria were other anorectal diseases (e.g., hemorrhoids, anal fistulae, and anal abscesses), substance abuse, alcohol usage, sexually transmitted diseases (STD), pregnancy and hypersensitivity to *Aloe vera* products. In addition, patients who had previously underwent anal surgery, pelvis radiotherapy or chemotherapy and received immunosuppressive drugs or had any drug sensitivities were excluded from this study.

Preparation of Aloe Cream

Powdered spray-dried aloe vera inner leaf juice (Zarban Phyto-Pharmaceutical Co, Iran) was used for preparing the *Aloe vera* cream. White liquid paraffin (2 g), stearyl alcohol (7.5 g), cetyl alcohol (7.5 g), solid white paraffin (3 g), and propylene paraben (0.015 g) were mixed and heated to a boil (oil phase). *Aloe vera* powder (0.5 g) and 70 mL deionized water were added to the mixture with propylene glycol (7 g), sodium lauryl sulfate (3 g), and methyl paraben (0.025 g). The mixture was heated until it reached an aqueous state (liquid phase). Next, the oil and liquid were mixed continuously while being gradually cooled. Once it had cooled, the uniform cream (50 g) was stored in an aluminum package. The cream contained 0.5% *Aloe vera* juice powder. The cream was prepared under sterile conditions and was confirmed to be free of microbes.

Patients and Study Procedure

Fully informed written consent was obtained from each patient prior to entry into the trial. The study duration was 6 months, and during this period, a total of 60 patients with a confirmed diagnosis of chronic anal fissures were selected for treatment with *Aloe vera* cream. Control group received no treatment. 30 Patients had cream applied to the wound site 3 times a day immediately after the instruction of a physician. A Sitz bath was indicated 3 times a day, consumption of a laxative was indicated once a day, and a full fiber diet was also recommended as a supplement to the treatment regimen. This treatment protocol was continued for 3 weeks. Patients had approximately 3 g of aloe cream applied to their wounds externally. Patients who were discharged from the hospital were re-

quested to visit the surgeon for follow-up. Patients were instructed to apply the cream with the tip of the index finger to their wounds three times daily. All patients were followed after discharge from the hospital. After 3 consecutive weeks of the treatment, patients were admitted to the hospital for examination. If there was no improvement in their anal fissure symptoms, patients underwent a sphincterotomy and fissurectomy surgery. However, if the aloe cream appeared to heal the fissure wounds, the treatment was continued for three additional weeks. Pain upon defecation was evaluated using the visual analogue scale (VAS), which was scored as 0 (no pain) to 10 (very severe pain). Pain scores were obtained before treatment and at the end of each week during treatment. At the end of each week of treatment, the same surgeon examined the patients' wounds. The surgeon was blinded as to whether the patient had or had not received treatment. The protocol of treatment for control patients was similar to the treatment group; however, control group received placebo cream. Wound healing was defined as a complete epithelial covering as observed by a physical examination. Wounds were classified as grade I (severe and fresh wound with inflammation), grade II (granulation tissue on wound), or grade III (completed layer of epithelia covering the wound). The amount and severity of bleeding were classified as grade I (there was no sign of hemorrhaging upon defecation), grade II (there was sometimes a sign of hemorrhaging upon defecation), and grade III (there was a sign of hemorrhaging upon defecation).

Statistical Analysis

All data and information were coded and analyzed using the paired *t*-test, and Wilcoxon Signed Rank. *p* < 0.05 was considered a signifi-

cant difference. Statistical analysis performed using SPSS software (version 12, SPSS Inc., Chicago, IL, USA).

Results

Among the patients who were initially enrolled in this study, nineteen patients were excluded from the study for one of the aforementioned reasons. The study population consisted of 30 patients in the treatment group and 30 patients in the control group. At the beginning of study, patients experienced hemorrhaging upon defecation based on the VAS standard, and the severity of pain upon defecation among these patients was 6.805±2.7 before treatment. Patients who received aloe cream experienced significantly less pain at the end of the first, second, third and fourth week of treatment. Additionally, there were no signs of pain upon defecation in patients at the end of the fifth and sixth week after treatment. Overall, there was a statistically significant difference in the degree of pain upon defecation before and after treatment and also in comparison with control group in the same weeks (*p* < 0.0001) (Table I). No significant differences were also observed in the control group in the degree of pain upon defecation before and after treatment and patients were excluded and underwent a sphincterotomy and fissurectomy surgery after 3 weeks.

Aloe vera cream significantly enhanced wound healing in patients at the end of the first week of treatment. This difference was statistically significant when compared to before application (*p* < 0.0001) (Table II). Before treatment with aloe cream, seven patients had grade I wounds, twenty-two patients had grade II wounds, and two pa-

Table I. Pain upon defecation before and after the treatment of chronic anal fissure with aloe vera cream.

Time	Pain score (mean ± SD)		<i>p</i> value Control vs Treatment
	Control	Treatment	
Before the treatment	6.96 ± 1.98	6.85 ± 2.007	> 0.05
After 1 week	6.89 ± 2.01	4.354 ± 1.87*	< 0.0001
After 2 weeks	6.73 ± 1.26	2.290 ± 2.15*	< 0.0001
After 3 weeks	6.75 ± 1.87	0.741 ± 1.34*	< 0.0001
After 4 weeks	–	0.322 ± 1.07*	
After 5 weeks	–	0.000 ± 0.00*	
After 6 weeks	–	0.000 ± 0.00*	

Pain scores ranged from 0 (no pain) to 10 (very severe pain). SD, standard deviation. *There was a statistically significant difference between before and after the treatment (*p* < 0.0001).

Table II. Wound healing among patients after application of aloe vera cream.

In total patients (30 patients) Time	With increasing in wound healing grade number of patients (%)		Mean rank*		p value Control vs Treatment
	Control	Treatment	Control	Treatment	
Before the treatment	0	0	4.00	4.00	> 0.05
After 1 week	0	15 (48%)*	4.00	8.00*	< 0.0001
After 2 weeks	0	22 (71%)*	4.50	11.50*	< 0.0001
After 3 weeks	0	27 (87%)*	5.00	14.00*	< 0.0001
After 4 weeks	-	29 (93%)*	-	15.00*	
After 5 weeks	-	29 (93%)*	-	15.00*	
After 6 weeks	-	29 (93%)*	-	15.00*	

Wounds were classified as grade I (severe and fresh wound with inflammation), grade II (granulation tissue on wound), and grade III (completed layer epithelial covering on wound). *There was a statistically significant difference between before and after the treatment ($p < 0.0001$).

tients had grade III wounds. At the end of the sixth week of treatment, a total of 29 patients (93%) in the treatment group had an increase in their wound healing grade. In addition, there were statistically significant differences in wound healing when comparing before treatment to six weeks after treatment ($p < 0.0001$).

In terms of bleeding severity, aloe cream significantly reduced hemorrhaging upon defecation. Among 30 patients, a total of 13 patients had a reduction in their bleeding grade after one week of treatment. This was statistically significant when compared to before treatment and also group did not receive cream ($p < 0.0001$). At the end of the sixth week of treatment, a total of 22 patients (71%) experienced decreases in hemorrhaging upon defecation grade (Table III). In addition, there were statistically significant differences in the rate of healing when comparing before treatment to six weeks after treatment ($p < 0.0001$).

No mortality was encountered. In addition, no side effects or allergic reactions were observed in patients who received aloe cream.

Discussion

Anal fissures are a very common problem across the world. They cause considerable morbidity and adversely affect quality of life; therefore, appropriate treatment is mandatory. Traditionally, surgical treatments, such as manual anal dilatation and an internal sphincterotomy, have been used for this condition. Because of the long recovery associated with surgery for anal fissures and the risk of incontinence, medical alternatives to surgery have been sought. This prospective clinical trial demonstrated that application of a topical cream containing 0.5% *Aloe vera* juice powder provided significant pain relief to pa-

Table III. The healing of hemorrhage upon defecation after application of aloe vera cream.

In total patients (31 patients) Time	With decreasing in bleeding grade number of patients (%)		Mean rank*		p value Control vs Treatment
	Control	Treatment	Control	Treatment	
Before the treatment	0	0	3.00	3.00	> 0.05
After 1 week	0	13 (42%)*	3.50	7.00*	< 0.0001
After 2 weeks	0	19 (61%)*	3.50	10.00*	< 0.0001
After 3 weeks	0	22 (71%)*	4.00	11.50*	< 0.0001
After 4 weeks	-	22 (71%)*	-	11.50*	
After 5 weeks	-	22 (71%)*	-	11.50*	
After 6 weeks	-	22 (71%)*	-	11.50*	

The amount and severity of bleeding were classified as grade I (there was no sign of hemorrhage on defecation), grade II (there was sometimes a sign of hemorrhage on defecation), and grade III (there was a sign of hemorrhage on defecation). *There was a statistically significant difference between before and after the treatment ($p < 0.0001$).

tients with chronic anal fissures. In addition, this cream significantly improved wound healing and reduced hemorrhaging upon defecation.

In recent years, various medical therapies have been used for the treatment of chronic anal fissures with the aim of reducing the resting anal canal pressure and improving the vascularity of the internal sphincter muscle. Some of the agents that have been previously used include glycerol trinitrate ointment (GTN)^{23,18}, botulinum toxin^{24,25}, diltiazem hydrochloride (DTZ), and bethanechol^{26,27}. All of these agents have been shown to uniformly reduce resting anal pressure and to increase the vascularity of the anal canal. Botulinum toxin has to be injected locally, and it has the advantage of being a one-time treatment; however, economic issues and the technical aspects of its delivery have prevented its widespread acceptance. Glycerol trinitrate ointment (0.2%) has been studied most extensively in a series of randomized controlled trials^{23,18}, and it has been shown to have an efficacy of 68%. However, headaches are a major side effect associated with this treatment^{18,28,29}. There is a large body of literature describing the use of topical GTN for the treatment of anal fissures^{18,11,23,30-34}; however, the results have varied. For example, Lund and Scholefield¹⁸ reported a 68% healing rate with no incidence of recurrence, while Kennedy et al.³³ showed only a 46% healing rate with a recurrence rate of 62%. Thus, GTN may provide prompt relief to symptoms and exhibit an initial high healing rate, but there is a high incidence of recurrence and side effects. In contrast, the local injection of botulinus toxin, which was introduced into clinical practice in 1989, appears to provide better results. Jost³⁵ treated one hundred patients with acute anal fissures and reported the healing rate at six months to be 82%. However, this method has not been generally adopted.

Oral and topical calcium channel blockers (CCBs) have recently been shown to lower the anal resting pressure by relaxing the internal anal sphincter^{24,29,36-38}. The transport of calcium through L-type calcium channels is important for the maintenance of internal anal sphincter tone²⁵. Compared to glyceryl trinitrate, which reduces the resting anal tone by releasing nitric oxide, nifedipine (a calcium channel blocker) reduces the tone and spontaneous activity of the sphincter by decreasing the intracellular availability of calcium^{25,39,40}. Oral administration of CCBs is associated with side effects, such as hypotension and flushing, which may decrease compliance⁴¹. Top-

ical diltiazem and nifedipine are highly effective and achieve healing rates of 67% and 95%, respectively^{27,24,36}. A recent randomized study by our group showed that the topical use of 0.5% nifedipine could achieve complete healing in 96.7% of patients, which was not significantly different from the group treated with an internal sphincterotomy⁴². The problem with a temporary "chemical sphincterotomy" is that after treatment, the anal pressure rises to pre-treatment levels, thereby resulting in a high rate of recurrence. Recurrence has been reported to occur in approximately 42% of patients treated with nifedipine⁴³. It should be noted that the above healing and recurrence rates were reported in patients with chronic anal fissures.

In another study, Chryzos et al.³⁷ demonstrated a reduction by 30% of high internal anal sphincter tone with nifedipine. However, recurrence has been reported in approximately 42% of patients treated with nifedipine⁴³.

Aloe vera preparations have many biological effects, including immunomodulatory, anti-inflammatory, antioxidant, and wound healing properties⁴⁴. A recent review of clinical trials investigating the effect of *Aloe vera* on burn wounds found that aloe vera significantly shortened the wound healing time compared to controls⁴⁵. *Aloe vera* preparations contain various carbohydrate constituents, such as polysaccharides, mannose, and acemannan⁴⁴. Polysaccharides are known to promote skin wound repair^{44,45}. Reducing inflammation is the first step in wound healing, and the anti-inflammatory effects of aloe preparations are believed to play a direct role in facilitating wound healing⁴⁵. Furthermore, wound healing involves biological processes, such as granulation tissue formation. Collagen is the predominant protein in the extracellular matrix and provides strength and integrity to the dermis and other supporting tissues⁴⁶⁻⁴⁸. *Aloe vera* enhances the production of collagen⁴⁷. Specifically, the glycoprotein fraction of aloe is the principal component that is involved in wound healing, which also promotes the growth of dermal fibroblasts^{49,50}. These studies demonstrated that the glycoprotein fraction of *Aloe vera* was able to stimulate cell proliferation, accelerate the recovery of keratinocytes after *in vitro* wounding, and enhance the thickening of the epidermal covering. Another research found that *Aloe vera* increased the collagen content of granulation tissue and the degree of cross-linking. It is thought that this increase in collagen content after aloe treatment is either due to increased collagen syn-

thesis directly or to increases in the proliferation of fibroblasts that synthesize collagen, or both⁵¹. In our study, aloe cream significantly improved wound healing in patients with chronic anal fissures. Recently, it has been shown that patients who were treated with *Aloe vera* cream had significantly less postoperative pain (up to day 14) than those in the placebo group. Additionally, wound healing at the end of the second postoperative week was significantly greater in the aloe group compared with the placebo group. Because inflammation is one of the main causes of pain in patients in the early postsurgical period⁵², the anti-inflammatory effects of aloe may contribute to the relief of postoperative pain. These results suggest that *Aloe vera* facilitates the healing process across various wound types. The therapeutic benefits of topical *Aloe vera* cream may be due to its anti-inflammatory properties and positive effects on wound healing.

Conclusions

In this study, a topical cream containing 0.5% *Aloe vera* juice decreased chronic anal fissures pain and hemorrhaging upon defecation as well as enhanced wound healing. Topical *Aloe vera* cream is an effective and safe form of treatment and represents a new therapeutic avenue towards treating chronic anal fissures. These promising results indicate that further comparative studies are justified.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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