The Effect Of Aloe-Vera In Recurrent Minor Aphthous Stomatitis Patients-A Pilot Study

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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. There are few clinical trials where Aloe Vera (AV) has been used in the treatment of oral diseases such as oral lichen planus, recurrent aphthous stomatitis, oral pemphigus, herpetic stomatitis, radiation induced mucositis. **Aims & Objectives:** The aim of this study is to evaluate topically administered AV gel on oral cavity minor aphthous healing. **Methods:** The retrospective multiple level clinical trials study done on having recurrent aphthous stomatitis patients comes for regular checkup in Department of Dentistry, S.P. Medical College Bikaner, Rajsthan. The sample population was recruited from patients visiting the Dentistry Clinic who had given written consent to participate in this double-blind (phase II) clinical trial from January 2014 till December 2014. **Results:** The present study shows that the healing times for pain and lesions (lesion diameter < 1 mm) in the AV-treated group were significantly lower than in the control group. **Conclusion:** The presnt study shows that AV 2% oral gel is not only effective in decreasing the recurrent aphthous stomatitis patient's pain score and wound size but also decreases the aphthous wound healing period.

Key-words: Aloe vera, Visual Analogue Scale (VAS), Aphthous ulcer, Wound Healing, Oral Disease.

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INTRODUCTION:

Aloe vera (AV) is an important and traditional medicinal plant belonging to the family Liliaceae. There are over 400 species of Aloe Vera plants in the Lily Family.[1] Aloe vera contains 75 potentially active constituents: vitamins, enzymes, minerals, sugars,lignin, saponins, salicylic acids, and amino acids.[2,3] These constituents are related to biological effects of aloe vera, [4,5,6] which are as follows:

1) Healing properties: In 1991, Thompson reported that topical application of the aloe vera-derived allatonin gel stimulated fibroblastic activity and collagen proliferation.[7] Yagi et al. reported that Aloe vera gel contains a glycoprotein with cell proliferating-promoting activity, while Davis et al. noted that Aloe vera gel improved wound healing by increasing blood supply (angiogenesis), which increased oxygenation as a result.[8] Glucomannan, a mannose-rich polysaccharide, and gibberellin, a growth hormone, interacts with growth factor receptors on the fibroblast, thereby stimulating its activity and proliferation, which in turn significantly increases collagen synthesis after topical and oral Aloe vera.
2) Protective effects on skin exposed to UV and gamma radiation: Following the administration of aloe vera gel, an antioxidant protein, metallothionein, is generated in the skin, which scavenges hydroxyl radicals and prevents

suppression of superoxide dismutase and glutathione peroxidase in the skin. Aloe vera gel has been reported to have a protective effect against radiation damage to the skin.

3) Anti-inflammatory action: Aloe vera inhibits the cyclooxygenase pathway and reduces prostaglandin E2 production from arachidonic acid. Recently, the novel anti-inflammatory compound called C-glucosyl chromone was isolated from gel extracts.
4) Effects on the immune system: Alprogen inhibit calcium influx into mast cells, thereby inhibiting the antigen-antibody-mediated release of histamine and leukotriene from mast cells. Acemannan stimulates the synthesis and release of interleukin-1 (IL-1) and tumor necrosis factor from macrophages which in turn initiates an immune attack that result in necrosis and regression of the cancerous cells.
5) Antiviral and antitumor activity: These actions may be due to indirect or direct effects. Indirect effect is due to stimulation of the immune system and direct effect is due to anthraquinones. The anthraquinone alone inactivates various enveloped viruses such as herpes simplex, varicella zoster and influenza. In recent studies, a polysaccharide fraction has shown to inhibit the binding of benzopyrene to primary rat hepatocytes, thereby preventing the formation of potentially cancer-initiating benzopyrene-DNA adducts. An induction of glutathione S-transferase and an inhibition of the tumor-promoting effects of phorbol myristic acetate has also been reported which suggest a possible benefit of using aloe gel in cancer chemoprevention.

Aphthous stomatitis (canker sores) is the recurrent appearance of mouth ulcers in otherwise healthy individuals. The cause is not completely understood, but it is thought that the condition represents a T-cell mediated immune response which is triggered by a variety of factors. The individual ulcers (aphthae) recur periodically and heal completely, although in the more severe forms new ulcers may appear in other parts of the mouth before the old ones have finished healing. Aphthous stomatitis is one of the most common diseases of the oral mucosa, and is thought to affect about 20% of the general population to some degree.[9] The symptoms range from a minor nuisance to being disabling in their impact on eating, swallowing and talking, and the severe forms can cause people to lose weight. There is no cure for aphthous stomatitis,[10] and therapies are aimed at alleviating the pain, reducing the inflammation and promoting healing of the ulcers, but there is little evidence of efficacy for any treatment that has been used.

Aloe Vera is used in various oral diseases like gingivitis, denture sore mouth,[11] Shingles and Herpetic stomatitis,[11] oral lichen planus,[12,13] minor recurrent aphthous ulcer,[14] leukoplakia, oral submucous fibrosis.[15] They are available in different forms like gel, ointment and also as drinks, capsules etc. The extraoral adverse effects reported are very few such as burning on topical application, contact dermatitis, and mild itching.[15] The present article aims in evaluation of these clinical trials to assess the efficacy of Aloe vera as a therapeutic modalities in recurrent aphthous stomatitis.

MATERIAL AND METHOD:

The retrospective multiple level clinical trials study done on having recurrent aphthous stomatitis patients comes for regular checkup in Department of Dentistry, S.P. Medical College Bikaner, Rajsthan. Approval from the institutional committee was taken before starting the study. The sample population was recruited from patients visiting the Dentistry Clinic who had given written consent to participate in this double-blind (phase II) clinical trial from January 2014 till December 2014. 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 AV 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.

Preparation and application of oral gel:

Freshly purified leaf juice extract of AV gel 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. Lubricant gel containing 2% normal saline was used as placebo. Both AV 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 AV 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.

RESULTS:

The present study shows that the healing times for pain (VAS < 2) and lesions (lesion diameter < 1 mm) in the AV-treated group were significantly lower than in the control group ($P \leq 0.05$). The pain and lesion in both the AV- and the placebo-treated groups at day 10 were considered healed based on the patient's self-reports. The circumscribed inflammation zone and lesion diameters in the AV-treated group became significantly smaller than in the control group day 7 respectively. [Table-1]

DISCUSSION:

Aloe vera has been proved to have multiple and few unique properties with very less side-effects and hence can be definitely tried in many oral and extra-oral diseases. AV gel has been used as a wound healing, anti-infection and anti-inflammatory agent since ancient times.16 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 AV 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).

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 AV-treated patients, which were observable just a few days after the treatment, might be attributed to the anti-inflammatory properties of AV [Table-1]. The anti-inflammatory properties of AV and its efficacy in some other diseases have been shown in several previously conducted studies.[17] Some well-known antioxidant constituents in AV gel (e.g., flavonoids,

saponins, sterols, terpenoids) might contribute to its anti-inflammatory properties.[5] Using anti-inflammatory medications in oral cavity disorders, including RAS, has a well-established basis in dentistry. The immunomodulatory role of some polysaccharides in AV gel is another possible mechanism involved in its anti-inflammatory properties that could facilitate the wound healing process as well.[5] Acemannan, a mucopolysacharide derived from AV gel, has shown immunomodulatory properties and might have a major contribution in AV wound healing effects.[18] Furthermore, the antioxidant properties of AV gel along with its inhibitory effects on prostaglandin E2 and interleukin-8 productions are other candidate mechanisms suggesting its potential curative benefits.[16]

Wound healing properties of AV have been suggested by some studies conducted on other medical conditions like skin injuries, burn, colorectal inflammation, cancer and infection.[5] Again, the anti-inflammatory and immunomodulatory properties of AV constituents are possible mechanisms involved in its potential wound healing effects.[5] The AV gel has been shown to be effective in alleviating oral lichen planus (OLP) symptoms, including patients' pain scores.[19] In that study, AV 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, AV gel showed a significant wound healing effect after oral irradiation by increasing TGF-β-1 and bFGF production.[20] In spite of uncertainty on the mechanism behind this immunomodulation, the antioxidative stress properties of AV might be involved. Immunomodulation has been suggested as the main mechanism of healing properties of some natural medicines like "tien-hsien liquid" in RAS.[21]

Based on our results, the wound healing effects of AV 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.

CONCLUSION:

Aloe vera proved to have multiple and few unique properties with very less side-effects and hence can be definitely tried in many oral and extra-oral diseases. It seems likely that AV 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. The future demand for more human clinical trials utilizing the unique properties of Aloe-vera in recurrent minor aphthous ulcers patients.

Conflict of Interest: None.
Funding: Nil.

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

Group	Day 0		Day 7		Day 10	
	Lesions Diameter	Inflammation Diameter	Lesions Diameter	Inflammation Diameter	Lesions Diameter	Inflammation Diameter
AV Group	2.54±0.64	3.98± 1.07	1.32±0.77	1.4102±1.01	‹1	NA
Placebo group	2.76±0.76	4.32±1.06	0.63±0.76	2.56±1.00	‹1	NA
P-Value	0.621	0.543	0.002	0.001	-	-

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