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# Topical tacrolimus with Colgate Oraguard-B paste for managing oral lichen planus: A prospective clinical study among northern Indian subjects

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Original Article

# Topical tacrolimus with Colgate Oraguard-B paste for managing oral lichen planus: A prospective clinical study among northern Indian subjects

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## Abstract

**Background:** As of today, no standard treatment protocol nor preventive measures either exists for oral lichen planus. The present investigation aimed to test topical 0.1% tacrolimus as compared to Colgate Oraguard-B paste for managing lesions of oral lichen planus. **Methods:** It was a hospital-based prospective study with histopathologically confirmed 135 patients of oral lichen planus as subjects, which were provided with 0.1% tacrolimus ointment with Colgate Oraguard-B paste. The duration of treatment ranged from three to four months, with a follow-up of till two years. Study subjects were followed up every fifteen days. The results were expressed using mean and standard deviation. Wilcoxon signed-rank test was used to test the significance. **Results:** At the time of the first visit, pain intensity was the worst (visual analogue scale (VAS) scores 9-10). Scores came down to 1-2 (significant reduction in pain) after two months of therapy. Mean values of pre and post VAS scores in the domain of erosive type of oral lichen planus were 9.47±1.22 and 2.84±0.27. Differences in pre and post VAS scores were found to be significant for oral lichen planus. **Conclusions:** Subjects reported a significant decrease in pain by the intervention (topical 0.1% tacrolimus ointment with Oraguard-B past) in a short period. This provided us with a new line of management with promising results for managing oral lichen planus.

**Key words:** Follow up, hospital-based, visual analogue scale

## Introduction

The lichen planus (LP) is an autoimmune disorder that manifests orally and dermally. In general, the overall prevalence of LP is less than three % (0.5 % to 2.6 %), and on a similar note about 2.6 % of Indians having oral lichen planus (OLP).[1] OLP is a condition having the potential of malignant transformation and among the Indian population, the malignancy transforming rate ranges between 0.5 % to 2.0 %.[2,3] OLP most commonly affects the tongue, gingiva, and buccal mucosa. World Health Organisation has tabulated OLP amongst the conditions of potentially malignant.[4] The commonly occurring malignancy from progressive transforming changes of OLP is oral squamous cell carcinoma (SCC).[5]

Exact underlying etiology is not clear, however, it is thought that stress, allergy, immunity, diabetes, and hypertension might act as a precursor for LP occurrence.[6] At the molecular level, proposed and accepted pathogenesis are activation of matrix metalloproteinases (MMP), deregulation of mast cells, and killing of keratinocytes from T cell (CD8+ cytotoxic).[7] Patients commonly report relapse and remissions, thus we must aim to deal with painful conditions, minimizing the risk of oral malignancy, and keep better oral hygiene.[8]

As of today, no standard treatment protocol, nor preventive measures either exists for OLP. Corticosteroids are being widely used for OLP management because corticosteroid modifies cell-mediated immune activity. It is time to test another

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alternative medicine for managing OLP. Tacrolimus inhibits mediators released from basophil and mast cell, along with that it stops activities for calcineurin phosphatase enzymes, which hinder formation and secretions of IL-2, finally leads to inhibit the multiplication of T cells. Colgate Oraguard-B paste has a property for providing faster and earlier relieving of pain due to its mucoadhesive nature, which acts as a protective barrier.[9] So, the present study was conducted to investigate the efficacy of topical 0.1% tacrolimus along with Colgate Oraguard-B paste in managing OLP lesions among north Indian subjects.

## Material and Methods

The present study was prospective and was carried out under the aegis of the department of dentistry in a tertiary care health centre of northern India. The study population were the patients with lesions of OLP and visiting the dentistry department for seeking care. Subjects were included in the study only after receiving confirmation reports from the histopathology department and after obtaining written informed consent. Patients taking medicines for other systemic disorders were excluded from this study. In the same way, subjects giving a history of kidney disease, disease of liver and gallbladder, or uncontrolled hypertension were also not included. A structured format was used to collect demographic data such as age, sex, relevant medical history and habits, duration of OLP, previous treatment history, the size of the lesion including its remission/size reduction, and scores for VAS. Clinical photographs of the lesion were also captured.

The reduction in size of LP lesion was defined into six categories including no lesion; white striae/s only; white striae/s with erosion/s ($<1$ cm$^2$ or $>1$ cm$^2$); and white striae/s with ulceration/s ($<1$ cm$^2$ or $>1$ cm$^2$).

The assessment and quantification of pain symptoms among study subjects were done using VAS. Worldwide, VAS rating is an accepted measure to assess the pain among adults. There are two continuous scale lines in VAS, i.e. horizontal visual analogue scale (HVAS) and vertical visual analogue scale (VVAS). In general, each scale line is 10 cm in length, based on two verbally fixed extreme forms for each symptom. Study subjects were explained in vernacular language that VAS has 0-10 cm line and were instructed to mark their experience of pain symptoms between that line where 0 cm and 10 cm denoted "no pain" and "worst pain" respectively.

Different forms of OLPs were recorded among study subjects viz. erosive, atrophic, reticular, and mixed. An oral intervention was given in the form of 0.1% tacrolimus ointment with Colgate Oraguard-B paste (500 mg of tacrolimus powder was mixed with 300 g Oraguard-B paste). The study subjects were instructed to apply the intervention sparingly over the lesions thrice a day (after meals and not to eat or rinse for at least 45 min after its application) until it gets resolved. Study subjects were followed up every fifteen days to assess the response of intervention. The total follow up period for the present study was two years including treatment duration ranging between three to four months.

Conduction of study initiated after getting clearance from the Institutional Ethics Committee (Approval letter number: SHKM/ME-I/2015/25). All the proforma were manually checked for completeness and data were entered in the MS Excel spreadsheet, coded appropriately, and later cleaned for any possible errors. The analysis was carried out using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp. Armonk, NY, USA). The continuous data were presented as mean and standard deviation, whereas categorical data were presented as percentages (%). Wilcoxon signed-rank test was conducted to capture the difference in the VAS scores before and after the intervention. All tests were performed at a 5% level of significance; thus, an association was significant if the p-value was less than 0.05.

## Results

The present study included 135 subjects with a histopathologically confirmed diagnosis of OLP. The mean age of study subjects was 41.25±3.4 years. Females outnumbered male subjects. At the time of the first visit, pain intensity was worst (VAS scores 9-10). Scores came down to 1-2 (significant reduction in pain) after two months of therapy.

**Table 1: VAS scoring of different forms of OLP among study subjects**

| Forms of OLP | Pre-VAS | | Post-VAS | | P-value* |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| **Erosive** | 9.47 | 1.22 | 2.84 | 0.27 | <0.001 |
| **Atrophic** | 7.90 | 0.74 | 1.80 | 0.18 | <0.001 |
| **Reticular** | 4.29 | 0.38 | 1.45 | 0.40 | <0.001 |
| **Mixed** | 7.42 | 0.95 | 3.28 | 0.53 | <0.001 |
| *Wilcoxon signed ranks test | | | | | |

Mean values of pre and post VAS scores in the domain of erosive type of OLP were 9.47±1.22 and 2.84±0.27. Mean pre and post VAS scores for atrophic forms of OLP were 7.90±0.74 and 1.80±0.18. In the same way, mean values of pre and post VAS scores for reticular and mixed forms of OLP were 4.29±0.38, 1.45±0.40 and 7.42±0.95, 3.28±0.53 respectively. Differences in pre and post VAS scores were found to be statistically significant among all forms of OLP (Table 1).

Complete remission/size reduction of the lesion was noted down in sixty-five subjects (≈48%) in 18-24 months of tacrolimus therapy and partial remission/incomplete size reduction of lesions was seen in fifty-seven subjects (≈42%) in 24-30 months of therapy (p<0.05) (Table 2).

**Table 2: Response to tacrolimus therapy for various time duration among study subjects**

| Response to therapy | Duration of tacrolimus therapy | Percentage of group (approximately)* |
|---|---|---|
| **No response/ recurrence** | 4-6 months | 10% (n=13) |
| **Partial remission/ incomplete size reduction of lesion** | 18-24 months | 42% (n=57) |
| **Complete remission/ size reduction of lesion** | 12-18 months | 48% (n=65) |

(*Level of significance; p<0.05)

No adverse effects including the development of candida infection were reported by any of the subjects under study. Moreover, the burning sensation diminished spontaneously on subsequent applications and it was present in only five patients.

## Discussion

Currently, OLP is clinically managed via corticosteroids (either orally or systemically). The second line of treatments includes retinoids; hydroxychloroquine; mycophenolate mofetil; azathioprines; UV phototherapies; and pimecrolimus.[9]

Topical tacrolimus is a new management modality that acts as an immunomodulator. It is a noncorticosteroidal agent. Pharmacologically it is a calcineurin inhibitor that has been approved for management of atopic dermatitis. This molecule comes from the macrolide family that is multifold more potent than cyclosporine with better percutaneous absorption.[10]

On analysis, the mean age (in years) including standard deviation of present study subjects was reported as 41.25±3.4 years. Females outnumbered male subjects. These findings were comparable with others.[11, 12]

We observed that mean values of pre and post VAS scores in the domain of erosive type of OLP were 9.47±1.22 and 2.84±0.27. These observations are comparable with another study from Maharashtra, where the completely resolved or distinctly reduced lesions after the intervention was captured among nearly half of study subjects (47.3% or 43.3% respectively) and only one-tenth of study subjects (9.3%) had complete remission.[13]

Comparable results were also obtained by Nishu Vakil, et al.,[14] who observed that mean values of pre and post VAS for the atrophic form or erosive form of OLP were 7.82±0.56, 1.71±0.22 or 9.35±1.02, 2.96±0.24 respectively. Similarly, mean pre and post VAS scores for reticular and mixed forms of OLP were 4.16±0.44, 1.32±0.34 and 7.36±0.59, 3.33±0.48 respectively. Statistically significant results were obtained between pre and post-treatment values on the VAS among all forms of OLP.

Azizi, et al.,[15] estimated the efficacies of the two different interventions for treating OLP (erosive form) where one group received the adcortyl (ointment, topical) and other group received the tacrolimus (ointment, topical) and it was revealed that nearly half of subjects have shown an improvement in both symptoms (57.3%) and signs scores (55.8%), but results for this study might not be comparable with present study due to inclusion of subjects with the only erosive form of OLP and application of some other score systems for symptoms, along with the short duration of the study (four weeks only) in that study. Giustina, et al.,[16] proved the efficacy of isotretinoin (0.1%, topical gel) as applying it over the lesion for two times a day continuously for nearly

wo months (eight weeks), effectively improved the symptom among the majority of subjects (90.0%) with OLP.

In a clinical study, Raj AC, et al.,[17] estimated the efficacy of the dapsone intervention for treating OLP (resistant and erosive form) and it was revealed that nearly half of subjects have shown an improvement in both symptoms scores of 0 (54.4%) and 1 (45.6%) while about four-fifth of subjects (83.3%) had shown improvement in signs scores of 0.16.

Sahebjamee M, et al., [18] estimated the efficacies of the two different interventions for treating OLP where one group received the retinoic acid (topical, 0.05%) and other group received the triamcinolone acetonide (topical, 0.1%) and it was revealed that there was a statistically significant difference in efficacies of two interventions for the treatment of different forms of OLP such as atrophic form ($p<0.05$) and erosive form ($p<0.05$) and retinoic acid was proven to be more effective.

To conclude, study subjects after intervention with topical tacrolimus (0.1%) and Oraguard-B paste reported significant improvement in pain within the short reference of time. No adverse effect was reported even after a follow-up period of two years. This provided us with a new line of management with promising results. Randomized-controlled trials are warranted to validate the results of this study.

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