

Original Article

Evaluation of the therapeutic effects of Aloe vera gel on minor recurrent aphthous stomatitis

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ABSTRACT

Background: Aphthous ulcer is one of the most common diseases of the oral cavity with no known effective treatment so far, which could cause severe discomfort in patients. Aloe vera (A.V.) is a tropical plant with anti-inflammatory and immunostimulant effects, which could be of benefit in a diversity of wound healing conditions. The aim of this study is to evaluate topically administered A.V. gel on oral cavity minor aphthous healing.

Materials and Methods: As a double-blind (case control) clinical trial, 40 patients with oral minor aphthous lesions were randomly allocated in either the case group (A.V. gel) or the control (placebo) group. The healing time (days after gel application), patient's pain score; the lesion and its surrounding inflammation diameters were recorded for 2 weeks. The obtained results were analyzed by either "Fishers exact" or *t*-student test using SPSS software.

Results: The mean (\pm SD) of patients' age was 29.25 ± 8.48 and 27.95 ± 7.96 years in the control and A.V.-treated groups, respectively, which were not significantly different ($P > 0.05$). The duration of complete wound healing, pain score, wound size and inflammation zone diameter in the A.V.-treated group were significantly lower than the control group ($P \leq 0.05$) on specific time points after treatment.

Conclusion: It seems likely that A.V. 2% oral gel is not only effective in decreasing the recurrent aphthous stomatitis patients' pain score and wound size but also decreases the aphthous wound healing period.

Key Words: Aloe vera, aphthous stomatitis, immunomodulation, mouth diseases

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INTRODUCTION

Recurrent aphthous stomatitis (RAS) is one of the most common oral cavity lesions, with a wide range of reported prevalences from 5 to 50% in different populations.^[1-3] It is a recurrent spontaneously healing lesion mostly affecting the lips, soft palate and throat in children and young adults.^[4] The frequency of RAS

recurrence declines by age, and it seems to be less common in males compared with females. It causes not only pain but could also decrease the quality of life by interfering with swallowing, drinking, eating and even speaking.^[3,5] The histopathology of RAS has not been clearly understood; hence, treatments are mostly miscellaneous and, because of its recurrent nature, double-blind prospective clinical trials with new therapies could not be easily conducted.^[4] A wide range of chemical drugs (mostly applied topically, i.e. chlorhexidine, cyclosporine, levamisole, steroids, sucralfate, tetracycline ...) have been showed to be partially effective in alleviating^[6] patients symptoms and disease length.^[1,3,7,8]

Natural products, especially herbal medicines, have found great attentions in the recent decades as

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they are assumed to have less adverse effects.^[1-2,5] Aloe vera (A.V.) is a tropical plant grown in north Africa and most parts of Asia with succulent leaves that has been used for thousands of years as herbal medicine.^[9-10] Recent studies on the gel of the A.V. leaves have shown that it might be of benefit in a wide range of inflammatory diseases, including healing of different types of wounds.^[1-14] The transparent gel derived from A.V. leaves contains a series of natural components with wound healing potential,^[14-15] which make it a good candidate for minor RAS. This study was designed to evaluate the efficacy of A.V. gel in alleviating minor RAS symptoms and its cure length.

MATERIALS AND METHODS

Patients who underwent the study

The sample population was recruited from patients visiting the Dentistry Clinic (Babol University of Medical Sciences, Babol-Iran) who had given written consent to participate in this double-blind (phase II) clinical trial from April 2010 till February 2011. Forty patients aged between 15 and 35 years with minor recurrent aphthous singular lesions on their buccal mucosa and mucosal zone of the lips (after a medical diagnosis of RAS minor) without any other medical complications who had noticed oral lesions during the last two days were randomly assigned to receive either A.V. gel or placebo. Patients with systemic diseases, major aphthous lesions, multiple minor lesions in the oral cavity, RAS lesions other than those located on the buccal mucosa and mucosal zone of the lips, pregnant mothers and smokers were excluded from the study. This study was conducted under the Babol University of Medical Sciences' Ethics Committee approval (Reg. No. 2436) and also has been officially registered on the Iranian Registry of Clinical Trial organization (Irct ID: IRCT201107277136N1).

Preparation and application of oral gel

Freshly purified leaf juice extract of A.V. gel (kindly supplied by Barij-Essence Co., Tehran-Iran) with 1.6% dry remnant and a density of 1.01 g/mL was used to prepare a 2% oral gel using sterile lubricant gel (CMC-based, Farayand-Nik Co., Iran). Lubricant gel containing 2% normal saline was used as placebo. Both A.V. and placebo gels were aseptically dispensed in similar 50-mL pump-cap polystyrene-coded containers with appropriate nozzle to apply the gel on the lesions three-times a day by the patients for at least ten days. The same numbers of containers were

filled by both gels (e.g., 22 A.V. and 22 placebos) and then all the containers were coded. Drinking or eating was avoided at least for half an hour after gel application.

Clinical observations and pain scoring

Patients' oral lesions were clinically observed at days 0 (just before entering the study), 3, 7 and 10. Using a metal caliper, the lesions' diameters and their inflammatory zone were measured. Also, patients were trained to record their orange juice-stimulated pain score (using Visual Analogue Scale [VAS]) every day for 10 days. Patients with stimulated pain score of 1 and lesion diameter less than 1mm were considered healed.

Statistical analysis

After decoding the containers at the end of the study, patients' median VAS scores, RAS healing period, mean of lesion and inflammation diameters were compared between the two groups using either Fisher exact or unpaired Student *t*-test. A $P < 0.05$ was considered statistically significant.

RESULTS

From the 87 patients admitted for oral aphthous lesions in the Dentistry Clinic (Babol University of Medical Sciences), only 49 patients had all the study criteria; however, only 40 patients succeeded in completing the study (five patients refused to give written consent and four patients stopped their treatment course before Day five for no specific reason). Decoding the containers showed that 20 patients in both the A.V. and the placebo group had successfully fulfilled the study. The female to male patients ratio (F:M) in the A.V.-treated group was 10:10 and in the control group (placebo gel) was 8:12, which were statistically not different ($P > 0.05$). Also, the mean (\pm SD) age in the A.V. group (27.95 ± 7.96 years) was not significantly different from that of the control group (29.25 ± 7.48 years) ($P > 0.05$).

The healing times for pain (VAS < 2) and lesions (lesion diameter < 1 mm) in the A.V.-treated group were significantly lower than in the control group ($P \leq 0.05$; Table 1). Also, the pain severity was lower in the A.V.-treated patients after 4 days compared with the control group [Figure 1]. The pain and lesion in both the A.V.- and the placebo-treated groups at Day 10 were considered healed based on the patients' self-reports. The circumscribed inflammation zone and lesion diameters in the

A.V.-treated group became significantly smaller than in the control group after day three and day seven, respectively [Table 1].

DISCUSSION

A.V. gel has been used as a wound healing, anti-infection and anti-inflammatory agent since ancient times.^[12,16] RAS minor is a common ulcerative oral cavity disease with no clearly defined pathophysiology so far.^[1,3] The inflammations and the accompanying pain, which interfere with patients quality of life (including eating, drinking and even speaking), are two important criteria of RAS with no universally accepted medication. Different agents including herbal medicines have been found effective after either systemic or topical administration. However, these medications are not effective in all cases, and the etiology of RAS tends to remain unclear. Clinical trials on new agents are still ongoing to introduce not only effective medications but also to elucidate the mechanisms involved in RAS pathophysiology. At this clinical trial, we have studied the therapeutic effects of A.V. oral gel on RAS lesions, which were shown to be effective in terms of alleviating the patient's pain score and lesion diameter compared with the control group (placebo).

Using the same numbers of coded containers of both A.V. and placebo gels, which were randomly administered to the patients, allowed the study to be double-blinded and randomized at the same time. To decrease the number of variables affecting the RAS pathophysiology and pharmacology, we narrowed the patients' age range between 15 and 35 yrs, and only the patients with minor RAS in their lips and inner cheeks were included in this study. Also, patients with obvious singular RAS lesion manifesting not more than 48 h prior underwent the study.

All other patients with major discrepant factors, including smoking, diabetes, allergy history,

systemic diseases, multiple RAS lesions and herpetic form lesions, had been excluded from the study. Because patients were randomly allocated in either the test or the control group, their mean age and the female to male ratios, which might be two important factors affecting pain perception and RAS healing process, were not significantly different.

The lower VAS scores in the A.V.-treated patients [Figure 1], which was observable just a few days after the treatment, might be attributed to the anti-inflammatory properties of A.V. [Table 1 and Figure 1]. This anti-inflammatory effect was detectable in the A.V.-treated group from three days after treatment. The anti-inflammatory properties of A.V. and its efficacy in some other diseases have been shown in several previously conducted studies.^[2,11-13,17,18] Some well-known antioxidant constituents in A.V. gel (e.g., flavonoids, saponins, sterols, terpenoids...) might contribute to its anti-inflammatory properties.^[10,14,19] Using anti-inflammatory medications in oral cavity disorders, including RAS, has a well-established

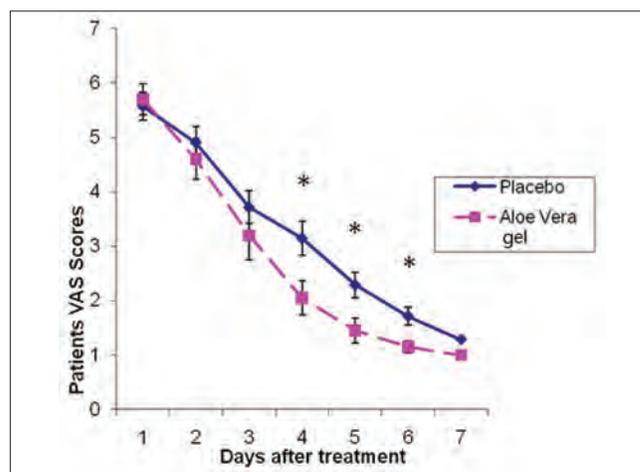


Figure 1: Stimulated pain score in the Aloe vera or placebo gel treated patients with recurrent aphthous stomatitis. Each point represents the mean ± SE of stimulated pain scores of 20 patients at each day after treatment

Table 1: The RAS lesion and circumscribed inflammation diameter (mm) (mean ± SD) after A.V. topical gel treatment compared with placebo (CMC base gel)*

Group	Day 0		Day 3*		Day 7*		Day 10**	
	Lesions diameter	Inflammation diameter						
A.V. group	2.53 ± 0.66	3.93 ± 1.00	2.22 ± 0.64	3.03 ± 0.97	1.29 ± 0.66	1.4101 ± 1.05	<1	NA
Placebo	2.65 ± 0.82	4.13 ± 1.02	2.09 ± 0.84	3.66 ± 0.93	0.60 ± 0.69	2.12 ± 0.97	<1	NA
P-value	0.615	0.525	0.556	0.044	0.003	0.001	-	-

*Number of patients in each group was 20 RAS: recurrent aphthous stomatitis AV: Aloe vera (2%) oral gel NA: not available, *P < 0.01, **Considered healed

basis in dentistry.^[20] The immunomodulatory role of some polysaccharides in A.V. gel is another possible mechanism involved in its anti-inflammatory properties that could facilitate the wound healing process as well.^[14] Acemannan, a mucopolysaccharide derived from A.V. gel, has shown immunomodulatory properties and might have a major contribution in A.V. wound healing effects.^[6] Furthermore, the antioxidant properties of A.V. gel along with its inhibitory effects on prostaglandin E2 and interleukin-8 productions are other candidate mechanisms suggesting its potential curative benefits.^[12]

Wound healing properties of A.V. have been suggested by some studies conducted on other medical conditions like skin injuries, burn, colorectal inflammation, cancer and infection.^[14,21] Again, the anti-inflammatory and immunomodulatory properties of A.V. constituents are possible mechanisms involved in its potential wound healing effects.^[10,14,19-20,22] The pathophysiology of RAS minor is not clear yet; however, anti-inflammatory drugs have been shown to be effective in alleviating lesion outbreaks.^[2-4,20] Some gastrointestinal disorders with probable immunological background, i.e. irritable bowel disease (IBD) and lichen planus, have extra intestinal symptoms including mouth ulcers. The A.V. gel has been shown to be effective in alleviating oral lichen planus (OLP) symptoms, including patients' pain scores.^[23] In that study, A.V. was used for 8 weeks as topical gel on OLP lesions, and complete clinical remission was seen in 7% of the patients; however, more than 81% of the patients had a good response overall. In another study, A.V. gel showed a significant wound healing effect after oral irradiation by increasing TGF- β -1 and bFGF production.^[24] In spite of uncertainty on the mechanism behind this immunomodulation, the antioxidative stress properties of A.V. might be involved. Immunomodulation has been suggested as the main mechanism of healing properties of some natural medicines like "tien-hsien liquid" in RAS.^[25]

Based on our results, the wound healing effects of A.V. gel (measured by RAS lesion diameters) seems to be less prominent than its anti-inflammatory effects [Table 1]. However, overall, its effects on RAS lesions is considered curative as it decreased the healing time to less than seven days.

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