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EFFECT OF TOPICAL ALOE VERA GEL IN THE MANAGEMENT OF ORAL LICHEN PLANUS

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ABSTRACT

Background: Tumor necrosis factor-alpha (TNF-α) is found to play a major immunopathological role in oral lichen planus. The efficacy of Aloe vera (AV) in the management of oral lichen planus was evaluated as it has immune-modulatory, anti-inflammatory and anti-oxidant properties and does not possess side effects of common treatments of OLP. **Materials and Methods:** A total of 22 patients with different clinical variants of OLP (12 male and 10 female patients, mean age 42 years) were included in the study. Salivary TNF-α level was analyzed by enzyme-linked immunosorbent assay (ELISA). Patients were advised to apply topical AV gel three times daily for 8 weeks, with regular follow up every 2 weeks. Outcome measures include burning sensation relief based on the Visual Analog Scale (VAS) and clinical improvement of lesion size by Thongprasom scoring system. The data was analyzed using Statistical Package for Social Science (SPSS)

version 21.0 software. **Results:** The clinical results showed an overall positive reduction in the clinical size of the lesion and a significant (P<0.001) reduction in burning sensation with topical AV gel treatment. There was also a significant (P<0.001) difference in mean saliva TNF-α level before and after the treatment. **Conclusion:** The findings in our study suggest that AV gel seems to be an effective alternative treatment for OLP and TNF-α may be a good indicator for monitoring the therapeutic response of the disease.

KEYWORDS: Aloe vera, Lichen Planus, Potentially malignant disorder**,** Pro-inflammatory cytokine, TNF-α, Salivary diagnostics.

INTRODUCTION

Lichen planus (LP) is a relatively common chronic inflammatory mucocutaneous disease characterized by outbreaks or flares. It was first described by the British physician, Erasmus Wilson in 1869. This disease primarily affects the skin and mucosal surfaces. The prevalence of oral lichen planus (OLP) in India is around 2.6% [1] having slight predominance in females, at a ratio of 1.4:1 with a mean age of onset in the fourth decade, although younger adults and children may be affected too. Despite the self-limiting nature of cutaneous lesions, oral lesions are chronic and rarely undergo spontaneous remission.[2]

The mechanisms of OLP pathogenesis have not been fully disclosed. It has been suggested that autoreactive cytotoxic CD8+ T-cells trigger keratinocytes apoptosis, when the T-cell-secreted TNF-α (Tumor necrosis factor) binds to TNFR-1 (Tumor necrosis factor receptor) on the keratinocyte surface, keratinocyte caspase cascade is activated.[3] Simultaneously with the expression of other pro-inflammatory and anti-inflammatory cytokines, all the OLP lesions have been shown to contain cells with mRNA for TNF-α.[4] Several other authors have suggested different salivary biomarkers for OLP diagnosis, treatment and prognosis monitoring.

There is no fully resolute and effective treatment till date. The major inconvenience of conventional treatments are the side effects they usually produce. The main focus in the management of OLP is the use of drugs that counter the tissue inflammation and the underlying immunological mechanisms with minimal side effects. Considering the same parameters, recent research proposes the use of Aloe Vera (AV) for the management of OLP.[5] Several in vitro and in vivo studies on AV have shown anti-inflammatory, immunomodulatory, analgesic, antineoplastic, anti-diabetic, antimicrobial, liver protection,

antiproliferative, and anti-aging effects along with a potent wound healing property.[6] Some data suggest that AV can suppress tumor growth and improve the survival of patients.[7] Hence, in this study, we decided to evaluate the therapeutic effects of topical AV gel on OLP lesions. Because AV does not possess the immunosuppressive and other side effects of common treatments of OLP, if found effective, usage of AV in the treatment of OLP lesions can be a significant advantage in the management of this chronic potentially malignant disorder of the oral cavity.

AIM AND OBJECTIVES

Aim: To evaluate the effect of topical AV gel in the management of OLP by estimating the pro-inflammatory cytokine (TNF-α) level in saliva.

Objectives

1) To compare the salivary TNF-α level before and after treatment in OLP patients.
2) To evaluate the therapeutic efficacy of topical AV gel in the treatment of OLP viz: a) reduction in burning sensation using VAS b) improvement in visual finding using Thongaprasom scoring c) occurrence of a new lesion.

METHODOLOGY

The present study was planned and conducted during the period between June - September 2016 in the Out-Patient Department of Oral Medicine and Radiology, Rajah Muthiah Dental College and Hospital, Annamalai University, Chidambaram. 22 patients with OLP were selected for participation in the study after obtaining a formal ethical clearance to conduct the study from the ethical committee of the institution. A written informed consent was obtained from all patients. All the selected patients fulfilled the modified WHO diagnostic criteria of OLP and OLL[8] with age ranging between 15-70 years.

All other patients who underwent treatment for OLP within 6 weeks prior to the study, the presence of other mucosal lesions, history of renal and liver diseases, psychiatric disorders, pregnancy, lactation and use of steroid hormone based contraceptives, other autoimmune and infectious diseases, trauma in last 1 month were excluded from the study.

A detailed case history was recorded for all patients and were subjected to thorough general, physical and oral clinical examination and details were recorded in standard proforma. In patients with OLP, the clinical features and size of the lesion were recorded according to

Thongprasom scoring system[9] and patient's symptom severity was recorded on 10-point VAS and asked to mark the number that would relate the pain experience. After establishing the clinical diagnosis of OLP, the patients were subjected to routine complete hemogram to rule out any systemic ailments. This was followed by a histopathologic confirmation of diagnosis by performing punch biopsy of the lesion.

In order to avoid diurnal variation, the whole unstimulated saliva (WUS) was collected between 9:00 a.m. to 11:00 a.m. The subjects were withheld from eating and drinking for at least 2 hours prior to the sampling. 10 mL of saliva was collected according to Navazesh[10] spitting method and immediately centrifuged for 2 minutes at 10,000 rpm and the supernatant was separated using micropipette (1000 µL) into a 2 mL aliquots and frozen at −80°C until assayed.

Saliva collection was done twice i.e., at baseline and 8 weeks after intervention. Salivary TNF-α levels were evaluated using ELISA kit (Diaclone SAS, France).

All patients were given AV gel obtained from Herboflora Biotech, Coimbatore (each 30 g tube contained AV gel-72 ml (90%), sodium alginate base-20 ml and potassium sorbate-8 g) and advised to apply sufficient quantity over the affected area, three times a day and to abstain food and drink for at least an hour, for a period of 2 months. Patients were recalled every 2 weeks for 8 weeks and were evaluated for reduction in size and symptom of the lesion using Thongprasom scoring system and VAS respectively, they were also assessed for relapse and appearance of the new lesion and is tabulated. A reduction in scale is considered to be an improvement of the condition in that area. Patients were also instructed to report immediately if there is any allergic reaction on topical gel application.

Statistical analysis

All the data was analyzed using SPSS, version 21.0 software. For comparison of the level of VAS at baseline, 1st and 2nd month after the intervention, one way ANOVA was calculated. Friedman test for comparisons performed to detect any differences in size of the lesion between baseline, 1st and 2nd month after intervention. Paired student 't' test was applied for comparison of the level of salivary TNF-α at baseline and at the end of treatment. To compensate for the data of the patients who lost follow-up, intention to treat analysis was used. $P<0.05$ was considered to be statistically significant.

RESULTS

The study sample consists of 54.55% males and 45.45% females with mean age of 42 years (range 19-70 years) (Table:1). Erosive OLP (36.36%) was the most common followed by reticular (22.72%) and then atrophic (18.18%) types, along with variations of lichen planus such as actinic OLP and lichen planus pigmentosus with lesser frequencies (4.55%) were encountered in this study (Table:2). Most of the patients had multiple oral lesions with buccal mucosa (77.27%) being the most commonly affected site followed by gingiva (27.27%) and then tongue (18.18%) (Table:3).

The VAS at baseline, 1st and 2nd month after intervention showed that there was a significant difference (<0.001) at every follow-up according to one-way ANOVA (Table:4). To get more details, repeated contrast test has been applied for the three comparisons namely baseline to 1st month, baseline to 2nd month and 1st month to 2nd month (Table:4a) which also was highly statistically significant (<0.001).

Friedman test for comparisons performed to detect any differences in size of the lesion between baseline, 1st and 2nd month after intervention showed an overall positive reduction in the clinical size of the lesion (Table:5, Graph:1, and Figs 1 through 6).

Paired student 't' test showed that there was a significant difference (<0.001) in the level of salivary TNF-α at baseline and at the end of treatment (Table:6).

Table 1: Demographic data.

Age (years)	*n*	*Sex*	*n*
<40	9	Male	12
>40	13	Female	10

Table 2: Baseline clinical characteristics of OLP.

Variable	*n*	*%*
TYPE OF OLP		
Actinic	1	4.55
Atrophic	4	18.18
Erosive	8	36.36
Lichen planus pigmentosus	3	13.64
Plaque-like	1	4.55
Reticular	5	22.72
SEVERITY OF BURNING SENSATION (VAS)		
Mild (0-3)	3	13.64
Moderate (4-6)	10	45.45
Severe (7-10)	9	40.91

Table 3: Presence of OLP based on anatomical site.

Site of the lesion		*N*	*%*
Buccal mucosa	Right	16	72.73
	Left	17	77.27
Gingiva	Upper	5	22.73
	Lower	6	27.27
Labial mucosa	Upper	1	4.545
	Lower	2	9.090
Lips		2	9.090
Palate		2	9.090
Retromolar pad	Right	0	0
	Left	1	4.545
Tongue	Dorsum	3	13.64
	Right lateral	4	18.18
	Left lateral	3	13.636

Table 4: Descriptive statistics of severity of burning sensation (VAS) at baseline, 1st and 2nd month after intervention.

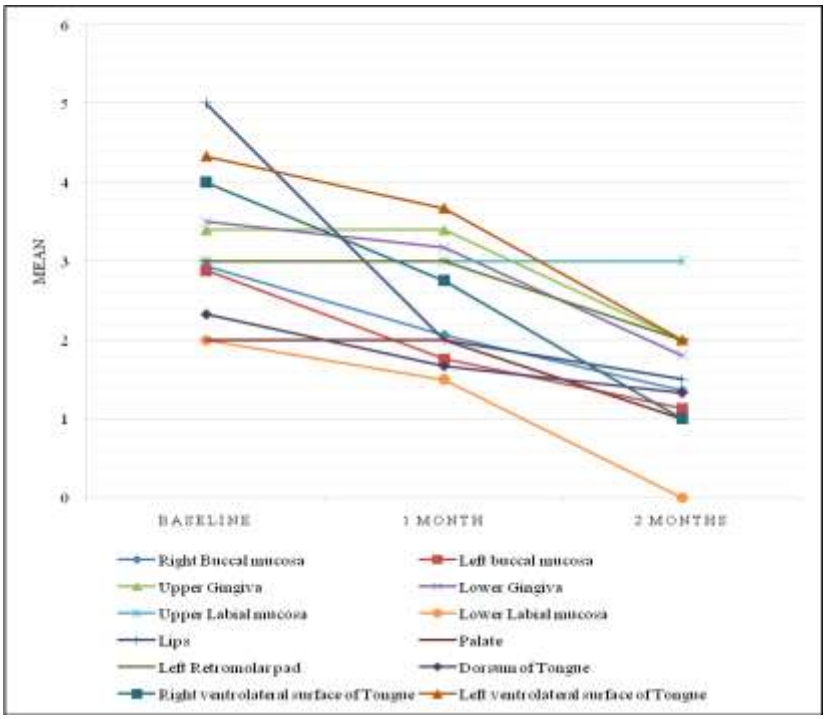
VAS	*Baseline*		*1 Month*		*2 Month*	
	n	**%**	**n**	**%**	**n**	**%**
Mild (0-3)	3	13.636	9	40.909	14	70
Moderate (4-6)	10	45.454	10	45.454	6	30
Severe (7-10)	9	40.909	3	13.636	-	-
Mean	6.27		4.64		2.70	
Standard deviation	2.37		1.97		1.46	

Table 4a: ANOVA repeated measurements.

ANOVA repeated measurements		*Repeated contrast test results*		
F-value	**p-value**	**Comparisons**	**Mean difference**	**p-value**
36.301	<0.001	Baseline Vs 1st month	1.800	<0.001
		Baseline Vs 2nd month	3.500	<0.001
		1st month Vs 2nd month	1.700	<0.001

Table 5: Overall outcome of Thongsprasom scoring system at various anatomical sites.

Site	*Clinical result*	*Statistical result*
• Right Buccal Mucosa • Left Buccal Mucosa • Lower Gingiva	Positive	Significant
• Lower Labial Mucosa • Dorsal Surface of Tongue • Right Ventrolateral Surface of Tongue • Left Ventrolateral Surface of Tongue • Left Retromolar Pad • Palate • Lips	Positive	Due to small sample size p-value was not acquirable
• Upper Gingiva	Positive	p-value obtained (0.156) but non-significant because of small sample size



Graph 1: Clinical response of OLP patients in various anatomical sites at baseline, 1 month and 2 months after application of topical aloe vera gel.

Table 6: Descriptive statistics of TNF-α before and after treatment.

OLP	*TNF-α (pg/ml)*	*n*	*%*	*Mean*	*SD*	*Paired 't' Test*	*p-value*
Before treatment	0-45	7	31.82	54.182	16.625	3.999	<0.001
	46-90	15	68.18				
After treatment	0-45	11	55	39.982	15.885		
	46-90	9	45				

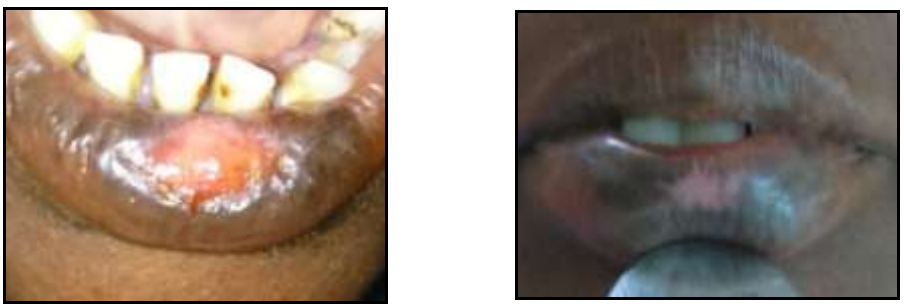


Fig 1: Actinic OLP on lower lip pre and post treatment

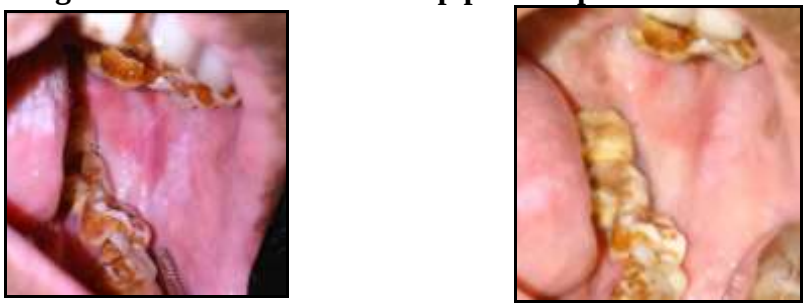


Fig 2: Atrophic OLP on left buccal mucosa pre and post treatment

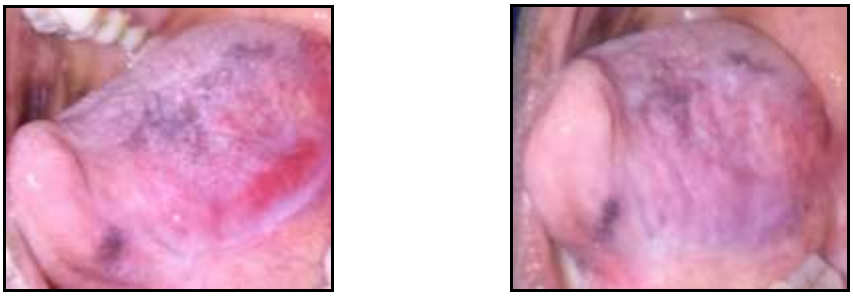


Fig 3: Erosive OLP on left ventrolateral surface of tongue pre and post treatment

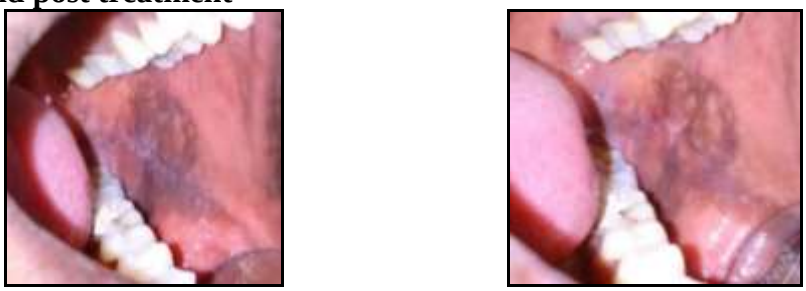


Fig 4: Lichen Planus Pigmentosus on left buccal mucosa pre and post treatment

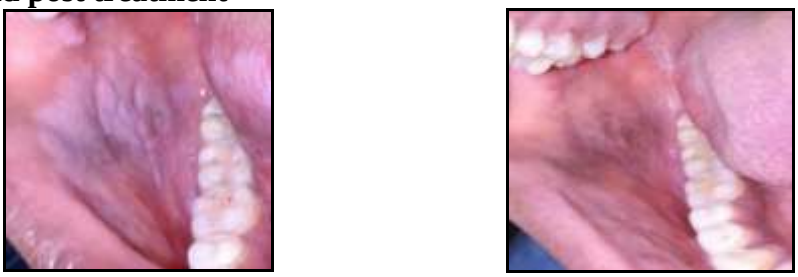


Fig 5: Plaque like OLP on right buccal mucosa pre and post treatment

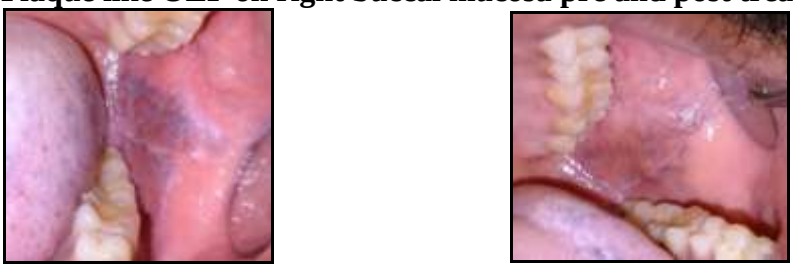


Fig 6: Reticular OLP on left buccal mucosa pre and post treatment

DISCUSSION

OLP is a T cell-mediated disease in which apoptosis of oral epithelial cells is triggered by cytotoxic CD8+ cells. Up-regulation of intercellular adhesion molecules, cytokines like, IL-2, IL-4, IL-10, and TNF-α can play a role in the pathogenesis of OLP.[3] AV inhibits the inflammatory process by interfering the arachidonic acid pathway via cyclo-oxygenase and also by decreasing leukocyte adhesion and TNF-α level.[11] Thus, the basis of this study is the anti-inflammatory, wound healing and immune modulating effects of AV where their therapeutic efficacy in the management of OLP has been studied by monitoring reduction in its signs and symptoms.

Our results showed that on topical application of AV gel over OLP lesions, there was a gradual improvement from white streaks with atrophic or erythematous areas measuring more than 1 cm^2 to white streaks with atrophic or erythematous areas measuring less than 1 cm^2 or only white streaks at the end of 2 months, we also found a significant reduction in VAS score when compared to baseline. The best results were recorded after 8 weeks of treatment. Our results were in agreement with the first case report about the successful treatment of OLP along with cutaneous manifestations using AV reported by Hayes S M,[12] where the oral lesions cleared up within 4 weeks on drinking 2.0 ounces of stabilized AV juice daily for 3 months. On using Aloe vera high molecular weight (AHM) ointment three times daily, significant decreases in both clinical signs and in pain scores were observed in OLP patients at the end of 2 months.[13] Topical AV also improved the total quality of life in patients with OLP[14] and was found to have similar therapeutic effect as Triamcinolone acetonide (TA) 0.1%.[15] However, AV on systemic administration had better efficacy than TA in OLP management.[16] it was also proved that the combined use of topical and systemic AV gel were more effective in reducing the burning sensation than topical alone.[17]

The obtained results of our study showed that TNF-α was detectable in salivary samples of all studied individuals; after reaching near normal clinical remission on topical application of AV gel for a period of 8 weeks, the OLP patients showed a highly significant decrease in levels of TNF-α compared to the baseline. Very early Rhodus N L et al., 2006,[18] encouraged the use of salivary cytokine levels, specifically TNF-α, IL-1 α, IL-6 and IL-8, to monitor the corticosteroid therapeutic outcome in OLP patients and registered a significant lowering in salivary TNF-α level with topical corticosteroid therapy. Subsequently, Fat'heya Zahran et al., 2015,[19] showed a highly significant decrease in salivary TNF-α after corticosteroid therapy. But, TNF-α level after corticosteroid therapy even with disease remission, was significantly higher than control level. This sustained level of salivary TNF-α, despite clinical remission could imply the basis of disease chronicity and can be used in monitoring the disease severity.[20] These authors indicated that detection of disease-related cytokines in saliva indeed has some clinical potential in monitoring therapeutic response and disease activity status of OLP, which is strongly supported by the data presented in this study.

In contrast, during the evaluation of the efficacy of IMOD (an Iranian new immunomodulator drug, containing selenium, carotene, and flavonoids) in the treatment of OLP, following treatment, though significant improvement in clinical signs and symptoms was present, no

statistical differences were found in the TNF-*α* level before and after treatment.[21] It is explained by the assumption made by Banno T et al., 2004,[22] that despite the ravaging effect of TNF-*α*, it has high-level beneficial effects of initiating an inflammatory response, promoting angiogenesis and as well as the reparative process. Corticosteroid drugs repress both the double-edged action of this cytokine. But IMOD being an immunoregulator, just regulates its action and promotes improvement in sign and symptom of OLP lesion, without deletion of the TNF-*α* beneficial effect that provides wound healing.

Stimulatory effects of AV can increase antibody production and accelerate wound healing by increasing growth factors. Furthermore, it has antioxidant properties and eliminates production of free radicals.[23] Thus, clinical improvement of OLP lesions after treatment with topical AV gel was accompanied by a significant simultaneous decrease in salivary TNF-α level; however normal control levels were not reached. Therefore, our results, which show the good efficacy of AV in the treatment of OLP, are of considerable pathophysiologic relevance. There was no recurrence of the lesion and similarly no side effects reported by the patients on topical use of AV gel for 2 months in our study. Two patients dropped out from the study as the transportation to the study area was inconvenient.

CONCLUSION

Salivary TNF-α level relates perfectly to the disease activity and the treatment progress and can be used for the diagnosis and prognosis for OLP patients.

Considering the chronicity of the disease, and the need for a long-term treatment modality, AV can be proposed as a good alternative treatment for the disease as it has both antioxidant and anti-inflammatory property. It also offers a non-invasive option that yields significant improvements in symptoms as well as objective signs of the condition. AV is quite economical, generally well tolerated and safe. Hence, appropriating AV in the treatment of OLP lesions can be a significant advance in the management of this chronic premalignant disease of the oral cavity.

FUTURE PERSPECTIVES

We consider that future studies involving larger patient series, longer periods of treatment with long-term follow-ups in different populations to gain further insight into the efficacy of AV gel in application to OLP and to understand it’s role in reducing the reoccurrence of OLP. In addition, further studies are also needed to compare the efficacy of different

orotransmucosal drug delivery methods concerning AV, as the therapeutic effect depends strongly on its bioadhesive properties, bioavailability, and solubility.

The heterogeneous nature of AV may contribute to the diverse biological and therapeutic activities. It is vital that AV products be certified with respect to content and identification of active compounds. Only then will this allow for an accurate comparison of products as well as their efficacy in the clinical trials.

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