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Clinical evaluation of 0.1% topical tacrolimus and 0.1% mometasone furoate in the management of erosive or ulcerative oral lichen planus

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Abstract
Aim: The aim of this randomized controlled clinical study is to clinically evaluate the efficacy of topical applications of 0.1% Tacrolimus ointment (Tacroz^{TM}-Forte), when compared with 0.1% Mometasone furoate ointment (Momtas^{TM}), in the management of erosive or ulcerative oral lichen planus
Materials and Methodology: The study population consisted of 30 patients with oral erosive or ulcerative lichen planus randomized into two groups. Group I applied 0.1% Tacrolimus ointment (Tacroz^{TM}-Forte), where as group II applied 0.1% Mometasone furoate ointment (Momtas^{TM}) twice daily to their oral lesions for 6 weeks and the patients were followed for 8 weeks after active treatment. In the clinical analysis the parameters evaluated included, erythema, ulceration, size of the lesion and severity of pain on a Visual Analogue Pain scale (VAS).
Results: Group I showed statistically significant improvement in ulceration, erythema, and VAS scores when compared to group II from baseline to subsequent recall appointments. 2 patients did not respond to 0.1% topical Mometasone furoate. At 8 weeks of post treatment period recurrence of erythema was observed in 7 patients (46.67%) in group I and 6 patients (50%) in group II. No severe adverse effects were observed in both groups, except for transient burning sensation at the site of application of the drug and dryness of the mouth in few patients.
Conclusion: Both 0.1% topical Tacrolimus and 0.1% Mometasone furoate are effective in the treatment of erosive or ulcerative OLP. The clinical efficacy of 0.1% topical Tacrolimus is observed to be superior to that of 0.1% Mometasone furoate.

Keywords: Oral lichen planus, Mometasone furoate, Tacrolimus

Introduction
Oral lichen planus (OLP) is a most common chronic mucocutaneous disease. The prevalence of oral lichen planus has been found to be 0.1% to 4%. [1, 2] Oral manifestations of lichen planus include reticular, papular, plaque-like, erosive-ulcerative, and bullous lesions. Oral erosive or ulcerative lesions are commonly associated with pain and discomfort [3-6].
The etiology of oral lichen planus (OLP) is still unknown, but it is documented that it represents a cell- mediated immune response with an inflammatory infiltrating cell population composed of T lymphocytes [6-10]. Diagnosis of OLP is often made by the clinical and histopathological characteristics. Patients with erosive- ulcerative OLP need treatment and the need to reduce morbidity perpetuates a continuing search for novel therapies.
Most of the treatment modalities for OLP are immunosuppressive in nature. For many years, topical or systemic administration of corticosteroids has been the first line of treatment for OLP [6, 11]. Studies on OLP suggest the high - potency topical corticosteroids such as mometasone furoate, triamcinolone acetonide, fluocinolone, clobetasol, and fluticasone for treating symptomatic OLP [11, 12]. where as systemic corticosteroids may be occasionally indicated for severe recalcitrant erosive OLP or patients with diffuse mucocutaneous involvement [11, 12, 13]. The efficacy of corticosteroids in OLP is mainly attributed to the local anti-inflammatory effect and the anti –immunologic properties of suppressing T-cell function [6, 13].
Mometasone furoate is a synthetic glucocorticoid 16 α-methyl analogue of beclomethasone. Topical mometasone has been classified as a ‘potent glucocorticoid’ and it has demonstrated a greater anti-inflammatory activity and a longer duration of action than betamethasone.

Mometasone has showed low adverse systemic effects such as suppression of the hypothalamic-pituitary-adrenal axis [14-17]. Recently a clinical study has evaluated the efficacy of topical Mometasone in the treatment of erosive-ulcerative OLP [18].

Cyclosporine, vitaminA analogues, photopheresis, dapsone, and griseofulvin have been used with varied results [13, 19]. The search for new topical anti-inflammatory agents without the adverse effects of topical corticosteroids has resulted in the development of new topical immunomodulators like tacrolimus. Tacrolimus inhibits T-cell activation at 10-100 times lower concentration than cyclosporine. Notably, topical tacrolimus seems to penetrate skin better than topical Cyclosporine [20].

Tacrolimus is a macrolide produced by streptomyces tsukubaensis, a soil bacteria. Closely related to cyclosporine, it acts by diffusing across T-lymphocyte membranes where it binds to proteins and inhibits the ability of calcineurin to dephosphorylate the transcription factor that activates interleukin (IL) -2 gene transcription. The resulting inhibition of the synthesis and release of IL-2, as well as other cytokines, inhibits T-cell activation, accounting for the anti-inflammatory action of tacrolimus [20]. Since lichen planus is a putative T-cell mediated inflammatory condition, it has been suggested as a target for topical tacrolimus treatment, especially for the oral form of lichen planus. Several clinical studies have been conducted and found tacrolimus to be effective in reducing the signs and symptoms of oral lichen planus [21-30].

There is a paucity of controlled clinical trials in the literature, comparing the efficacy of high potency topical corticosteroids like mometasone with new topical immunomodulators like tacrolimus in the treatment of symptomatic OLP. The aim of the double blind randomized controlled clinical study is to clinically evaluate the efficacy of topical applications of 0.1% tacrolimus ointment, when compared with 0.1% mometasone furoate ointment, in the management of erosive or ulcerative oral lichen planus.

Materials and Methods

The present randomized controlled double blinded study was conducted in the department of oral medicine and radiology, government dental college and hospital, Hyderabad. The study population consisted of 30 patients with mean age of 53.5 years [range 37 to 65 years] with oral erosive –ulcerative lichen planus. The following criteria was adopted to enroll the patients in the study.

Inclusion Criteria

Clinical and histopathological diagnosis of erosive or ulcerative oral lichen planus.

Exclusion Criteria

- Treatment with corticosteroids during the previous year
- Hypersensitivity to corticosteroids and tacrolimus
- Liver or renal insufficiency
- Diabetes or glaucoma
- Oral candidiasis
- Pregnancy or lactation
- Notable abnormalities in full blood cell count and hepatic and renal biochemistry
- Immunosuppressive disease
- Social and personal reasons preventing regular clinical review
- Local and systemic pathologies likely to hinder accurate clinical examination
- History of drug induced lichenoid reactions and malignancy
- Uncontrolled hypertension or recurrent acute infection

The study protocol was approved by institutional ethical committee. All patients signed an informed consent document stating their understanding and agreement to enroll in the study. The patients were randomly assigned into either group I or group II. Group I applied 0.1% tacrolimus ointment (Tacroz TM-Forte, Glenmark, India) to and group II applied 0.1% mometasone furoate (Momtas TM, Cosme health care, India) to OLP lesions. Baseline laboratory investigations, including a complete blood picture (CBP) with differential count and a complete metabolic panel (glucose, SGOT (serum glutamic oxaloacetic transaminase), SGPT (serum glutamic pyruvic transaminase), alkaline phosphatase, total bilirubin, creatinine, urea/ BUN [blood urea nitrogen]) were performed.

Clinical Evaluation

The clinical parameters including size of erythema, ulceration, type of OLP lesion and Visual Analogue Pain scale(VAS) were recorded by the investigator(VC) at baseline, 2,4,6 weeks of active treatment and 4,8 weeks post treatment follow up visits. Size of erythema, ulceration were measured at each visit using calipers in mm^2 by multiplying length and width of lesion. Patients were asked to rank the severity of their pain and discomfort on a Visual Analogue Pain scale (VAS) from 0 (no pain) to 10 cm (extreme pain).

Treatment Protocol

Group I applied 0.1% tacrolimus ointment (Tacroz^{TM}-Forte) twice daily to their oral lesions for 6 weeks, where as group II applied 0.1% mometasone furoate (Momtas^{TM}) twice daily to their oral lesions for 6 weeks. Both tacrolimus and mometasone ointments were supplied in white colour tubes by the investigator (MM). The investigator (VC) who measured the parameters and the patients were unaware of the medication supplied. All patients were instructed to gently dry the affected areas of the mouth before applying the medication to the lesions with clean fingers. No eating, drinking, smoking, or gum chewing was permitted for 30 minutes after the application.

The patients were advised to report immediately if they develop any adverse reactions like increased itching or burning sensation of mucosa, or any other allergic reactions. Each patient was examined at 1, 2, 4 and 6 weeks of active treatment and at 4 weeks and 8 weeks of follow up. The clinical data obtained was compared to assess the clinical efficacy and superiority, if any, of one mode of treatment over the other.

Statistical Analysis

Statistical analysis was done using SPSSver16 software to compare study outcomes. Multivariate repeated ANOVA was used for comparison of clinical parameters within the group, independent samples t test was used to compare the clinical responses between the groups.

Results

30 patients with erosive or ulcerative oral lichen planus (9 female and 21 male) were included in the study. All the patients were having OLP lesions on buccal mucosa. 17 patients had gingival involvement and 5 patients had tongue involvement (Table 1).

Table 1: Demographic details of patients in group I and group II

Variable	Group I	Group II	Significance (P value)
Gender	10 males and 5 females	11 males and 4 females	
Mean age	347.6±175.77	360±148.76	> 0.05
Erythematous OLP lesions	15	15	> 0.05
Ulcerative OLP lesions	11	10	> 0.05
Buccal mucosal OLP lesions	15	15	
Gingival OLP lesions	8	9	
Tongue OLP lesions	3	2	

Patients on 0.1% tacrolimus ointment showed clinical improvement within 1 week of commencement of treatment. 9 patients had complete healing of ulcers and 2 patients had partial healing of ulcers at the end of 2 weeks of treatment (fig. 1a&1b). At 4 weeks of treatment all the patients with ulceration showed complete healing.10 out of 15 patients with erythema showed complete disappearance of erythema at the end of 6 weeks of active treatment period (fig. 1c).(Table 2)

Table 2: Comparison of clinical parameters in group I

Parameter	Baseline	At 1week of treatment	At 2weeks of treatment	At 4weeks of treatment	At 6weeks of treatment	At 4weeks follow-up	At8weeks follow-up	Significance (P value)
Size of the lesion (in mm^2)	582.6±296.95	469.40±247.94	404.8±214.37	378.07±203.03	345.73±211.2	381.93±253.2	407.2±300	< 0.01*
Erythema (in mm^2)	347.6±175.77	177.53±139.42	100.67±99.37	52.6±76.71	31.8±47.98	43.93±62.69	68.6±94.58	< 0.01*
Ulceration (in mm^2)	38.8±49.68	16.87±23.29	3.73±11.56	0	0	1.07±4.13	3.07±9.09	< 0.01*
Visual Analogue Pain scale [VAS] Score (1-10 cm)	4.47±0.83	3.26±0.79	1.53±1.13	0.8±1.08	0.66±0.98	0.87±1.19	1.13±1.35	< 0.01*

*Statistically significant

Patients on 0.1% mometasone furoate ointment showed clinically significant reduction in pain and surface area of erythema and ulceration during the first two weeks of treatment. 8 out of 10 patients with ulceration, 7 out of 15 patients with erythema showed complete disappearance of ulceration and erythema at the end of active treatment period (fig. 2a & 2b), but 2 patients did not respond to 0.1% topical mometasone furoate. At the end of 6 weeks of active treatment, complete resolution of OLP lesions were observed in 3 patients on 0.1% tacrolimus ointment and in 1 patient on 0.1% mometasone furoate ointment (fig. 2c). (Table 3).

Table 3: Comparison of clinical parameters in group II

Parameter	Baseline	At 1week of treatment	At 2weeks of treatment	At 4weeks of treatment	At 6weeks of treatment	At 4weeks follow-up	At 8weeks follow-up	Significance (P value)
Size of the lesion (in mm^2)	573.4±223.51	496.53±227.49	455.07±216.3	396.20±368±5	368.53±236.57	411.27±261.24	427.93±268.8	< 0.05*
Erythema (in mm^2)	360±148.76	282.6±129.19	219±112.22	121.07±133.12	85.87±110.14	102.67±123.25	144.13±125.6	< 0.01*
Ulceration (in mm^2)	37.27±49.55	27.4±44.96	19±44.59	12.93±43.89	12.46±44.74	16.4±44.74	18.27±46.1	< 0.05*
Visual Analogue Pain scale [VAS] Score (1-10 cm)	4.6±0.83	3.53±0.83	2.93±1.16	1.93±1.79	1.6±1.72	1.87±1.81	1.93±1.79	< 0.05*

*Statistically significant

The most significant changes in the clinical parameters evaluated occured in the first two weeks of treatment in both groups. Change in ulceration, erythema, size of the lesion and pain scores using VAS from baseline to subsequent recall appointments in both groups were statistically significant (table 4-6).

Table 4: Inter group comparison erythema of OLP lesion

	Mean Change in group I (mm^2)	Mean Change in group II (mm^2)	Mean Change between group I&II (mm^2)	Significance (P value)
Base line to 1 week	170.73±91.61	77.4±49.59	93.033±26.89	< .01*
Base line to 2 weeks	246.26±121.72	141 ±85.82	106.26± 38.45	< .01*
Base line to 4 weeks	295 ±146.98	238.93±142.31	54.07± 52.83	> .05
Base line to 6 weeks	315.8±162.39	274.13±154.58	41.67±57.89	> .05
Base line to 4 weeks follow-up	303.67±152.35	257.33±159.26	46.34±56.9	> .05

Table 5: Inter group comparison of change in Ulceration of OLP lesion

	Mean Change in group I (mm^2)	Mean Change in group (mm^2)II	Mean Change between group I & II (mm^2)	Significance (P value)
Base line to 1 week	21.93±35.57	9.87±12.83	12.06±9.76	> .05
Base line to 2 weeks	35.07±45.52	18.27±19.33	17.20±12.77	< .05*
Base line to 4 weeks	38.80±49.68	24.33±26.61	14.47±14.55	< .05*
Base line to 6 weeks	38.80±49.68	24.80±26.52	14.00±14.54	< .05*
Base line to 4 weeks follow-up	37.73±46.50	20.87±25.59	16.86±13.70	< .05*
Base line to 8weeks follow-up	35.73±43.04	19.0±25.84	16.73±12.97	< .05*

Table 6: Inter group comparison of change in Visual Analogue Pain Scale (VAS) Scores

	Mean Change in group I	Mean Change in group II	Mean Change between group I & II	Significance (P value)
Base line to 1 week	1.2±.69	1.07±.89	0.13±0.29	> .05
Base line to 2 weeks	2.93±.58	1.67±.97	1.26±0.29	< .01*
Base line to 4 weeks	3.67±.51	2.67±1.25	1.15±0.35	< .05*
Base line to 6 weeks	3.8±.43	3±1.24	0.8±0.37	< .05*
Base line to 4 weeks follow-up	3.6±.75	2.73±1.78	0.87±0.50	< .05*

*Statistically significant

Group I showed statistically significant improvement in ulceration, erythema, size of the lesion and VAS scores when compared to group II from baseline to subsequent recall appointments. At 8 weeks of post treatment period recurrence of erythema was observed in 7 out of 15 patients in group I and 6 out of 12 patients in group II. Recurrence of ulceration was observed in 2 out of 11 patients in group I. In group II, among the 10 patients with ulcerations, 2 patients did not respond to the treatment and 2 patients had recurrence of ulceration.

No severe adverse effects were observed in both groups. Transient burning sensation at the site of application of the drug was observed in 8 patients in group I and 6 patients in group II. Dryness of the mouth was observed in 4 patients in group I and 3 patients in group II. Transient alteration in taste sensation was observed in 4 patients in group I and in 6 patients in group II.

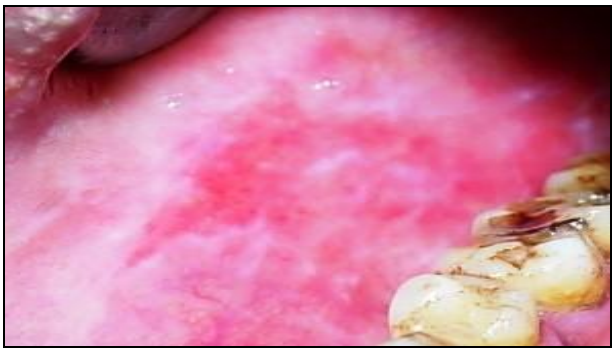

Fig 1a: Pretreatment view showing erosive-ulcerative OLP on right buccal mucosa of patient in group I

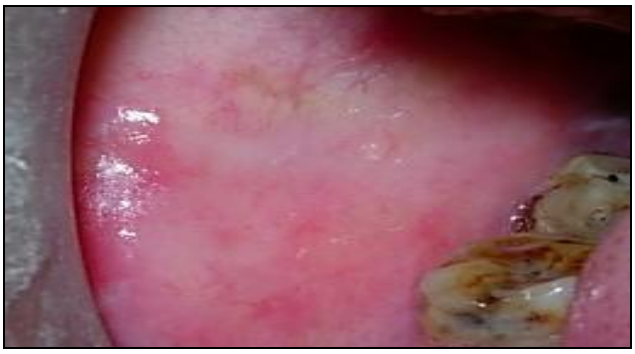

Fig 1b: 2weeks treatment view showing complete healing of ulceration on buccal mucosa

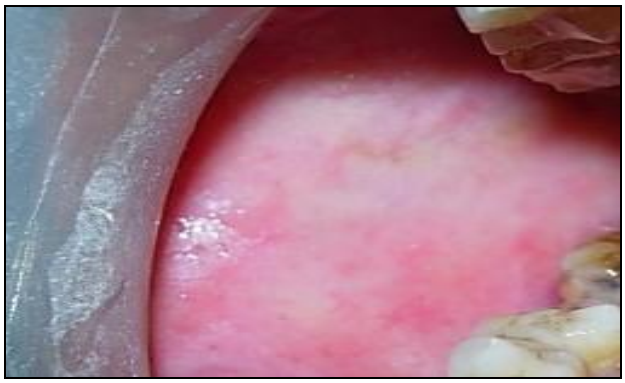

Fig 1c: 6weeks treatment view showing disappearance of erythema on buccal mucosa

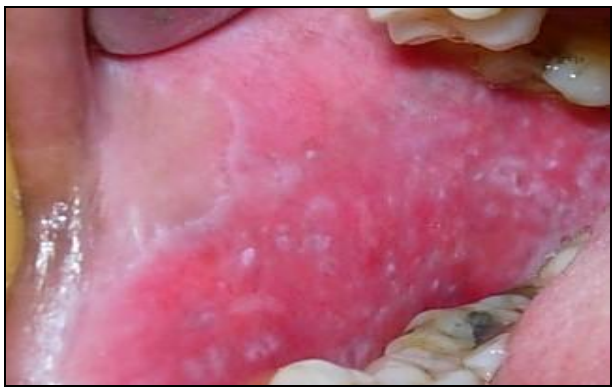

Fig 2a: Pretreatment view showing erosive-ulcerative OLP on left buccal mucosa of patient in group II

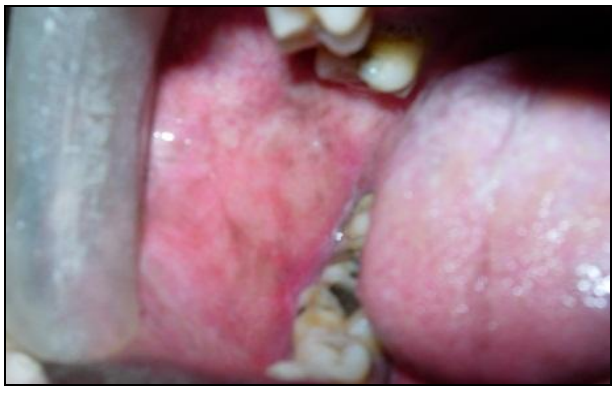

Fig 2b: 2weeks treatment view showing complete healing of ulceration on left buccal mucosa

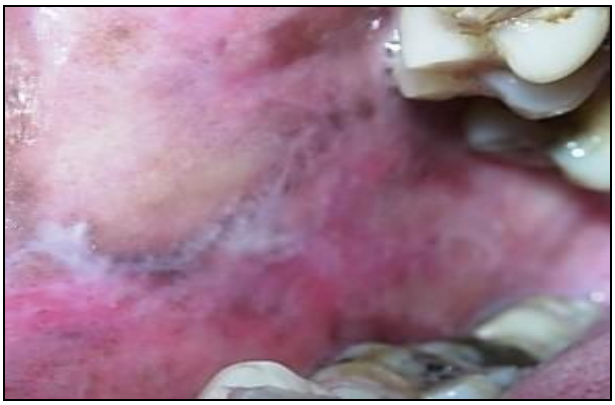

Fig 2c: 6weeks treatment view showing disappearance of erythema on left buccal mucosa

Discussion

The results of the present study demonstrated the efficacy of 0.1% topical mometasone furoate and 0.1% topical tacrolimus in patients with erosive–ulcerative OLP. The results were similar to other studies using 0.1% topical mometasone furoate[18] and tacrolimus [21-29] in OLP patients. The efficacy of topical mometasone furoate in erosive–ulcerative OLP may be due to its local anti-inflammatory effect and the anti-immunologic properties of suppressing T-cell function. The efficacy of tacrolimus in erosive–ulcerative OLP may be due to its inhibitory effect on the activation and proliferation of T lymphocytes.

Despite mucosal erosions and subsequent compromised barrier function, no systemic adverse effects to either topical mometasone furoate or tacrolimus were reported. This finding was likely due to the low concentration of topical mometasone furoate and tacrolimus used in the study.

In the present study, recurrence of erythema and ulceration was observed in few patients at 8 weeks after discontinuation of treatment with 0.1% topical tacrolimus and 0.1% topical mometasone furoate suggesting that both treatments have purely palliative and not a curative effect. However, intermittent treatment could probably be used on a long term basis, with minimal discomfort and adverse effects for the patients.

In the present study, 0.1% topical tacrolimus demonstrated better improvement in clinical parameters than 0.1% topical mometasone furoate in the treatment of erosive- ulcerative OLP. The present study results were in accordance with studies comparing topical tacrolimus with topical corticosteroids [30, 31, 32].

All the patients responded to 0.1% topical tacrolimus, whereas two patients did not respond to 0.1% topical mometasone furoate. This emphasizes that topical tacrolimus might eliminate the need for systemic corticosteroid therapy in patients with erosive-ulcerative OLP who are not responsive to topical corticosteriod therapy.

Conclusion

The results of the present study suggests an alternative treatment approach of using 0.1% topical tacrolimus to topical corticosteroids in the treatment of erosive or ulcerative OLP. The results obtained in this study were derived from a small sample population and a short duration of study, further long term follow-up randomized controlled studies with large sample size are required to validate the results of the present study.

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