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Efficacy of Aloe Vera and Clobetasol Propionate in the Management of Oral Lichen Planus: A Randomized Parallel Clinical Trial

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A B S T R A C T

Objectives: The purpose of this randomized parallel clinical trial was to assess and compare the efficacy of 97% Aloe Vera (AV) gel and 94.7% AV juice against an active control (0.05% Clobetasol Propionate) in the treatment of oral lichen planus (OLP).

Materials and Methods: Age and sex matched patients with histologically proven OLP were divided into two groups. One group received 97% AV gel for topical application and 10ml 94.7% AV juice to consume twice daily. The active control group received topical 0.05% Clobetasol Propionate ointment twice daily. Treatment lasted two months followed by four months of observation. Monthly evaluation of various clinical features of OLP was done using the OLP disease scoring criteria. Burning sensation was evaluated using Visual Analog Scale (VAS). Mann Whitney–U (followed by Bonferroni adjustment) and Wilcoxon's signed-rank tests were used for intergroup and intragroup comparisons, respectively. Interclass correlation-coefficient test was applied to assess the intra-observer variation ($P<0.05$).

Results: In total, 41 females and 19 males participated in this study. The most common site was the buccal mucosa followed by the gingivobuccal vestibule. The reticular variant was most frequently encountered. Wilcoxon's signed-rank test showed significant differences in both groups between baseline and end-of-treatment for VAS, site-score, reticular/plaque/papular score, erosive/atrophic score and OLP disease score ($P<0.05$). Mann–Whitney revealed significant difference between both groups in the 2nd, 3rd and 4th months ($P<0.0071$).

Conclusion: Clobetasol Propionate is more effective for OLP management but in our study AV proved to be a safe treatment alternative for OLP management.

Keywords: Medicine; Traditional; Aloe; Clobetasol; Clinical Trial; Oral Lichen Planus

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INTRODUCTION

The most preferred treatment modality for Oral Lichen Planus (OLP) is the administration of systemic or topical corticosteroids like Triamcinolone Acetonide (0.1%), Clobetasol Propionate (CP, 0.05%) and calcineurin inhibitors like Cyclosporin (2.5-5mg/kg/day orally) and Tacrolimus (0.1%) [1-3]. The therapeutic responsiveness may differ in patients. The current treatment management strategies for OLP focuses on the use of drugs that reduce tissue inflammation, provide symptomatic relief and oppose the underlying immunologic mechanism. Even after prolonged treatment with steroids and accompanied numerous side effects, the fact that the disease process could

still last for years is the reason why an alternative therapy is desirable.

Recently the popular interest and use of Aloe Vera (AV) gel has increased dramatically. It is one of the most widely used ingredients in healthcare and cosmetic products and is readily available all over the country. AV has also been used for treatment of lichen planus. Hayes SM [4] was the first to use it in a patient who experienced improvement of her oral lesions after four weeks of therapy. Acemannan and Aloe Emodin are two molecules present in AV which restore and boost the immune system by stimulating the production of macrophages and improving the activity of T-Lymphocytes thus accelerating the wound healing [5-7]. The anti-inflammatory compound called C-glucosyl chromone present in AV inhibits the cyclogenase pathway and reduces prostaglandin E2 production from arachidonic acid as well as the peptidase bradykinase which breaks down bradykinin that induces pain [5-7]. Therefore, AV has to be evaluated as an alternative treatment for patients with OLP. The objective of this study was to assess the efficacy of topical application of 97% AV gel along with 94.7% AV juice versus 0.05% CP ointment (active control) topical application for the treatment of OLP.

MATERIALS AND METHODS

The present study was conducted at the Oral Medicine & Radiology Department of our institution. The patients who reported to the department from May 2016 to August 2017 were included in this prospective and parallel clinical trial. The study was designed in compliance with Helsinki Declaration and Ethical clearance was obtained from the Institutional Ethical Committee (Ethical Code: Ethical Comm./GDCH/2016/-4/OMR-4). This clinical trial was registered in the Clinical Trial Registry of India (CTRI), Reg. No: CTRI/2017/11/010321. The efficacy of AV versus CP was compared in controlling and alleviating OLP symptoms and lesions as measured by the OLP Disease Score (especially designed for this study in order to have better understanding of status of OLP lesions). This study included 60 subjects with clinically and histologically diagnosed cases of OLP, divided into 2 groups (AV group and Clobetasol group) by simple random sampling (Figure 1).

2.1 The Inclusion Criteria:

- Patients with clinically diagnosed and histologically confirmed OLP were included.
- Age group above 18 years.
- Patients with chronic symptomatic OLP, who were already on systemic medications or topical treatment; were included in this study after three months of cessation of the systemic treatment and one month after the cessation of the topical treatment at the time of initial examination.

2.2 The Exclusion Criteria:

- Patient who were not willing to participate in the study and give their written informed consent.
- Patients who were clinically diagnosed as OLP but thereafter not confirmed histologically.
- Patients who presented with lichenoid reaction either due to presence of metallic restorations (amalgam) or secondary to certain drugs which may induce lichenoid like reaction in patients.
- Known history of allergy to 0.05% CP ointment or AV.
- Pregnant or lactating females.

2.3 Materials:

The 97% AV gel was prepared in the Bhaskara Biotech Research Laboratory, Hyderabad, India. (Mfg. License No: T–1841/ AYUR). One-hundred grams of AV gel composed of 97% stabilized AV clear juice, 1.2% Carbopol 940 and 1.6% Triethanolamine. This gel was used for topical application over the lesions. Commercially available AV juice (Patanjali Aloe Vera juice, manufactured by Patanjali Ayurved, Haridwar, India) was used which contained 9.47 ml of Aloe Barbadensis extract per 10ml. Patients were instructed to consume 10ml with or without equal quantity of water twice daily preferably 20 minutes before the morning and evening meals (empty stomach). Clobetasol Propionate (0.05%) was also commercially available as Tenovate (GSK Pharmaceuticals Limited, Mumbai, India), 15g tube. The patients from either group were instructed to apply the medication with a clean finger on the affected area twice daily (preferably after morning and evening meals) and were instructed to abstain from eating and drinking for 15–20 minutes.

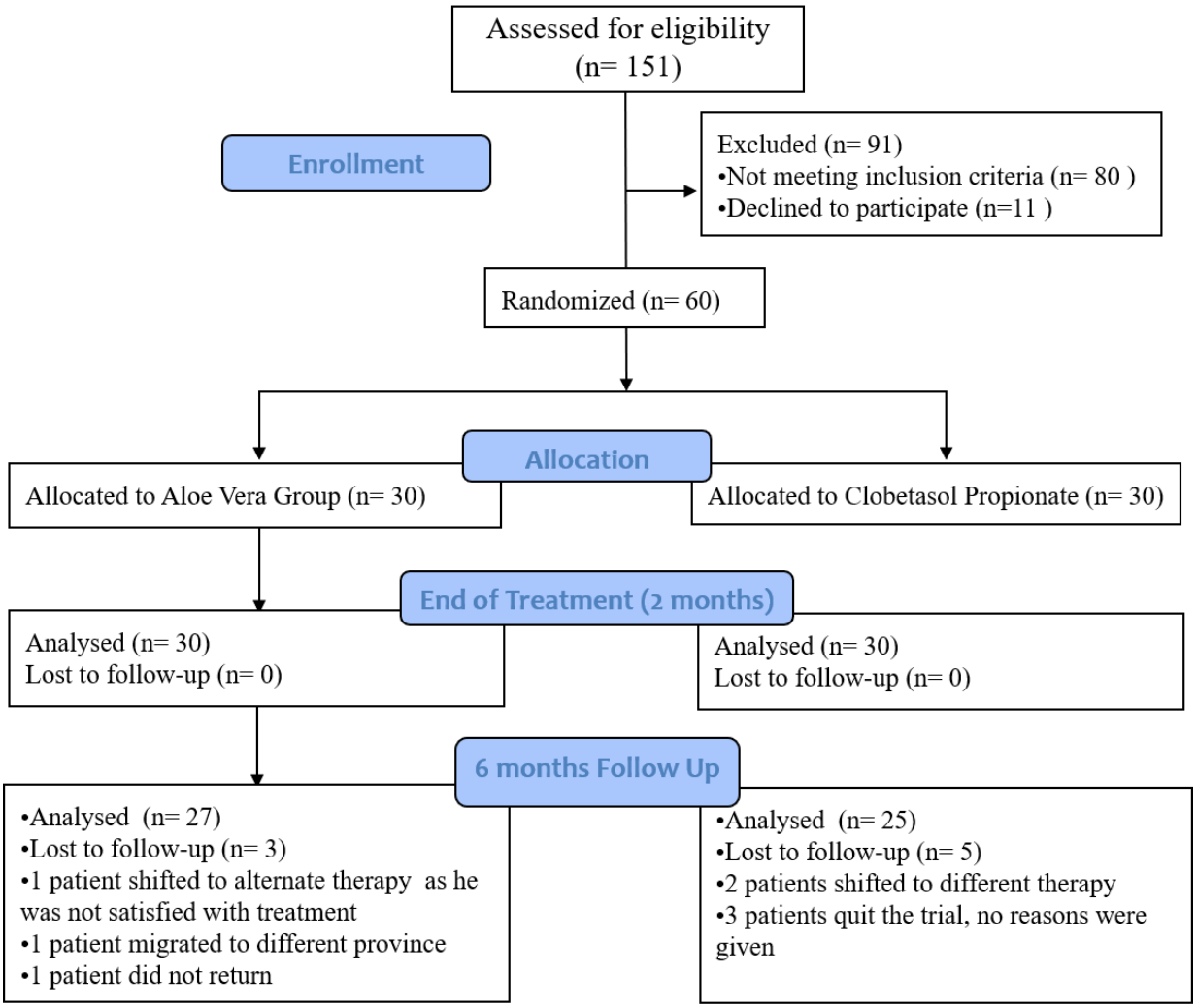

Fig 1. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram

2.4 Method:

All patients who met the inclusion criteria were included in the study. After selection of the patient, written informed consent was obtained, a thorough case history was recorded and clinical examination was performed for all the patients. The baseline data was recorded using the 'Oral Lichen Planus–Disease Scoring System' and the same parameters were recorded at beginning of the treatment, at an interval of one month, two months (end of therapy), three months, four months, five months and six months. All the patients were assessed by a primary investigator who was blinded to the treatment protocols. To evaluate inter-observer correlation a blinded secondary investigator assessed 20% of the study population selected by using simple random numbers table.

OLP–disease scoring system comprises of three components; [A] Site score, [B] Burning Sensation score and[C] R/E/U score. The final score was calculated as summation of score [A], [B] and [C]. The following are the details of the scoring system.

2.4.1 [A] Site Score:

Twenty-three intra oral sub sites were identified as listed in Table 1. The site score was '0' if the lesion was absent. The site score was '1' if the lesion was present on the lips/gingiva/alveolar mucosa/gingivobuccal sulcus/ covered <50% surfaces of buccal mucosa, dorsum of the tongue, floor of the mouth, hard palate and soft palate. While the site score was '2' if it covered more than 50% of the surfaces of buccal mucosa/dorsum of the tongue/floor of the mouth/hard palate/soft palate.

Table 1: Twenty-three examined intra-oral sub-sites and the numerical scores for each site (site score)

Site		Site score
Upper labial mucosa		0 or 1
Lower labial mucosa		0 or 1
Left buccal mucosa		0, 1 or 2
Right buccal mucosa		0, 1 or 2
Gingiva/alveolar mucosa:	Upper right (distal), distal to tooth 1-3	0 or 1
	Upper central, from mesial of tooth 1-3 to mesial of tooth 2-3	
	Upper left (distal), distal to tooth 2-3	
	Lower left (distal), distal to tooth 3-3	
	Lower central, from mesial of tooth 3-3 to mesial of tooth 4-3	
	Lower right (distal), distal to tooth 4-3	
Dorsum of tongue		0, 1 or 2
Right lateral tongue		0 or 1
Left lateral tongue		0 or 1
Ventral surface of tongue		0 or 1
Gingivobuccal sulcus:	Upper right (distal), distal to tooth 1-3	0 or 1
	Upper central, from mesial of tooth 1-3 to mesial of tooth 2-3	
	Upper left (distal), distal to tooth 2-3	
	Lower left (distal), distal to tooth 3-3	
	Lower central, from mesial of tooth 3-3 to mesial of tooth 4-3	
	Lower right (distal), distal to tooth 4-3	
Floor of the mouth		0, 1 or 2
Hard palate		0, 1 or 2
Soft palate		0, 1 or 2

2.4.2 [B] Burning Sensation Score:

Patients were evaluated for burning sensation using Visual Analog Scale (VAS), consisting of a 10cm line drawn/printed on paper. 'No pain' and 'extreme pain' were depicted as 0cm and 10cm, respectively. The patient marked a point along the line that best represented his/her burning sensation.

2.4.3 [C] R/E/U Score:

It consists of three components; reticular or plaque or papular score (R), erosive score or atrophic score (E) and ulcerative or bullous score (U) as shown in Table 2. Score 0 corresponds to absence of lesion and 3 describes its most severe form. Final OLP clinical score = Score A + Score B + Score C.

2.5 Safety:

During the course of treatment, if the patient developed *Candidal* infection secondary to topical CP then suitable antimycotic prophylaxis was provided. The patient's weight and blood pressure was obtained at every monthly visit and blood tests were advised at baseline (beginning of therapy) and at the end of therapy. The patients in the AV group were also made aware and warned of the possible side effects and contraindications of AV. At each check-up visit, patients were also asked to report any unusual effects that might be linked to the protocol therapy.

2.6 Statistical Analysis:

Statistical analysis was done using SPSS 14.0 software. Wilcoxon's Signed-Rank Test was used for intragroup data analysis. Mann Whitney–U Test was applied for intergroup comparisons of OLP disease score between the AV and CP groups. Alternative hypothesis was that difference was present (positive at $\alpha=0.05$). Since seven pairwise comparisons were done we used a Bonferroni adjustment on the results of Mann-Whitney Test. Hence, the new significance level was $0.05/7=0.0071$.

Table 2: R, E and U scores based on clinical characteristics of oral lichen planus

Type	Score	Description
'R' Reticular or plaque or papular lesion score	0	No reticular striae / No plaque or papular lesion/mucosa appears normal
	1	Diffuse, thin, wispy, white striae with or without branching or lace like pattern/annular pattern Or Focal thin white plaque with central area of normal mucosa < 0.5 cm^2 Or Papular lesion 0.5–1 cm^2 in area without erythema
	2	Thick raised confluent white striae with or without branching or lace like appearance with mild erythema or without erythema. Or Thick white plaque which is 0.5–1 cm^2 in area Or Papular lesion 0.5–1 cm^2 in area with mild erythema
	3	Thick white striae with dense white lace like formation with marked erythema. Or Thick white raised plaque>1cm^2 Or Papular lesion > 1 cm^2 in area with marked erythema
'E' Erosive or atrophic lesion score	0	No erosive/atrophic lesions
	1	Erosive/atrophic lesions < 1 cm^2
	2	Erosive/atrophic lesions 1–3 cm^2
	3	Erosive/atrophic lesions > 3 cm^2
'U' Ulcerative or bullous lesion score	0	No Ulcerative lesions or vesicles
	1	Ulcerative lesions < 1 cm^2 or intact bullae or vesicle
	2	Ulcerative lesions 1–3 cm^2
	3	Ulcerative lesions > 3 cm^2

To assess the inter-observer variation in the study group, the scoring was performed on 20% of the study population by random sampling method. The secondary investigator was also blinded to the treatment provided to the patients. Interclass Correlation Coefficient Test was applied to assess the intra-observer variation.

RESULTS

The demographic data of the study population is presented in Table 3. There was no attrition during the treatment phase (end of 2 months). Three patients in the AV group and five patients in the CP group were lost to follow-up during the observation period (Figure 1). The majority of cases 46 (76.67%) were more than 4 cm in size at baseline evaluation. The reticular type was the single most common type of OLP seen in 54 (90%) cases, followed by 37 (61.67%) patients presenting with the erosive type. The mean OLP disease score during the entire study duration is presented in Table 4. There was a considerable decrease in the mean VAS score after AV therapy from baseline value of 8.67 to End of the treatment 2.33. There was marked reduction in the mean VAS score with CP from 8.40 to end of treatment 1.70. At the end of the treatment, six patients in AV group and 11 patients in CP group had no burning sensation (VAS=0). There was substantial decrease in the mean Final OLP Disease score in AV group from 34.31 (baseline) to 16.40 (end of the treatment). Wilcoxon Signed-Rank test showed that treatment in study group and control patients did elicit a statistically highly significant change ($P<0.001$) with decrease in Site score, R score, E score, U score and OLP disease score

between baseline and end of treatment (Table 5). CP was more effective in reduction of OLP Disease score as compared to AV therapy (P<0.0071) (Table 6). Interclass correlation coefficient indicated high agreement of both observers for inter-observer variability(a> 0.685, P<0.05) (Table 7). None of the patients in the AV group reported any adverse reaction or discomfort on application of the gel.

Table 3. Background and features of patients evaluated in the study population

Study Groups		Age (years)			Subtotal	Total
		18–35	36–55	56–80		
Aloe Vera	Males	1	4	3	8	30
	Females	7	11	4	22	
Clobetasol Propionate	Males	7	3	1	11	30
	Females	3	8	8	19	
Total:		18	26	16		60
Complaint at presentation						
		Burning sensation	White patch	Sudden onset	Slow onset	Mean duration of lesions (months)
Aloe Vera		27	3	18	12	10.47
Clobetasol Propionate		26	4	19	11	10.5
Association of systemic diseases in the study population						
		HTN	DM	HTN+DM	Thyroid disorder	No systemic disease
Aloe Vera		6	0	3	2	20
Clobetasol Propionate		5	0	4	3	19
Size distribution of lesions						
		< 2 cm	2 - 4 cm	> 4 cm	Unilateral lesions	Bilateral lesions
Aloe Vera		0	6	24	2	28
Clobetasol Propionate		2	6	22	7	23
Type of oral lichen planus						
		Reticular	Plaque	Papular	Erosive	Bullous/Ulcer
Aloe Vera		27	7	3	26	1/3
Clobetasol Propionate		27	8	2	37	0/2
Extraoral site involvement						
		Scalp	Face	Arms/Back	Genitals	Legs
Aloe Vera		0	1	1/0	1	3
Clobetasol Propionate		1	2	1/1	0	2

HTN: Hypertension; DM: Diabetes Mellitus

Table 4. Descriptive statistics for the sample during the study period

Group		A	C			(A+C)	(B)	Sum of means* (A+C) + B
		Site score	R score	E score	U score	Total of means	Mean VAS	
AV, N=30 (baseline)	Mean	8.5	11.67	4.87	0.60	25.64	8.67	34.31
	SD	4.23	5.19	4.62	0.85	-	0.84	-
AV, N=30; 1st month	Mean	7.27	8.60	2.83	0.47	19.17	5.03	24.20
	SD	3.87	3.80	3.24	1.04	-	1.86	-
AV, N=30; 2nd month (end of treatment)	Mean	5.90	6.07	1.77	0.33	14.07	2.33	16.40
	SD	3.06	3.11	2.12	1.47	-	2.17	-
AV, N=30; 3rd month	Mean	5.43	5.27	1.60	0.33	12.63	2.30	14.93
	SD	2.89	2.46	2.25	0.99	-	2.58	-
AV, N=30; 4th month	Mean	5.27	5.53	1.20	0.10	12.1	2	14.1
	SD	2.71	2.56	1.69	0.40	-	2.31	-
AV, N=29; 5th month	Mean	4.69	5.31	1	0.24	11.24	1.93	13.17
	SD	2.50	3.02	1.46	0.78	-	2.43	-
AV, N=27; 6th month	Mean	4.44	5.04	0.93	0.21	10.62	1.67	12.29
	SD	2.651	2.86	1.38	0.68	-	1.92	-
CP, N=30 (baseline)	Mean	7.10	9.47	3.07	0.47	20.11	8.40	28.51
	SD	3.55	4.84	3.93	1.16	-	0.93	-
CP, N=30; 1st month	Mean	5.37	6.03	1.63	0.27	13.30	4.27	17.57
	SD	2.81	3.47	3.44	0.69	-	1.99	-
CP, N=30; 2nd month (end of treatment)	Mean	3.27	3.27	0.60	0.10	7.24	1.70	8.94
	SD	2.42	2.93	1.56	0.40	-	1.55	-
CP, n=30; 3rd month	Mean	2.87	2.87	0.53	0	6.27	1.37	7.64
	SD	2.01	2.19	1.19	0	-	1.58	-
CP, N=28; 4th month	Mean	2.96	3.32	0.57	0	6.85	1.86	8.71
	SD	2.51	2.76	1.136	0	-	2.17	-
CP, N=25; 5th month	Mean	2.80	3.04	0.56	0.08	6.48	1.76	8.24
	SD	2.04	2.37	1.29	0.27	-	2.33	-
CP, N=25; 6th month	Mean	3.32	3.44	0.72	0.12	7.6	2.20	9.8
	SD	2.21	2.45	1.06	0.60	-	2.43	-

*Mean final oral lichen planus disease score. A: site score; C: R score + E score + U score, B: VAS score: Sum: A+C+B
AV: Aloe Vera; CP: Clobetasol Propionate; SD: standard deviation; VAS: visual analog scale score

Table 5: Wilcoxon's signed-rank test for OLP disease score in the study population

	Site score		R score		E score		U score		OLP Disease Score	
	Z	P	Z	P	Z	Z	P	Z	P	Z
Aloe Vera therapy group										
Baseline-end of treatment	-4.122	0.001*	-4.670	0.001*	-3.933	0.001*	-2.012	0.044*	-4.783	0.001*
Baseline-end of observation period	-3.957	0.001*	-4.486	0.001*	-3.878	0.001*	-2.097	0.036*	-4.542	0.001*
Clobetasol Propionate group										
Baseline-end of treatment	-4.360	0.001*	-4.300	0.001*	-4.312	0.001*	-1.897	0.058	-4.705	0.001*
Baseline-end of observation period	-4.131	0.001*	-4.248	0.001*	-3.435	0.001*	-1.219	0.223	-4.287	0.001*

OLP: oral lichen planus

Table 6: Mean rank values, Mann-Whitney U value, Z value, and level of significance for Visual Analog Scale score between both groups during the entire study period

	Group	N	Mean rank	U value	Z	P*
Baseline	**Aloe vera**	30	34.43	332.0	-1.746	0.081
	Clobetasol Propionate	30	26.57			
First month	**Aloe vera**	30	35.87	289.0	-2.383	0.017
	Clobetasol Propionate	30	25.13			
Second month	**Aloe vera**	30	38.23	218.0	-3.436	0.001*
	Clobetasol Propionate	30	22.77			
Third month	**Aloe vera**	30	38.85	199.5	-3.717	0.001*
	Clobetasol Propionate	30	22.15			
Fourth month	**Aloe vera**	30	35.53	239.0	-2.823	0.005*
	Clobetasol Propionate	28	23.04			
Fifth month	**Aloe vera**	29	31.76	239.0	-2.148	0.032
	Clobetasol Propionate	25	22.56			
Sixth month	**Aloe vera**	27	28.59	281.0	-1.037	0.300
	Clobetasol Propionate	25	24.24			

N: study sample; Z: z value; *P: significant at <0.0071

Table 7: Interclass correlation coefficient for inter-observer reliability

Parameters	Interclass correlation*	Cronbach's alpha	Value*	df1	df2	P
Site score	0.83	0.91	11.08	19	114	0.001*
R score	0.81	0.93	15.15	19	114	0.001*
E score	0.87	0.91	11.28	19	114	0.001*
U score	0.68	0.72	3.66	19	114	0.001*

* F Test with true value 0
df: degree of freedom

DISCUSSION

Current systemic and topical treatments for OLP aim at symptomatic relief or suppression of immunity but cause local and systemic adverse effects. An active therapeutic approach, which will provide symptomatic relief and complete resolution of the lesions with minimal adverse effects is desired. Apart from treatment, there is a need for an elaborate, universally accepted scoring system which can precisely record the clinical presentation of OLP. Majority of the authors relied on Thongprasom's criteria for clinical scoring of the lesion which primarily stresses on size of the lesion with higher scoring for ulcerative lesions as compared to erosive lesions on scale of 0 to 5 [8-12].

This method is not site specific and there is no inclusion of various types of white component of the lesion apart from 'white striae'. The OLP Disease Score adopted in this study enabled us to record the finest differences at monthly follow up in all forms of OLP.

Piboonniyom et al. [13] proposed an elaborate clinical scoring system for evaluation OLP which included 10 intra oral sites and had grading for presence of reticular, erythematous and ulcerative lesions. Park HK et al. [14] used similar criteria but correlated it with numerical pain rating scale. They concluded that separate scores for reticular, erosive and ulcerative lesions helps to easily record OLP lesions. Further, combining the clinical scores with a pain scale reflects better on post treatment changes, if any. Escudier et al. [15] method was site specific as it included 17 intra oral sites and had good reproducibility but did not include a pain score. Wang et al. [16] has extensively reviewed the 22 various scoring systems used for clinical evaluation of OLP. They concluded that there is lack of universally acceptable disease scoring system for OLP. During the follow up visits we observed diverse nature of OLP in its clinical presentation. One of the interesting observations in the studied patients was involvement of multiple sites at different times. During the healing phase, the resolution of the lesions was variable presenting with change in the type of lesion. The OLP Disease Scoring System was useful in all such cases. In this regards, the following points are highlighted:

4.1 Size:

It was noted that healing of atrophic, erosive and ulcerative lesions consistently occurred from periphery towards the center. Hence, changes in the presentation of such lesions were scored based on decrease in their extent (Figures 2, 3).

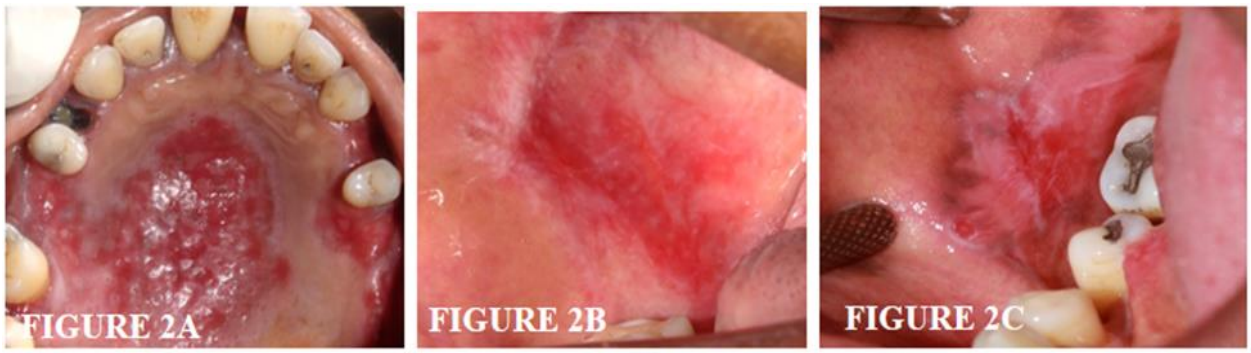

Fig 2. Scoring of changes in erosive lesions based on the decrease in size (A) Extensive erosive lesion on the hard palate >3cm^2 (E score=3); (B) Erosive lesion measuring 1–3 cm^2 with thin delicate white striae along the periphery (E score=2, R score=1); (C) Erosive lesions <1cm^2 with raised white striae along the periphery (E score=1, R score=2)

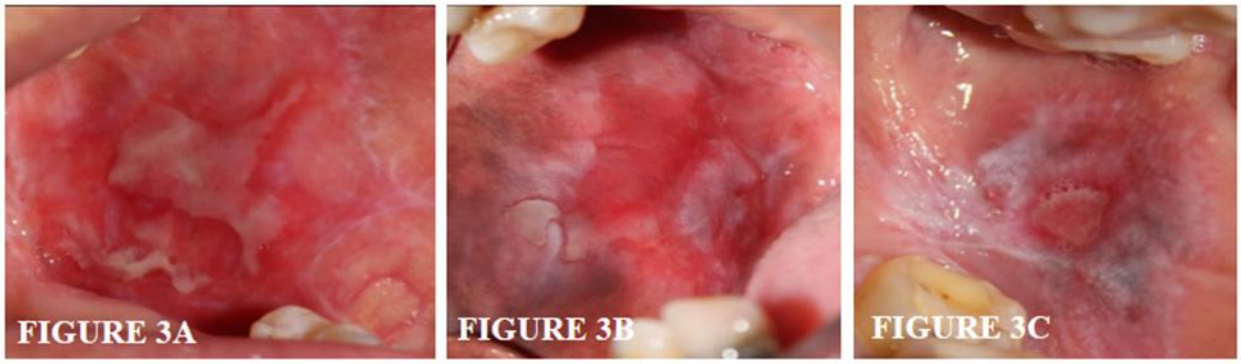

Fig 3. Scoring of changes in ulcerative lesions based on the decrease in size (A) Large ulcerative lesions on right buccal mucosa >3 cm^2 interspersed with erosive mucosa and delicate white striae in the periphery (U score=3, E score=2, R score=1); (B) Ulcerative lesions on left buccal mucosa 1–3cm^2 with erosive lesion posteriorly and thick raised white keratosis (U score=2, E score= 2, R score=2); (C) Ulcerative lesions <1 cm^2 with thick white striae surrounding the ulcer, (U score=1, R score=3)

The healing of the reticular lesion may either show gradual dissolution of keratotic striae of the entire lesion from periphery towards the centre or complete resolution in the central portion of the lesion with persistence of the striae along the periphery, forming an annular pattern. Hence scoring of the reticular lesion by measuring the clinical size does not properly reflect upon the response to the treatment. Thus reticular lesions were not classified based on their size but the grading was done based on the various clinical patterns seen in different stages of the disease course.

4.2 Site:

In this method, 23 sites are to be examined inside the oral cavity. Six new sites in the gingivo-buccal sulcus region were identified, namely upper right, upper central, upper left, lower left, lower central and lower right. Gingivo-buccal sulcus region was found to be second most commonly involved site, the most common site being buccal mucosa. In most of the cases, the buccal mucosal lesions extended into the gingivo-buccal sulcus region while in some cases isolated lesions were seen in the sulcus region. To the best of our knowledge, only one study by Pindborg et al. [17] in their epidemiological survey, have stated that a large number of lesions were present in the mandibular buccal groove. But prevalence percentage for lesions in the gingivo–buccal sulcus region was not mentioned.

4.3 Type:

Chainani-Wu et al. [18] and Escudier et al. [15] have attempted to score keratotic lesions separately but have not provided detailed scoring system for reticular, plaque and papular type of OLP. After observing the pattern of reticular striae, we propose a scoring for reticular lesions based on change in the clinical presentation of degree of keratosis as detailed in Table 2 and Figure 4. This enabled us to record the fine alterations in clinical characteristics of reticular lesions and helped to precisely assess the response to the treatment. Due to the limited number of cases it was not possible to generate a scoring criteria based on the change in degree of keratosis for evaluation of papular and plaque OLP. As such, the scoring was done based on size and presence or absence of erythema for papular and plaque type of lesions in the study (Figure 5, Table 2).

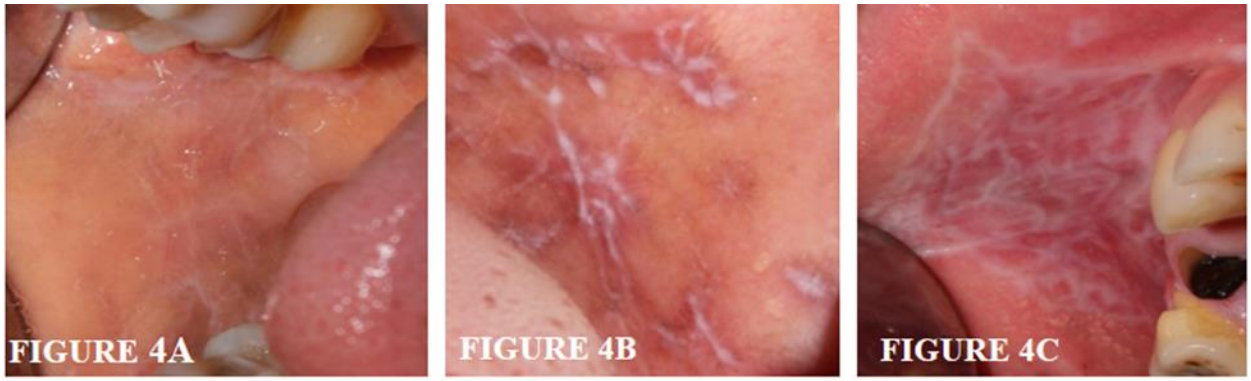

Fig 4. Proposed scoring for reticular lesions based on change in the clinical presentation of the degree of keratosis (A) Diffuse thin white striae with branching or lace like pattern or thin wispy striae with annular pattern (R score=1); (B) Thick raised confluent white striae with branching with mild erythema (R score=2); (C) Thick white striae with dense white lace like formation with marked erythema, (R score=3)

4.4 Subjective Evaluation:

Majority of the authors used VAS score for of burning sensation [16]. OLP Clinical Score also includes VAS score for burning sensation. No other formal quality of life assessment was done.

4.5 Inter-observer Consistency:

Cronbach's Alpha was in the range of 0.72-0.93 for site score, R, E and U score, indicating an excellent consistency between primary and secondary investigator. (Table 7).

The OLP Disease Scoring system is a very comprehensive clinical criterion for OLP because of the following reasons; The OLP Disease Score allows the investigator to record the clinical appearances of OLP at 23 different intraoral sites. It incorporates different types of clinical appearances of OLP with individual type-specific scoring. It enables correlation of clinical scoring with the symptomatic pain scale (VAS) and is highly reproducible. We highly recommend the use of OLP Disease scoring criteria to evaluate treatment response of OLP in clinical trials as it helps to understand the progression/ resolution/recurrence of OLP over a long follow up period. The possible limitations of this scoring system are; It is time consuming. The time required for recording data of each patient is 2–5 minutes. To be able to use this scoring criteria, the investigator must be aware of the variety of clinical appearances utilized in this criteria and must have an eye to differentiate between them.

The AV gel was specially prepared from fresh AV mucilage with 97% AV extract as compared to 70% gel used in the previous studies by Choonhakarn et al. [10] and Salazar Sanchez et al. [19] The AV gel consists of 98.5% water and the active substances such as polysaccharides amino acids and vitamins are present in minute concentrations. [20-24] No attempt was made in the present study to isolate the active substances in AV gel so as to directly test their efficacy. Therefore, highest achievable concentration of AV gel was desired in order to achieve better results and hence 97% AV gel was used.

In our study, AV proved to be more effective as compared to other clinical trials [8, 10,11,19,25]. Illustrative cases are shown in Figure 6.

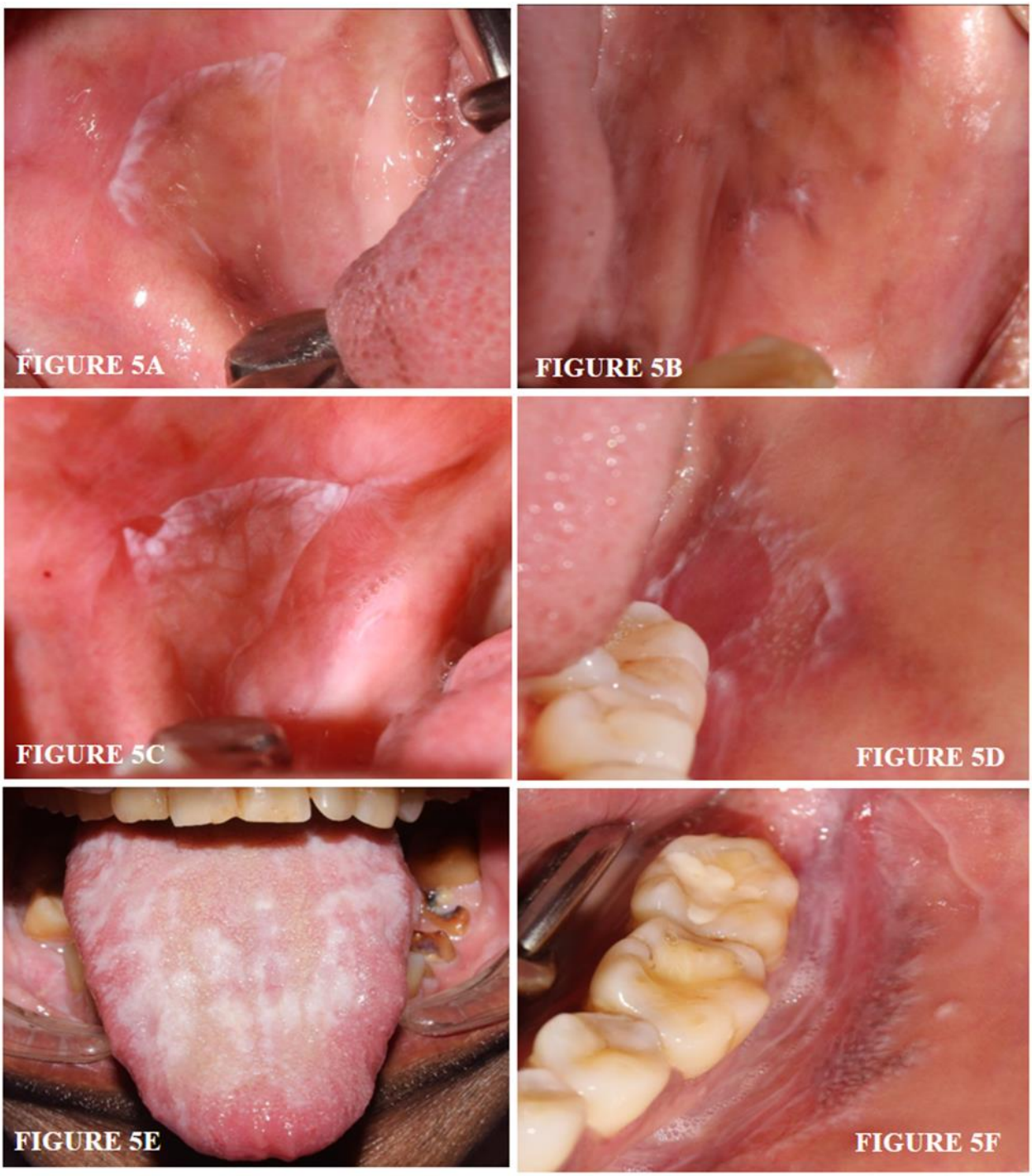

Fig 5. Scoring based on size and presence or absence of erythema for papular and plaque lesions. (A) Focal thin white patch with central area of normal mucosa <0.5cm^2, (R score=1); (B) Incipient papular lesion 0.5cm^2 in area without erythema (R score=1); (C) Thick white plaque type lesion which is up to 1cm^2 in area, (R score= 2); (D) Papular lesion 0.5– 1cm^2 in area with mild erythema (R score = 2); € Thick white raised plaque type lesion >1cm^2, (R score= 3); (F) Papular lesion >1 cm^2 in area with marked erythema (R score=3)

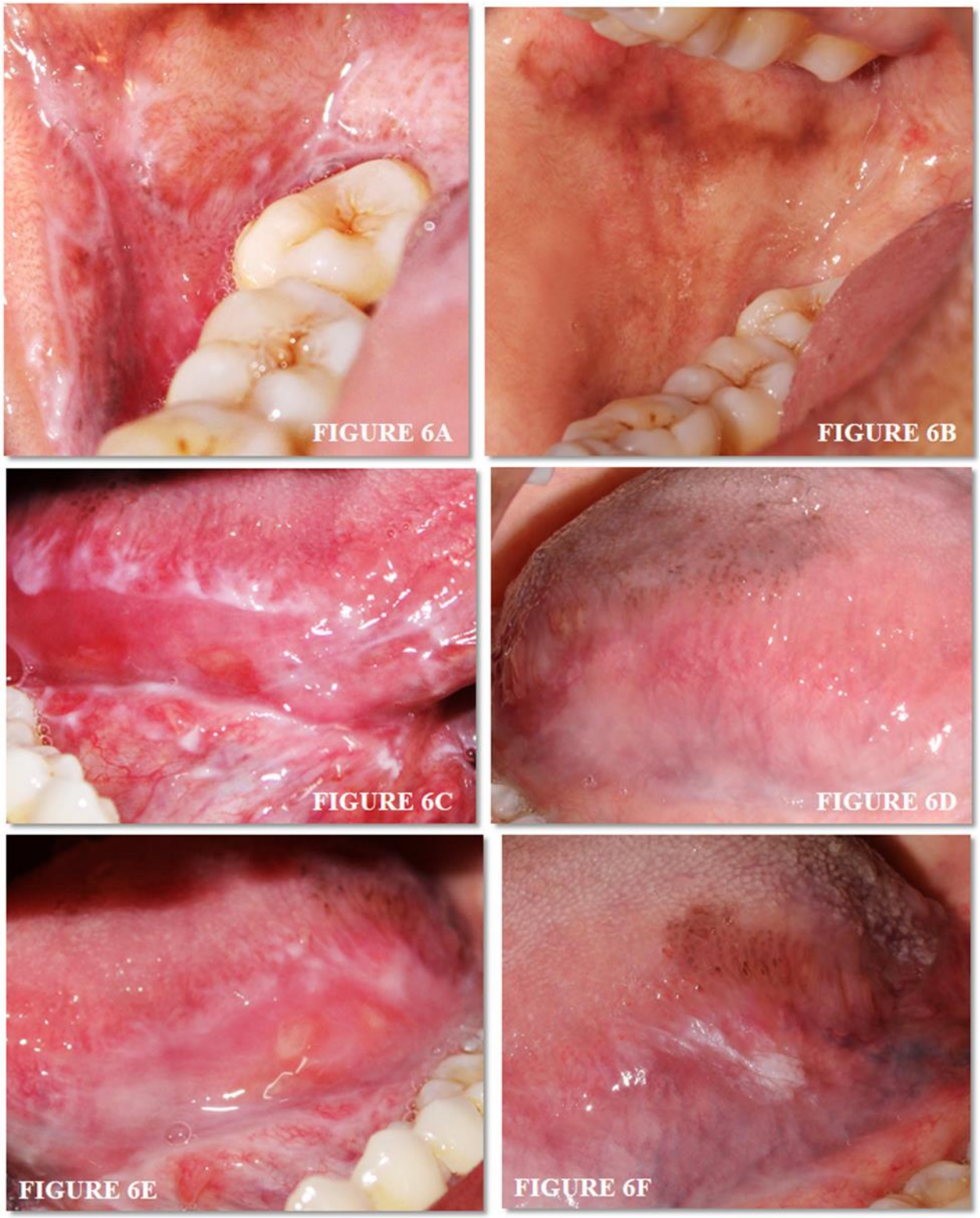

Fig 6. Illustrative cases from Aloe Vera therapy group. (A) (B) Reticular and erosive lesion on right buccal mucosa before and after treatment; (C) (D) Reticular and erosive lesion of the right lateral border of the tongue before and after treatment; (E) (F) Reticular and ulcerative lesion on the left lateral border of the tongue before and after treatment

The following reasons may have led to better results; the use of higher concentration of Aloe vera gel (97%) as compared to other studies [10,19]. The additive synergistic effect of topical application of 97% AV gel and systemic administration of 94.7% AV juice resulted in higher improvement in the clinical scores [11]. Statistically significant difference was observed in final OLP Disease Score at end of treatment, 3rd and 4th month ($p<0.0071$). The decrease in OLP Disease score was far more with Clobetasol Propionate. However, there was no statistically significant difference between both groups towards the end of observation period (5th & 6th month). A possible explanation to this may be that there was steady reduction in the score in AV group whereas there was increase in the score for CP group at 6th month. The rise in the mean value in CP group can be attributed to the relapse of the lesions after treatment.

The effectiveness of AV in controlling inflammation and aiding in wound healing can be attributed to composition of the gel. The AV gel contains 1–1.5% polysaccharides of varied molecular weight (Pectins, Alprogen, Glucomannan, Acemannan, and Mannose derivatives), Amino Acids, enzymes (Carboxypeptidases, Cycloxegenase) etc. [21,24]. Carboxypeptidase in AV inhibits oxidation of arachidonic acid, which might decrease inflammation [8,25]. AV can also exert anti-inflammatory effect by reduction of leukocyte adhesion and Tumor Necrosis Factor alpha (TNF-alpha) levels [26-29]. AV also contains three malic acid acylated carbohydrates: Veracylglucans A, B and C which have anti-inflammatory effect. Veracylglucan A and B has anti proliferative effect while Veracylglucan C enhances cell proliferation [27]. Glucomannan (polysaccharide) and Gibberellin (a growth hormone), can cause activation and proliferation of fibroblasts [28]. Acemannan (β-(1,4)-linked acetylated mannose), is an immunomodulator, it activates macrophages and enhances cytokine release. [26].

To the best of our knowledge, this study is the first clinical trial aimed at evaluating the effectiveness of CP and AV gel in treatment of OLP. AV and CP were almost equally effective against erosive and ulcerative lesions. Such lesions result in disruption in the integrity of the epithelium which could have resulted in better permeability and significant absorption of the both the drugs. The CP was in an ointment base which has superior adhesive properties to the oral mucosa as compared to the gel base of AV. Reynolds and Dweck [28] mentioned that AV in an ointment base did speed up the process of healing of wound but did not cause much change in the final result. In the light of the above, this study suggests that CP gives rapid symptomatic relief and better clinical improvement. AV gel is also proved to be beneficial in treatment of OLP.

CONCLUSION

This study has successfully demonstrated, that AV can be used safely as an effective treatment modality for OLP and was well tolerated by all patients. It neither produced any serious adverse effects nor any visible complications of possible drug interaction with any other systemic allopathic medications that were concomitantly taken by the patients. There was no atrophy or scarring of the tissue with AV during and after healing of the lesions.

This study has successfully identified and used six new intraoral sub-sites and put forth a new scoring criteria for reticular, plaque and papular lesions. The OLP Disease Scoring System is well-structured, comprehensive, highly reproducible and allows meticulous evaluation of clinical presentations of various types of OLP and allows precise recording of the lesion characteristics. Hence, it will be particularly useful in randomized clinical trials to achieve a standardized evaluation protocol. The systematic site-wise and month-wise recording of lesions in the OLP Disease score can also be used for the purpose of patient education and reassurance.

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CONFLICT OF INTEREST STATEMENT

None declared.

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