

Original article

Healing effect of aloe vera gel, in non-healed ulcers

Majid Avijgan¹, Victoria Beigi Broujeni², Ali Akbar Beigi³, Hojatollah Rohi Borojeni⁴, Seyyed Kamyar Mostafavizadeh⁵, Iraj Karimi⁵, Abbas Ali Javadi⁵

¹Iranian Traditional Medicine Research Center and Department of Infectious and Tropical Diseases, Isfahan University of Medical Sciences

²Department of Internal Medicine, Shahr-e-kord University of Medical Sciences

³Department of Surgery, Isfahan University of Medical Sciences

⁴Department of Pharmacology, Shahr-e-kord University of Medical Sciences

⁵Department of Infectious and Tropical Diseases, Isfahan University of Medical Sciences

Abstract

Objective: Aloe Vera gel (AVG) has a prominent role as a contemporary folk remedy. The Non-healed chronic ulcers of 16 non-responders to conventional treatment were treated with AVG for which the clinical efficacy was studied. **Methods:** This study included 16 patients having chronic ulcer (9 males and 7 females) with mean age of 41.8 ± 14.6 who following failure treatment to conventional therapy, were dispensed AVG to apply. AVG is consisted from gel part of Aloe Vera plant plus one preservative material, in this study ECG jelly. The patients were assessed as responder whenever intensity of inflammation, the number and /or the size of ulcers have been reduced. **Results:** The period of time till healing (complete or reduction in size of ulcer), were from 5 to 160 days with mean of 31.2 ± 36.4 days. The mean time of decreasing for secreting, swelling and redness was from 5-11 days. Spearman coefficient of correlation, showed no significant correlation between first size and depth of ulcer and timing till 50% reduction in size of ulcer. **Conclusion:** All patients had been treated with conventional treatment all to no avail. There were some full thickness ulcer which at the end of treatment we observed an improvement and normal skin for those ulcers. There was a minor complication like itching in one patient but no leading to stop treatment. These findings suggest that AVG is an excellent and safer choice than current conventional therapeutic management of chronic ulcers.

Keywords: Aloe Vera; Chronic ulcer; Medicinal plant; Traditional medicine

INTRODUCTION

Herbs have been used in clinical medicine for thousands of years. Virtually all cultures worldwide have relied on medicinal plants for primary health care. Approximately one-third of all traditional medicines are for treatment of skin or wounds disorders^[1].

Surgeons, dermatologists and general practi-

tioners have been concerned with ulcer healing since the time of the Egyptians^[2]. In every healing process, the reduction in inflammation, rapid closure of the wound, elimination of foreign material and bacteria allow the wound to progress and to achieve structural integrity.

Aloe Vera plant is an endemic plant of tropical area such as Madagascar, Saudi Arabia and south of Iran. Aloe Vera mucilaginous gel has been used for centuries as a topical treatment for various conditions^[3]. Modern clinical use of Aloe Vera Gel (AVG) began in the 1930s^[4]. Chemical analysis revealed, that AVG contains various carbohydrate

Correspondence to: Dr Majid Avijgan, Professor of Infectious and Tropical Diseases, Isfahan University of Medical Sciences, PO Box 795, Al-Zahra Hospital, Isfahan, Iran.
Tel: +98 913 181 80 85
E-mail: avijgan@yahoo.com

polymers, notably glucomannans^[5], several pharmacologically active ingredients, including a carboxypeptidase that inactivates bradykinin in vitro, salicylates, and a substance(s) that inhibits thromboxane formation in vivo. Scientific studies reported Aloe Vera has an antibacterial and antifungal effect^[6] or combats the local vasoconstrictive effects of thromboxane^[7]. Oral AVG is widely used by patients with inflammatory bowel disease and is under therapeutic evaluation for this condition^[8]. Acemannan (ACM 1) was able efficiently and durably to increase the activation capacity of macrophages from the systemic immune compartment^[9].

There are some studies reporting about effectiveness of AVG on bed sores^[6, 10]. We had a previous experience on the effect of AVG on a case of chronic non-healed ulcer who responded wonderfully to AVG^[10].

In this case series of clinical trial, we are going to present the effectiveness of AVG on some non-healed chronic ulcers, which did not respond to conventional treatment.

MATERIALS AND METHOD

After coordination and approval of proposal by research committee of University and after getting permission from ethics committee of University, we started study in which, the patients were selected from Infectious disease and tropical medicine clinic affiliated to Shahr-e-kord and Isfahan University of Medical Sciences. This study includes 19 patients with chronic ulcer, 10 males and 9 females, whose informed consent was obtained at the commencement of study. Site of wounds can be divided into the following categories: Head/Neck (Myasis) (one patient); Limbs Hand & Foot (Burnt & DFU *) (eight patients); Abdomen, Buttock and Sacrum (Surgical and pressure ulcers) (nine patients); Groin (Scorpion Bite) (one patient).

The responsible person of this study, who was dealing with patients and their wounds, was our Internist colleague. She was trained and approved on wound assessment by our surgeon colleague. The patients have been visited and must be approved by our surgeon colleague for failure treatment to conventional therapy. If any patients had a presenting ulcer for

more than one month which was not responded to conventional therapy and had a size of at least 10 cm square was included into the study.

Some of the patients have diabetic mellitus, who continued their treatment as previous and with the same drugs as they would use. The patients having underlying diseases like osteomyelitis, approved malignancy of skin have been excluded. The previous conventional therapy for these patients includes: washing, anti-septic, anti-biotic, debridement and sometimes skin grafting. 2 cases of this study had failed skin grafting after 2 months of surgery. (Due to unknown reason) In period of conventional therapy, almost all patients have been treated with antibiotics orally or topically.

In this step, such patients, referred to surgeon, for debridement before AVG apply. (If they have any necrosis) They were explained the study and after getting informed consent, were selected to be applied AVG on chronic ulcers.

Data collections were conducted by observation, interview, questionnaire form and photograph. These patients had chronic ulcers in different parts of the body. They were dispensed AVG and instructed to apply it twice daily over the affected area. Identification numbers were given to all patients with standard instructions to inspect, clean, and redress their wounds twice daily. In the first two days of AVG applying, they were demonstrated the technique of applying AVG and advised to keep away from contamination and dust. This process was observed by our internist colleague.

Preparation of gel

Gel has been prepared as follow: After detaching the lower leaves of the plant, the inner mucilage was collected and mixed with a preservative lubricant (ECG lubricant gel), five parts to one.

The collection of inner mucilage and mixing was done by sterile glove and as the method as preparation in traditional use and method. Because we did not want to change the traditional method of usage of this AVG, we did not use any other way or method to sterile the AVG.

Follow up of Patients

They were visited and followed up every 5 days till

the lesions started to heal and complete closure. At every follow up, proper debridement, if necessary, was done. This debridement was not a surgical debridement but was consisted of washing by solution of normal saline and then cleaning the necrotic material from the surface of ulcer. They were evaluated for clinical infection (like secretion, inflammation, foul smelling and redness) and if they were presented, gone to therapy.

The overall clinical assessment was defined as cured (Closure of ulcer), improved (Reduced in size of ulcer but not closure) and unchanged (Neither closure nor size reduction). The patients were assessed as responder whenever intensity of inflammation like (secretion, swelling and redness), the number of ulcers and the size of ulcers (at least 50% for square of ulcer) have been reduced. This respond was recorded by photographs which some of them are presented. (Figure 1, 2, 3)

No other topical or systematic antibiotics were permitted during the trial. The prescription of antibiotic in patients (before entering into this study) was probably for prevention of infection rather than treatment. In such cases we discontinued antibiotics in all patients because there was not any evidence of infections. Statistical analysis was done using descriptive methods (such as Mean, Standard Deviation, and Frequency) and analytical methods (Spearman coefficient of correlation) by SPSS 11.5.

RESULTS

This study conducted from Jan 2004 to Dec 2005 in Kashani Educational Hospital of Shahr-e-kord University of Medical Sciences, Iran.

16 out of the 19 cases enrolled in the study, completed the trial period, 3 patients were lost for follow up. These 3 cases included one patient diagnosed as Myasis, the other one was a tribe woman having a scorpion bite in her groin (who was lost for follow up due to immigration of tribe) and the third one was a diabetic deep foot ulcer (whose diabetes was not managed properly because of living alone and no relative to manage him). These 16 patients included 9 male and 7 female. Their ages were from 25 to 70 years and with mean of 41.8 ± 14.6 . The table 1 summarizes the size of ulcer(s) of 16 cases.

(Table 1) In the first visit, size of ulcer was between 10 to 180 cm² with mean of 55.2 ± 43.6 cm².

Table 1 Size of chronic ulcers in different parts of the body of each case ($n = 19$).

No. of Cases	Size in square in cm ²
1	10
9	21-50
4	51-100
1	101-150
1	151-200

There was a wide range of period of time for mean time of present ulcers, at least one month and in one case maximum 4 month (case with skin grafting) for conventional treatment with no avail.

The range for period of time till healing (complete or reduction in size of ulcer) with AVG, was varied, so that it ranged from 5 to 160 days with mean of 31.2 ± 36.4 days.

Time of decreasing for secreting was from 5 to 7 days with mean of 5.5 ± 0.8 days. Time of reduction for swelling was from 5 to 8 days with mean of 6.3 ± 0.8 days and time of improving for redness was from 7 to 11 days with mean of 8.9 ± 1.2 days.

16 patients who completed this study, had relief of symptoms of inflammation (swelling, secretion and redness) and their ulcers had healed (healing of $\geq 50\%$ for size of ulcer) and/or showed formation of good granulation tissue, and finally all of these 16 cases were healed completely.

By using Spearman coefficient of correlation, there were no significant correlation between first ulcer size (in square) and timing till 50% reduction in size of ulcer ($P = 0.413$, $r = 0.155$) also, there were no significant correlation between depth of ulcer and timing till 50% reduction in size of ulcer ($P = 0.245$, $r = -0.219$).

DISCUSSION

This study included 16 patients who suffered from

chronic ulcers for a long time (1 to 4 months). All of them were treated with conventional treatment all to no avail. In fact the purpose of this study was to further investigate and to explore the effect of agents such as AVG that might have on chronic ulcers. Since there was several reports on the effect of AVG on several skin condition like ulcer^[4, 6, 10], we attempted to try AVG on the healing process of non-responder chronic ulcer to conventional therapy. This study showed that applying AVG on ulcers led to cure and/or improvement of ulcers in all patients who completed follow up.

In one study, inhibition of wound contraction by topical anti microbial agents has been described. Wound contraction was delayed by saline and silver sulphadiazine (SSD). Aloe Vera, when added to SSD, reversed that effect^[11]. In our patients, probably, there is the same effect that has inhibited the wound contraction. Although this effect of conventional therapy depends on several factors.

Modern clinical use of the AVG began in the 1930s, with reports of successful treatment of X-ray and radium burns^[4]. Previous studies provided support for the use of AVG in the treatment of ulcers and burns in man^[6, 10].

AVG is known to contain several pharmacologically active ingredients, which show various effect like anti- bradykinin, anti-thromboxane formation, antibacterial, antifungal^[6] a dose-dependent inhibitory effect on reactive oxygen species production^[12], the phycoerythrin assay, the production of prostaglandin E2, and the release of interleukin-8^[8]. The production of specific thromboxane as a mediator of progressive dermal ischemia in frostbite injuries^[13] is blocked by AVG (14). AVG causes to increase the activation capacity of macrophages^[6] and its capacity to promote differentiation of immature dendritic cells^[15] and has both anti-inflammation and wound healing promotion when applied on a second degree burn wound^[16]. All of these features confirm the wound healing promoter character of AVG.

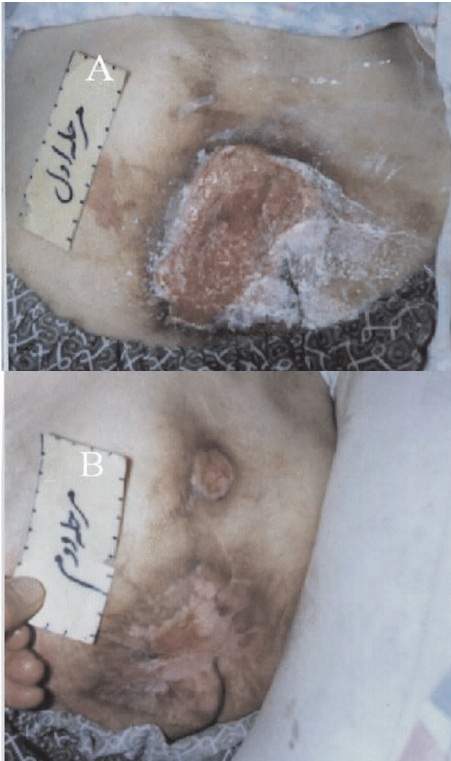
In one study on burn ulcer, it has been shown that AVG is able to reduce significantly the vasodilatation and increased post capillary venular permeability during one week but on day 14 to increase the arteriolar diameter increased up to normal condition. The amount of leukocyte adhesion was also less ob-

served compared to the untreated cases. Besides, the healing area of the Aloe vera-treated wound was better than that of the untreated groups during 7 and 14 days after burn^[16]. As was seen in our study, it has been reported that the signs and symptoms of inflammation of ulcer started to reduce after applying of AVG on ulcers as decreased secretion, redness and swelling of ulcer at 5th -11th day following AVG usage. There were not any changes in these signs and symptoms of inflammation with previous conventional therapy. (During 1 to 4 month treatment of conventional try) Such inhibition effect of AVG on inflammatory process has been reported previously too. Aloe vera could inhibit the inflammatory process following burn injury, as characterized by the reduction of leukocyte adhesion, as well as production of pro-inflammatory cytokines (TNF-alpha and IL-6)^[17], so that a 47.1% inhibition of inflammation was obtained by 5% decolorized irradiated Aloe vera^[5].

The mean time of treatment by AVG leading to cure/improve was 31.2 ± 36.4 days and this was 57 ± 60.8 days for conventional therapy all to no avail.

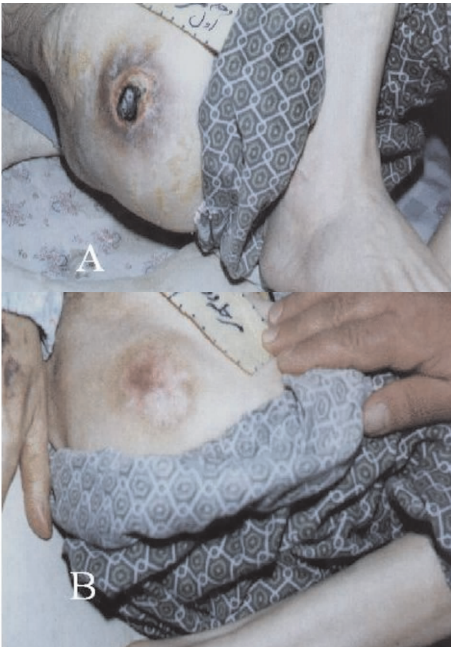
An open wound fills with granulation tissue and contraction enhances wound closure by pulling the surrounding uninjured tissue over the affected area. A fibrin clot will seal the wound permanently by epithelialisation. Tensile strength is achieved by deposition of collagen and other matrix proteins. During the maturation phase, the wound further contracts as collagen cross-linking occurs. AVG must promote the dynamics of wound healing. The reduction in inflammation, rapid closure of the wound, elimination of foreign material and bacteria allow the wound to progress to synthesize scar formation and achieve structural integrity. In this study, we encountered with some full thickness ulcers (epidermis, dermis and hypodermis) (Figure 1 A, 2 A, 3 A). At the end of treatment we observed a cure/improvement and normal skin for those ulcers. (Figure 1 B, 2 B, and 3 B)

While one study reported that the two treatments of normal saline and AVG have equally efficacious in promoting wound healing^[18], but similar to our study, AVG dressings are significantly more cost effective than conventional therapy^[18].



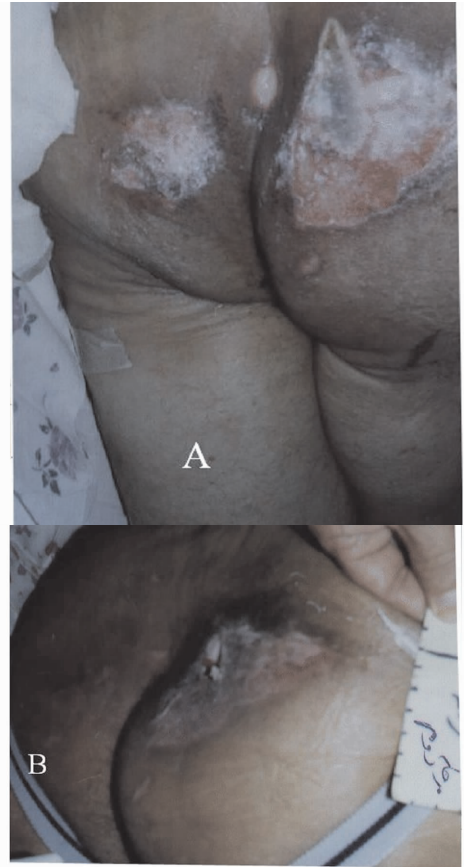
A chronic sacral pressure ulcer is seen (A), which is healed with AVG (B).

Figure 1 A Chronic sacral pressure ulcer is seen (A), which has been healed with AVG (B).



The greater necrotic trochanter pressure ulcer (A) is seen with black appearance which is healed with aloe wregel (B)

Figure 2 The greater trochanter pressure Ulcer (A) is seen with black appearance which has been healed with AVG (B).



A- The Ulcer Before Treatment.
B-The Ulcer After Treatment.

Figure 3 The ulcer before treatment (A) and after treatment with AVG (B).

A previous study reported that hypersensitivity, manifested by generalized nummular eczematous and papular dermatitis, and presumably by contact urticaria, developed in a 47-year-old man after four years of using oral and topical aloe. Patch tests for aloe were positive in this patient^[19]. Another study reported only some minor adverse effects, following AVG usage, such as discomfort and pain^[20]. Among our 16 cases, we encountered a minor complication, itching in one patient, but it was not so severe which could lead to stop treatment.

Similar to what we reported in this study, folk medicine tradition provides different indicators for use than the medical disease model. They serve as therapeutic alternatives, safer choices, or in some cases, as the only effective treatment^[21].

Although this study may be mentioned as an uncontrolled trial study, but in fact these cases may be mentioned as themselves control because of long time

conventional study all to no avail. The minor results gotten from this study is that in some recalcitrant ulcers, (in this study, DFU, pressure ulcer and surgical ulcer) healing process in made faster by AVG.

CONCLUSION

This study confirmed and concluded that AVG used in the treatment of chronic ulcers stimulates and accelerates the healing process. These findings suggest that AVG is an excellent and safer choice than current conventional therapeutic management of chronic ulcers. This Gel can promote healing of ulcers of failed treatment. Neither size nor depth of ulcers is the factor which could affect the outcome of improvement by AVG.

ACKNOWLEDGEMENT

This study was done under one of the hypothesis (for MD course) approved in Shahr-e-kord University of Medical Sciences. Here by I thank from Dr Soleiman Kheiri for his co-operation in statistical analysis.

REFERENCES

- 1 **Mantle D**, Gok MA, Lennard TW. Adverse and beneficial effects of plant extracts on skin and skin disorders. *Adverse Drug React Toxicol Rev.* 2001; 20(2):89-103.
- 2 **Avijgan M**. Phytotherapy; an alternative treatment for non-healing ulcers. *J Wound Care.* 2004; 13(4):157-8.
- 3 **Thomas DR**, Goode PS, LaMaster K, Tennyson T. Acemannan hydrogel dressing versus saline dressing for pressure ulcers. A randomized, controlled trial. *Adv Wound Care.* 1998; 11(6):273.
- 4 **Grindlay D**, Reynolds T. The Aloe vera phenomenon: a review of the properties and modern uses of the leaf parenchyma gel. *Journal of. Ethnopharmacology.* 1986; 16(2-3):117-5.
- 5 **Eshun K**, He Q. Aloe vera: a valuable ingredient for the food, pharmaceutical and cosmetic industries--a review. *Crit Rev Food Sci Nutr.* 2004; 44(2):91-6.
- 6 **Klein AD**, Penneys NS. Aloe vera. *J Am Acad Dermatol.* 1988; 18(4 Pt 1):714-20.
- 7 **McCauley RL**, Hegggers JP, Robson MC. Frostbite. Methods to minimize tissue loss. *Postgrad Med.* 1990; 88(8):67-8, 73-7.
- 8 **Langmead L**, Makins RJ, Rampton DS. Anti-inflammatory

- ry effects of aloe vera gel in human colorectal mucosa in vitro. *Alimentary pharmacology& therapeutics.* 2004; 19(5):521-7.
- 9 **Djeraba A**, Quere P. In vivo macrophage activation in chickens with Acemannan, a complex carbohydrate extracted from Aloe vera. *Internal journal of immunopharmacology.* 2000; 22(5):365-72.
 - 10 **Avijgan M**. Phytotherapy; An alternative treatment for non-healing ulcers. *J Wound Care.* 2004; 13(4):157-158.
 - 11 **Muller MJ**, Hollyoak MA, Moaveni Z, Brown TL, Herndon DN, Hegggers JP. Retardation of wound healing by silver sulfadiazine is reversed by Aloe vera and nystatin. *Burns.* 2003; 29(8):834-6.
 - 12 **Hart LA**, Nibbering PH, van den Barselaar MT, van Dijk H, van den Berg AJ, Labadie RP. Effects of low molecular constituents from Aloe vera gel on oxidative metabolism and cytotoxic and bactericidal activities of human neutrophils. *Int J Immunopharmacol.* 1990; 12(4):427-34.
 - 13 **Hegggers JP**, Robson MC, Manavalen K, Weingarten MD, Carethers JM, Boertman JA, et al. Experimental and clinical observations on frostbite. *Ann Emerg Med.* 1987; 16(9):1056-62.
 - 14 **Zachary LS**, Smith DJ, Hegggers JP, Robson MC, Boertman JA, Niu XT, et al. The role of thromboxane in experimental inadvertent intra-arterial drug injections. *Hand Surg [Am].* 1987; 12(2):240-5.
 - 15 **Lee JK**, Lee MK, Yun YP, Kim Y, Kim JS, Kim YS, et al. Acemannan purified from Aloe vera induces phenotypic and functional maturation of immature dendritic cells. *Int Immunopharmacol.* 2001; 1(7):1275-84.
 - 16 **Somboonwong J**, Thanamitramanee S, Jariyapongskul A, Patumraj S. Therapeutic effects of Aloe vera on cutaneous microcirculation and wound healing in second degree burn model in rats. *J Med Assoc Thai.* 2000; 83(4):417-25.
 - 17 **Duansak D**, Somboonwong J, Patumraj S. Effects of Aloe vera on leukocyte adhesion and TNF-alpha and IL-6 levels in burn wounded rats. *Clin Hemorheol Microcirc.* 2003; 29(3-4):239-46.
 - 18 **Capasso VA**, Munro BH. The cost and efficacy of two wound treatments. *AORN J.* 2003; 77(5):984-92, 995-7, 1000-4.
 - 19 **Morrow DM**, Rapaport MJ, Strick RA. Hypersensitivity to aloe. *Arch Dermatol.* 1980; 116(9):1064-5.
 - 20 **Visuthikosol V**, Chowchuen B, Sukwanarat Y, Sriurairatana S, Boonpucknavig V. Effect of aloe vera gel to healing of burn wound a clinical and histologic study. *J Med Assoc Thai.* 1995; 78(8):403-9.
 - 21 **Dattner AM**. From medical herbalism to phytotherapy in dermatology; back to the future. *Dermatol Ther.* 2003; 16(2):106-13.