

A Self-controlled Single Blinded Clinical Trial to Evaluate Oral Lichen Planus after Topical Treatment with *Aloe Vera*

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ABSTRACT

AIM: The object of this study was to evaluate the efficacy of a self-controlled single blinded clinical trial of the topical application of *Aloe vera* in oral lichen planus (OLP).

METHODS: Twenty patients (15 male and 5 female) aged at least 18 years recruited from the outpatients. In all cases the diagnosis met currently accepted criteria. Each patient was instructed to manually apply *Aloe vera* (AV) high molecular weight fractions (AHM) on the affected side oral mucosa three times daily and examined at the beginning of treatment and then after 4 and 8 weeks of therapy. AHM were obtained from water-washed gel part of AV and processed by the patented hyper-dry system in combination of freeze-dry technique with micro wave and far infrared ray irradiations. The macromolecular aloe ointment is a mixture of the hydrophilic ointment and AHM at 0.1% by weight.

RESULTS: A self-controlled single blind protocol to assessment clinical improvement and pain response was used in this study. The clinical results showed a rapid subjective and objective improvement with topical AHM treatment. Fifteen patients (75%) had complete remission at treated side and two patients (10%) had partial remission, while one patient showed no response to treatment (5%), and placebo sides showed partial remission responded in two cases only (10%) and no responded in other sides.

CONCLUSION: The effect of AHM ointment on OLP was significantly effective than that of placebo. The results showed

decrease both in clinical signs and in pain scores. AHM ointment showed well tolerated, safe and effective treatment to OLP.

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Key words: *Aloe vera*; Oral lichen planus; Single-blinded self controlled clinical trials

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INTRODUCTION

Lichen planus (LP) is a relatively common disorder of the stratified squamous epithelium^[1]. It is a chronic, immunological, mucocutaneous disease with a wide range of clinical manifestations. Oral lichen planus (OLP) affects one to two percent of the general adult population and is the most common non-infectious oral mucosa disease. The history of OLP is characterized by liquefaction degeneration of basal epithelial cells and sub-epithelial band-like infiltrate of mononuclear cells, which comprise principally macrophages and CD4+ cells in early lesions and predominantly CD8+ cells in the later lesions^[2,3]. In addition, the majority of intra-epithelial T cells are CD8+ and the proportion of CD8+ cells is higher in the superficial rather than deeper lamina propria^[3]. Current treatments for OLP are not curative but are aimed at relieving pain and therefore usually restricted to managing the painful, erosive and ulcerative forms. Many treatments have been tried including (but not limited to) topical, intra-lesional and systemic corticosteroids, topical cyclosporin, topical and systemic retinoids, anti-microbials, azathiopurine, photo-chemotherapy and surgery^[4,5].

Patients with symptomatic OLP often require intensive therapy to reduce the sign and symptoms. The disease can produce considerable morbidity and alter patient quality of life, particularly in the presence of ulcerative lesions^[6,7]. There is not fully resolute and effective treatment, but there is the management strategy focusing on the use of drugs that counter tissue inflammation and the underlying immunological mechanisms. The main inconvenience of these treatments is represented by the side effects they usually produce^[6,8,9].

Aloe vera (*Aloe barbadensis* Miller) is a member of Liliaceae family in tropical regions, and the cosmetic and medicinal products are made from the mucilaginous tissue in the centre of the plant called aloe vera gel. The peripheral bundle of sheath cells produces intensely bitter, yellow latex, commonly termed as aloes. Unlike aloes, AV gel contains no anthraquinones, which are responsible for the strong laxative effects of aloes. The pharmacological actions of *Aloe vera* was studied *in vitro* and *in vivo* including anti-inflammatory, anti-arthritis, antibacterial and hypoglycemic effects^[10]. It is widely used as a natural treatment and alternative therapy for various types of diseases. Several studies have suggested the healing, cosmetic and nutritional benefits of this plant^[11,12]. AV has also been used for treatment of lichen planus. Hayes^[13] was the first to use it in a patient who experienced improvement of her oral lesions after 4 weeks of therapy. Choonhakarn^[14] compared the efficacy of AV and placebo in the topical management of OLP. The authors reported that 81% of the patients treated with AV experienced improvement and AV gel was statistically significantly more effective than placebo in inducing clinical and symptomatological improvement of OLP. Therefore, AV gel can be considered a safe alternative treatment for patients with OLP. Salazar-Sanchez^[15] evaluated the efficacy of the topical application of AV to OLP compared with placebo. The study concluded that the topical application of AV improves the total quality of life in patients with OLP. The objective of our study was to compare the efficacy of topical applied AHM and placebo for the treatment of OLP in a self-controlled single blind protocol after 8 weeks of treatment.

MATERIAL AND METHODS

Material

Extraction of AHM: AHM were obtained from water-washed gel part of AV leaves cultivated in Okinawa, Japan. Voucher specimens of AV collected in Okinawa, were compared and determined to be AV plant (syn. *Aloe barbadensis* Miller, Herbarium number 54-3 in Medicinal garden, Fukuyama University by Emeritus Prof. A.Yagi). AHM were processed by patented hyper-dry system in combination of freeze-dry technique with micro wave and far infrared-ray radiation.

Characterization and formulation of AHM to dental study: One g of AHM sample was homogenized in 2 mL of 0.2 M NaNO₃ in a homogenizer. Then, centrifugation of homogenate at 2 000 x g for one minute was done. Upper solution was introduced as 200 µL aliquots to size exclusion chromatography. Barbaloin content in AHM was less than 10 ppm in AHM by HPLC analysis^[16]. The powder size of AHM was 5.090 µm by use of Master size 2000 of Malvern Instrument LTD. Japan. Water content: 3±0.5 %, Colony formulating unit: less than 300/g, Na⁺: approx. 430 mg/100 g, Ca²⁺: approx. 2 100 mg/100 g. AHM contain the following ingredients: neutral polysaccharides with molecular weight (MW) of about 1 000 KD, containing 90% carbohydrate. Glycoprotein, verectin, with MW of 29 KD composed of carbohydrate and protein in a ratio of 10.7 and 82.0%, respectively, was obtained in a ratio of 20% by immunochemical assay in AHM^[17]. The macromolecule AHM ointment (AHM ointment) is a mixture of a hydrophilic ointment composed of carboxymethylcellulose sodium, white vaseline and water at a ratio of 1:1:1 and AHM at 0.1% by weight.

Patients

Twenty patients (15 women, 5 men) aged at least 18 years were recruited from the outpatient clinic of the Department of Periodontology and Oral Medicine, Faculty of Dentistry, 6th October

University and Tanta University. For all cases patients were gave written informed consent. All patients were volunteers that received no economical compensation for participating in the study. In all cases the diagnosis met currently accepted criteria. Clinical criteria included the presence of bilateral lesions, with erythematous and/or erosive lesions, painful and no specific treatment within 4 weeks prior. The exclusion criteria were (1) the pregnant or breast feeding women, (2) lesions in contact with dental amalgam, (3) the use of drugs possibly causing lichenoid reactions, (4) any treatment for OLP or immuno-suppressive drugs for pre-existing diseases within the 4 weeks prior to the study, and (5) a history of hypersensitivity to AV.

Treatment protocol

The protocol of the study was explained to the patients and they agreed to participate by signing a written consent form. All procedures used in the protocol were in accordance to the Helsinki Declaration.

Self-controlled single blind and placebo-controlled studies were adopted and AHM ointment was used for present study.

Patients were instructed to manually apply AHM ointment on the affected right side oral mucosa three times daily with the aid of gauze and the placebo gel to left and all patients were blinded to the treatment assignment. Patients were instructed not to eat or rinse their mouth for at least one hour after application of the treatment. Also, all patients were instructed for oral hygiene measure. Each patient was examined at the beginning of treatment, and then after 4 and 8 weeks of therapy. The clinical effect of treatment response was evaluated based on the criteria of Carrozzo and Gandolfo^[18]. Complete remission (few or no symptoms), Partial remission (the symptoms have decreased with erythematous areas) and No response (the symptoms persist).

RESULTS

The clinical results showed a rapid subjective and objective improvement with topical AHM treatment. Fifteen patients (75%) had complete remission at treated side (asymptomatic and absence of mucosal erosion) and two patients (10%) had partial remission (decrease in symptoms with incomplete resolution erosion), while one patient showed no response to treatment (5%). Only one patient dropped out of the study. While placebo sides showed partial remission reproduced in two cases only (10%) and no response in others sides (Table 1, Figures 1 and 2).

Table 1 Clinical results of treated group.

Clinical	Number of patients	Percentage
Complete remission	15	75%
Partial remission	2	10%
No response	1	5%
Patient dropped out	1	5%
Side effect	-	- %

DISCUSSION

OLP affects cts one to two percent of the general adult population and is the most common non-infectious oral mucosal disease. OLP affects women more than men at a ratio of approximately 1.4:1 and occurs predominantly in adults over 40 years old. Current treatments for OLP are aimed at alleviating pain and eliminating the lesion. Many treatments have been tried but there is a lack of strong evidence supporting their efficacy^[6]. Some recalcitrant lesions require systemic medications. Various systemic agents have been reported to be beneficial in the treatment of OLP, e.g. acitretin, azathiopurine and systemic corticosteroids^[19,20]. Topical treatments have been widely



Figure 1 Right side treated with AHM at baseline (lower-right), 4 (lower-left) and 8 (upper) weeks.



Figure 2 Right side treated with AHM ointment at baseline (lower-right), 4 (lower-left) and 8 (upper) weeks.

used in patients with OLP, including corticoids and calcineurin inhibitors, although toxicity and side-effects sometimes limit such therapies^[6,9]. The management of OLP is sometimes complicated, with a potential risk of malignant transformation^[21,22]. In this context, patients with erosive lesions often require prolonged treatment. Immuno-suppressor, tacrolimus has been used particularly although this drug has been associated with malignant transformation^[9]. Consequently, in some cases, it is important to use alternative therapies.

OLP is a T cell-mediated disease in which cytotoxic CD8+ cells trigger apoptosis of oral epithelial cells. Up-regulation of inter-cellular adhesion molecules and cytokines, IL-2, IL-4 and IL-10, secreted by activated lymphocytes and keratinocytes, and tumour necrosis factor (TNF- α) can play a role in the pathogenesis of OLP^[19,23]. AV can inhibit the inflammatory process by its interfering action on the arachidonic acid pathway via cyclooxygenase^[24,25]. Recent data suggest that AV also has anti-inflammatory effects by the reduction of leucocyte adhesion and TNF- α level^[26,27]. There have been few studies to date on the application of AV in OLP, although it has been used to treat a range of other disorders such as skin burns, psoriasis and mucositis, for example, with variable results. Khorasani *et al*^[28] conducted the study of second-degree burn patients with burns in two different body areas. One area was treated with topical silver sulfadiazine, whereas the other area was treated with AV in cream. The burn re-epithelization and

healing rates were significantly faster in the area treated with AV (16 d) than in the area treated with sulfadiazine (19 d). The authors thus demonstrated good efficacy for AV in cream for the treatment of second-degree burns. The efficacy of AV in clinical studies remains controversial. Su *et al*^[29] conducted a double-blind study to determine whether it is able to reduce the incidence, severity, and duration of radiotherapy-induced mucositis in head and neck cancer patients. The authors reported no benefits of adding AV to oral care in the management of mucositis. In addition, the use of AV at the start of radiotherapy did not improve either mucositis or the quality of life of the patients vs. placebo. Rajar *et al*^[30] in turn used aloe to treat vulval lichen planus in 34 women for a period of 2 months. Fifty percent of the patients treated with AV showed clinical improvement after 8 weeks of treatment, vs. only one patient in the group, the difference being statistically significant. Hayes^[13] described the first case of treatment with AV juice and AV cream (75%) in a 52-year-old woman with lichen planus lesions of the oral cavity and hands. After 4 weeks of treatment, oral lesions had disappeared, with improvement of the hand lesions and symptoms.

Our results showed that the group treated with AHM ointment showed improvement from initial white streaks with atrophic areas measuring over 1 cm² in size to white streaks without erythematous areas as a result of treatment. Complete remission became gradually more frequent from 4 to 8 weeks after the start of treatment. The best results were recorded after 8 weeks of topical AHM ointment treatment (Figures 1 and 2). Pain scores decreased from baseline in most of the AHM ointment-treated patients compared with the placebo-treated patients. Lichen planus is an autoimmune disease that is known to worsen during periods of stress. Immunomodulatory responses to neutral signals may play a significant role in affecting the natural history of this disease. This may be the reason why a pronounced placebo effect was observed in two cases in this study. Our results were in agreement with Choonhakarn *et al*^[14] who carried out a randomized, double-blind study to explore the efficacy of AV gel in the management of OLP. They treated a group of 54 patients, of which one-half received AV whereas the other half received placebo. The patients applied the treatment twice a day during 8 weeks and the results revealed that AV gel is statistically significantly more effective than placebo in inducing clinical and symptomatologic improvement of OLP. Also, Salazar-Sanchez *et al*^[15] evaluated the efficacy of the topical application of AV in OLP compared with placebo. A total 64 patients with OLP were randomized in a double-blind study to either AV (32 patients) or placebo (32 patients), at a dose of 0.4 mL (70% concentration) three times a day. The patients were evaluated after 6 and 12 weeks and a Visual Analog Scale was used for rating pain, with the application of a clinical scale for scoring the lesions. Their results concluded that the topical application of AV improves the total quality of life score in patients with OLP.

Our study used a self-controlled single blind protocol to assess the clinical improvement and pain response which in our opinion may be better than double-blind study, to make each patient assess him/herself to be more accurate of pain and clinical response. Existing evidence indicated that AV used in a variety of concentrations might be effective in shortening the duration of wound healing^[25]. The amount of active drug substance in AV varies depending on the age of the plant, the growing and harvesting conditions, the part of the plant, and the extraction methods used. Our previous study on AHM as a treatment of bed sores^[31] showed that AHM contain rich and good molecular polysaccharides with acetyl groups and glycoprotein fraction, verectin^[32], to cure bed sores. AHM ointment was shown to penetrate tissue, relief pain, reduce inflammation and increase blood

supply to the damaged area. Our hypothesis is that macromolecular polysaccharides as an adjuvant^[33] can physically absorb and hold the exudates through the osmotic pressure differences, so that the desirable moisture condition to cure wound is maintained. AHM also provide rich nutritions, playing a part in the regeneration of tissue, texture and epidermis that need to be restored. The remarkable point of AHM preserved by new technology is that it does not lose the high molecular weight of structure with acetyl groups and glycoprotein, verectin, moiety for the first time.

CONCLUSION

A self-controlled single blinded clinical trial to evaluate OLP after topical treatment with AHM showed that AHM ointment was significantly effective than that of placebo. The results showed decreases both in clinical signs and in pain scores. AHM ointment were generally well tolerated, safe and effective treatment for OLP. We consider that future studies involving larger patient series and longer periods of treatment are needed to gain further insight to the efficacy of AHM ointment in application to OLP. The findings of novel low-cost and no side-effect drug from natural source are promising for developing countries.

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