A Clinical Comparative Evaluation of Steroid and Tacrolimus in Oral Lichen Planus: A Pilot Study

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Abstract:

Background:

There are various pharmacological approaches for Oral Lichen Planus (OLP), but mainstay of therapy always tends to be corticosteroids. Irrespective of innumerable therapies, attaining permanent cure is still far from reach. Considering the limitations of steroids, a relatively novel therapeutic option is provided by immunosuppressants like Tacrolimus.

Thus, the aim of this pilot study is to clinically compare and evaluate the effectiveness of Tacrolimus over corticosteroids in OLP patients.

Materials And Methods:

Four cases of bilateral OLP administered with 0.1% topical Triamcinolone acetonide (S group) and four other cases administered with 0.1% topical Tacrolimus (T group) were selected and their response to the treatment based on changes in symptoms and signs were recorded on follow up visits. Both the groups were followed up for 3 months. Visual Analogue Scale (VAS) was used for recording the burning sensation and Modified Oral Mucositis Scale (MOMI) for measuring the extent of the lesion.

Results:

Although the post-follow up results were insignificant between 2 groups, T group had more stable reduction in symptoms without flare up with a significant reduction in post follow up VAS and MOMI score.

Conclusion:

Tacrolimus can be considered as an effective alternative to steroid, and a potential drug of choice for OLP.

Key Words: Oral Lichen Planus, Tacrolimus, Corticosteroid, Burning

Introduction

Oral lichen planus (OLP) is a chronic autoimmune mucocutaneous disease with a prevalence of 0.5 to 2% of the population. Although it has various clinical forms such as papular, reticular, bullous, erosive, and atrophic, it often coexists in combinations of these types. The atrophic-erosive form can greatly affect patients' quality of life as it causes symptoms ranging from mild burning sensation to severe pain.[(1)] World Health Organization (WHO) identified OLP as a potentially malignant disorder, with an approximate malignant transformation rate of 1.09%. The known etiopathogenesis is thought to be autoimmune that can be antigen-specific cell-mediated immunity which involves local recruitment of auto-cytotoxic T-lymphocytes (CD8+) inducing apoptosis of basal epithelial cells. The clinical presentation of OLP is typical with the presence of bilateral, symmetrical fine white striae called Wickham's striae, most commonly observed on buccal mucosa, lateral border of tongue, gingiva, and palatal mucosa. Given the obscure etiology, complete curative therapy is not known, and is usually focused on symptomatic relief to reduce the inflammatory response and subjective discomfort of the patients. Corticosteroids have always been the mainstay of therapy, but their therapeutic benefits are not evident, which leads to the need for treatment alternatives, especially for patients who are refractory to routine therapy.[(2)]

Other therapeutic measures that aided as an adjunct to corticosteroids are topical and systemic retinoids, cyclosporin and other immunosuppressants, psoralen-U-VA, photochemotherapy, photodynamic therapy, griseofulvin, hydroxyquinone, dapsone, mycophenolate, CO2 laser, thalidomide, and low-molecular-weight heparin. Irrespective of innumerable therapies, attaining permanent cure is still far from reach. Considering the remarkable side effects and limitations of steroids, a relatively novel therapeutic option is provided by calcineurin inhibitors like tacrolimus in patients refractory to steroids.[(1)] They inhibit the dephosphorylation of nuclear factor in activated T lymphocytes, reduce the release of cytokines, and suppress the T-cell-mediated pathophysiological reaction in OLP.[(2)]

In the past decade, tacrolimus had been tried in various clinical trials and had significant effect for erosive OLP with less side effects. Most of the trials showed complete or partial remission using 0.1% tacrolimus topical application.[2] But, irrespective of numerous studies, tacrolimus have not come to the front-line therapy of OLP.

Thus, the aim of this pilot study is to clinically compare and evaluate the effectiveness of Tacrolimus over corticosteroids in OLP patients by comparing the reduction of symptoms and extent of lesion over a period of 3 months.

Materials And Methods

Eight clinically diagnosed cases of erosive OLP were recruited from Department of Oral Medicine and Radiology and were divided equally into two groups- S (Steroid) group and T (Tacrolimus) group. S group was administered with 0.1% topical Triamcinolone acetonide and T group administered with 0.1% topical Tacrolimus and followed up for 3 months.

Only patients with chief complaint of burning sensation along with presence of bilateral white striations with erosive or atrophic areas in oral mucosa that were necessary to make a clinical diagnosis of oral lichen planus (Modified WHO Clinical Criteria, 2003) were selected for the study.[3] Only patients who were not under any treatments for the same for last 4 weeks have been selected.

Patients with presence of amalgam or other metal restorations, those with habit history of tobacco, gutkha and other smokeless tobacco forms, and cigarette or bidi smoking were not included in the study group. Patients with burning sensation in the absence of typical lichen planus lesion were excluded.

Patients were asked to apply the ointment using finger after drying the lesion area post meals without eating, drinking, or speaking for at least half-an-hour and not spitting out during this time. They were asked to apply for 4 times per day, only over erythematous and ulcerated areas by seeing a mirror and not on normal oral mucosa, and were asked to report back every 15 days.

Each visit consisted of evaluation of the burning sensation using Visual Analogue Scale (VAS) and measuring the extent of the lesion using Modified Oral Mucositis Index (MOMI). Visual analogue Scale consists of a 10 cm horizontal line marked from 0 to 10 and patients were shown and asked to point out on every visit. Modified Oral Mucositis Index (MOMI), 2008 is a semiquantitative scale in which erythema and ulceration are graded from 0 to 3 based on the extent. Separate scores for erythema and ulceration are obtained by summing up the scores of each site.[4]

The values were recorded 4 times – on initial visit, after 15 days, after 1 month, and after 3 months. The difference between the values on each visit expresses the clinical and symptomatic improvement. These values were compared within the group and between the groups and statistical analysis were performed.

All data were entered into a computer by giving coding system, proofed for entry errors. Data obtained was compiled on a MS Office Excel Sheet (v 2019, Microsoft Redmond Campus, Washington). Data was subjected to statistical analysis using SPSS v 26.0, IBM. Descriptive statistics like frequencies and percentage for categorical data, mean & standard deviation for numerical data has been depicted.

Demographic data comparisons have been done using parametric tests. Inter group comparison was done using t test and comparison of frequencies of categories of variables with groups was done using chi square test.

Since sample size was a limitation, non-parametric tests have been used for comparisons. Inter group comparison was done using Mann Whitney U test. Intra group comparison was done using Friedman's (for >2 observations) followed by pair wise comparison using Wilcoxon Signed rank test.

The intragroup and intergroup median values of VAS score and MOMI values during initial visit, after 15 days, after 1 month and after 3 months were calculated.

For all the statistical tests, $p<0.05$ was considered to be statistically significant, keeping α error at 5% and β error at 20%, thus giving a power to the study as 80%.

Results:

Out of the eight patients selected, 3 were females and 5 were males. Mean age of S group was 56.75 years (SD±22.5 years) and that of T group was 47 years (SD±22.55years). All the cases selected had erosive type of oral lichen planus with symptom of burning sensation. Duration of the symptoms ranged from 6 months to 2 years. All the cases had lesions on bilateral buccal mucosa, followed by maxillary and mandibular gingiva and lateral aspect of tongue in 3 cases, hard palate in 2 cases, and ventral surface of tongue and floor of mouth affected in 1 case. Respective topical applications were given and were followed up for 3 months.
(Figures 1 and 2)

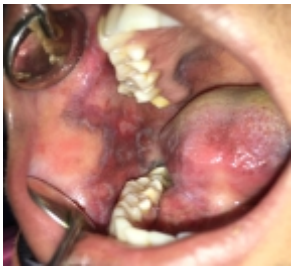

Figure 1 A: S Group – Initial Visit

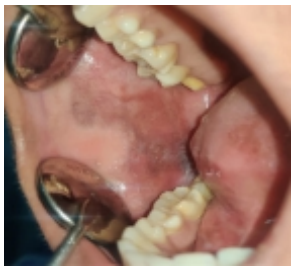

Figure 1 B: S Group – After 3 Months

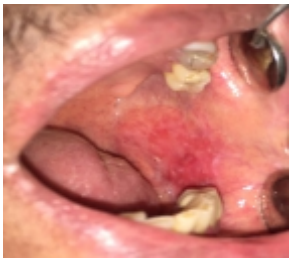

Figure 2 A: T Group – Initial Visit

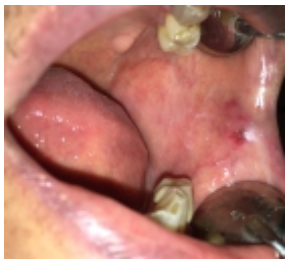

Figure 2 B: T Group – After 3 Months

Demographics are presented in table 1.

Table 1: Demographic data

Groups	Case No.	descriptive Analysis				
		Age	Mean Age	Gender	Type of lichen planus	Follow up period
S Group	Case 1	81	56	Male	Erosive	3 months
	Case 2	67		Male	Erosive	
	Case 3	43		Female	Erosive	
	Case 4	36		Male	Erosive	
T Group	Case1	23	47	Female	Erosive	
	Case 2	62		Female	Erosive	
	Case 3	33		Male	Erosive	
	Case 4	70		Male	Erosive	

Intragroup comparison of VAS and MOMI of erythema pre and post follow up were statistically significant in both the groups with highly significant value of intragroup VAS score in T group ($p<0.05$). Intragroup comparison of MOMI of ulceration in both the groups were statistically non-significant ($p>0.05$). Intergroup comparison of VAS score after 1 month gave statistically significant value. Intergroup comparison of all other variables was statistically non-significant. There were clinically significant difference noted in T group compared to S group in all the variables. (Table 2 and 3)

TABLE 2: Scoring of burning sensation using VAS score with intra group and inter group p values

Groups	Case No.	Vas Score				P Value
		Initial	15 Days	1 Month	3 Months	
S Group	Case 1	8	6	4	3	0.023
	Case 2	10	7	8	3	
	Case 3	10	6	9	6	
	Case 4	8	8	4	2	
Median		9	6.5	6	3	
T Group	Case 1	10	8	3	1	0.008
	Case 2	9	6	3	3	
	Case 3	9	8	2	0	
	Case 4	8	6	2	0	
Median		9	7	2.5	1	
P Value		1	0.752	0.019	0.074	

TABLE 3: MOMI score measuring the extend of lesion, and inter and intra group P values
Total Momi

		Erythema					Ulceration				
		Initial	15 Days	1 Month	3 Months	P Value	Initial	15 Days	1 Month	3 Months	P Value
S Group	Case 1	3	1	2	1	0.023	1	1	1	0	0.093
	Case 2	18	12	11	8		5	3	2	2	
	Case 3	5	4	4	3		2	1	1	1	
	Case 4	3	0	2	1		0	0	0	0	
	Median	4	2.5	3	2		1.5	1	1	1	
T Group	Case 1	17	8	6	6	0.010	7	3	2	2	0.067
	Case 2	5	3	1	1		1	1	1	0	
							1	1	0	0	
	Case3	4	4	2	0						
	Case4	12	6	3	2		0	0	0	0	
	Median	8.5	5	2.5	1.5		1	1	0.5	0	
P Value		0.465	0.468	0.554	0.554		0.882	1.000	0.647	0.617	

Discussion:

In this study, burning sensation of the patients decreased significantly after 1 month after application of topical tacrolimus as compared to corticosteroid application. Even though all other variables were statistically non-significant, the efficacy of topical tacrolimus is evident clinically with a decrease in the VAS and MOMI scores in T group compared to that of S group during the follow up periods. This shows an initial symptomatic improvement in T group as compared to S group, but due to smaller follow up period, the complete therapeutic efficacy of tacrolimus could not be assessed.

A meta-analysis by Guo et al in 2015 assessed the efficacy and safety of topical tacrolimus for erosive OLP and found that there was no evidence to support topical tacrolimus to be more effective and safer than topical corticosteroids. However, no serious adverse events were reported in topical tacrolimus group.[5]

But there is a black box warning for tacrolimus by FDA due to increased risk of malignant transformation, and stated that tacrolimus should be used only in short periods of 6 weeks and combined with a rotational therapy of topical steroids. This treatment strategy has shown to be effective, where patients' earlier recalcitrant to steroid treatment responded following a period of topical tacrolimus treatment.[6] But, according to Ribero et al, the use of topical tacrolimus was not associated with any significant side-effect, except mild burning sensation or altered taste sensation.[7]

In a network meta-analysis by Sridharan et al in 2021, multiple treatment interventions of OLP were compared and was found that topical corticosteroids were the most effective drug class, and even though pimecrolimus and cyclosporine were effective, there were significant adverse effects which contributed to its limitation in use.[8]

The studies included in these meta-analyses had lack of power to detect significant differences between treatments if indeed such a difference existed. It is essential to standardise the methodology of clinical trials in assessment of therapeutic response. It is very important to use reliable and sensible indices, which are accurate, feasible, and reproducible. There should be sufficiently longer follow-up periods to determine whether treatment confers an important long-term benefit.[7]

The internal consistency reliability of the MOMI scale used in this study is good.[4] Scaling of the extent of lesion is done in our study which was missing in the cases that were selected in the mentioned systematic review and meta-analysis. This study recorded burning sensation which is the clinical feature of OLP, and not pain which was the recorded clinical feature in most of the other studies. This study can thus be a framework for future large scale randomised controlled trials, in which both symptom as well as erythema and ulceration have been scaled with equal follow up time of the two treatment groups.

Limitations Of The Study:

Larger sample size is required to have a significant comparison between two groups. Medical history of patients was not

considered in the study. Diagnosis was done only based on clinical criteria and lab parameters were not used pre and post treatment.

Conclusion:

Tacrolimus can be considered as a potential drug of choice similar to steroids and can be considered as the drug of choice in patients refractory to steroids. However, long term follow-up study with large sample size and overcoming other limitations has to be carried out for better understanding of the effects and adverse effects of tacrolimus.

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Conflict of Interest: None

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