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Comparison Between the Efficacy of Clobetasol Ointment and Tacrolimus Ointment for the Treatment of Oral Lichen Planus

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ABSTRACT

Objectives: To evaluate the effectiveness of topical Tacrolimus 0.1% versus Clobetasol 0.05% in treating symptomatic oral lichen planus in terms of clinical score and visual analogue scale.

Materials and Methods: A one year randomized, comparative research of 60 patients with clinically and histologically proven Oral Lichen Planus was carried out. The patients were divided into two groups and given topical Tacrolimus or Clobetasol for a period of six weeks. The Data analysis was undertaken using SPSS Version 20.0.

Results: The mean Visual Analogue Scale (VAS) score in the Tacrolimus group decreased from 8.1± 1.1 to 1.4± 0.5 at the end of treatment at 6 weeks while in the Clobetasol group, mean VAS score declined from 8.9±0.9 to 1.5±0.5. Similarly, the clinical score in terms of the lesion size decreased from 3.8±0.8 to 1.0±0.6 in the Tacrolimus group and from 4.2±0.9 to 0.9±0.8 in the Clobetasol group. Overall, despite a significant drop in mean lesion size from baseline, the two groups showed comparable mean sizes at the end of the trial period. (*p*-value, 0.61).

Conclusion: It was found Topical Tacrolimus is equally efficacious as Clobetasol in the treatment of symptomatic Oral Lichen Planus.

Keywords: Clobetasol, Data Analysis, Humans, Oral Lichen Planus,Tacrolimus, Visual Analogue Scale

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INTRODUCTION

Oral Lichen Planus (OLP) is a debilitating condition affecting the oral cavity of unknown etiology requiring long-term management and clinical surveillance. Lichen planus (LP) was initially described as a chronic inflammatory disease that affects the skin, scalp, nails, and mucosa, with the potential for malignant transformation, by English dermatologist Erasmus Wilson in 1869. [1] OLP affects people from all ethnic backgrounds and is more common in women. It

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constitutes 9% of all white lesions affecting the oral cavity. While around 25% of all LP patients have solitary oral lesions, roughly 50% of patients with cutaneous lesions also have oral lesions. In contrast, only 15% of patients with Oral Lichen Planus acquire cutaneous lesions. OLP is designated as a potentially malignant condition with a malignant transformation rate from 0.4 to 12.5% .[2]

OLP is chronic in nature with periods of quiescence alternating with periods of exacerbations. Signs and symptoms of OLP are reduced during periods of inactivity. Precipitating factors similar to Koebner phenomenon such as sharp cusps, dental procedures, rough dental restorations, irritation from tobacco products, para functional habits like lip biting or cheek biting and ill-fitting dental prosthesis can all act as potential triggers and aggravate the lesions during the active phase of the disease.[1]

Though the precise etiological agent is unknown, it is hypothesized that the CD8 +T cell-driven immunological response is a key mediator in the pathogenesis of OLP.[4]

The bilateral buccal mucosa is the most commonly involved location. [5]. The spectrum of clinical manifestations ranges from asymptomatic lesions to incapacitating pain and burning sensation along with intolerance to hot and spicy foods that adversely affects the quality of life.

The diagnosis of oral lichen planus is based on a combination of clinical and histological characteristics, as proposed by Van der Meij and van der Waal in the 2003 updated World Health Organization Criteria.[6]

The treatment's primary purpose is to alleviate symptoms and extend periods of remission. Traditionally, corticosteroids have been the time-honored therapy for Oral Lichen Planus. Depending on the severity of the lesions and the degree of systemic involvement, they can be administered topically or systemically. Other treatment modalities include topical and systemic retinoids, steroid-sparing agents like Sirolimus and Mycophenolate mofetil (MMF), topical immune modulators like tacrolimus, pimecrolimus, levamisole, antimalarials, azathioprin, thalidomide, photo-chemotherapy, laser treatments, and surgery.[7]

Corticosteroids reduce inflammation by reducing leukocyte exudation and forming soluble inflammatory mediators, while maintaining cell membrane integrity by inhibiting phagocytosis, releasing lysozymes, and stabilizing lysosome membranes.The efficiency of corticosteroid therapy in OLP patients varies between 30-75% for moderate to highly efficient Corticosteroids and 56-75% for clobetasol propionate.[8]

Tacrolimus (FK-506 or fujimycin) is a macrolide immunosuppressive agent belonging to the category of calcineurin inhibitors. Streptomyces tsukabaensis, a bacteria identified in the soil near Tsukuba, Japan, is responsible for its production.

Tacrolimus reverses OLP pathogenesis by binding to FK506-binding proteins, impairing the calcium-dependent signal transduction pathway required for T lymphocyte activation. It inhibits mast cells as well as pro-inflammatory mediators including interleukin-8 (IL-8). It also suppresses T lymphocyte IL-2 synthesis by decreasing calcineurin phosphatase, which then inhibits nuclear gene transcription of IL-2 cytokines alongside other pro-inflammatory cytokines such as IL-4 and IL-5. As a result, activation and differentiation of inflammatory cells such as T lymphocytes, eosinophils or neutrophils is suppressed.[9]

The US Food and Drug Administration (FDA) authorized Tacrolimus in the year 2000 for the management of moderate to severe atopic dermatitis in individuals older than two years. It is approximately 100 times more potent than cyclosporine and having a lower molecular weight compared to cyclosporine, it has a greater mucosal penetration which makes it suitable for topical use.[10]

Tacrolimus 0.1% ointment is an efficient and well-accepted topical treatment for OLP with minor local adverse effects.[11] Topical Tacrolimus has been proposed for OLP treatment since 1999.

Clobetasol, a synthetic corticosteroid analogue of prednisolone, is recognized as an extremely powerful halogenated topical steroid, with a reported rate of complete remission ranging from 47% to 75%. It works by stopping inflammatory processes such edema, fibrin deposition, vasodilation, and phagocytic activity.[12]

Previous research and clinical trials have compared topical steroids including Triamcinolone to Tacrolimus. However, only three clinical studies that directly compared tacrolimus with Clobetasol have been

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conducted so far, according to a systematic review and meta-analysis by Chamani et al.[13] Tacrolimus was found to be more effective presumably according to two investigations, although Radfar et al. found no discernible change.[14] A similar investigation comparing an ultra -potent corticosteroid with an immunosuppressive has not been carried out previously in Pakistan. Thus, the present investigation sought to examine the effectiveness of topically applied tacrolimus 0.1% and clobetasol 0.05% for the treatment of symptomatic OLP in a randomized clinical trial.

MATERIALS AND METHOD

To evaluate the effectiveness of topical Clobetasol 0.05% and Tacrolimus 0.1% in terms of Clinical Score and Visual Analogue Scale as the primary outcomes for the treatment of symptomatic Oral Lichen Planus, a randomized controlled trial was carried out in the department of Oral and Maxillofacial Surgery at PIMS. Sample size calculation was done using the WHO sample size calculator at the significance level of 5% which turned out to be 60 patients with 30 patients in each group. All in all 60 patients from either gender in the age range between 30 to 70 years were recruited with clinically and histologically proven OLP based on the 2003 modified WHO criteria. Pregnant and lactating women, patients with systemic and multi-focal disease involvement having concomitant skin and genital lesions, patients with suspected or known hypersensitivity to the used medicaments, and patients with histologically proven dysplastic lesions were excluded from the study.

A formal approval from the Ethical Review Board (ERB) was obtained. Informed verbal and written consent given by all the participants in the study. A total of sixty patients were recruited in the study. A comprehensive clinical evaluation was conducted on the screening day for OLP, followed by a diagnosis and histopathological confirmation through a biopsy under local anesthesia. Study participants were randomly allocated to the two interventional groups, Group A and Group B. Group A patients received 0.1% Tacrolimus ointment while Group B patients received 0.05% Clobetasol ointment. Following screening, all participants were subjected to a washout period of 2 weeks during which they received no treatment. After the washout period, the patients were directed to apply 0.1% Tacrolimus ointment or 0.05% Clobetasol ointment (depending on the group) three times per day with their finger on dried lesions for a total of six weeks. They were instructed to refrain from eating, smoking, or drinking for half an hour after application to permit prolonged adherence of the medication with the oral mucosa. To gauge their adherence to the prescribed regimen, it was advised to maintain a diary throughout the research period. During the research, no rescue medications were permitted. Performa-based evaluations were carried out during the three consecutive visits after commencing treatment at four-time points i.e. at baseline (before starting treatment) and on the 1st, 4th, and 6th week. Using a visual analog scale (VAS) with pain scores ranging from 0 (no pain) to 10 (the most severe pain experienced), patients were asked to rate their level of pain at each visit. Objective recording of the lesion in terms of the target lesion size and the surface extent of the atrophic, erosive, or striated lesion area was performed using a meter ruler utilizing the five-tiered scoring system devised by Thongprason et al. in 1992 and photographs were taken simultaneously with the rule in place. The Thongprasom Classification (TC) classifies white striae based on their erosive area, atrophic area, mild white striae without an erythematous area, and normal mucosa, with scores ranging from 0 to 5. The aforementioned protocol has been summarised in Figure 1.

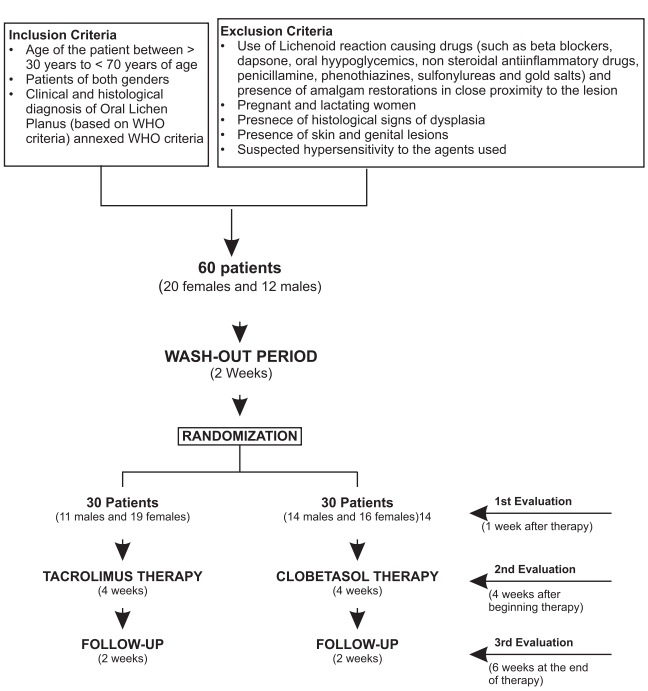

Figure 1:Trial diagram

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The data was analyzed by using SPSS version 20.0. For quantitative variables including the patient's age, the Clinical Score for determining the size of the lesion, the duration of the lesion, and the VAS score for pain. Mean and standard deviation were determined. For qualitative elements including the patient's gender and the type of oral lichen planus, frequency and percentage were calculated. The mean lesion size and VAS were compared between the two interventions using independent samples t-test. The mean lesion size was stratified according to sex, age, and lichen planus variant using t-test and ANOVA test.

Chi-square test was used to test the proportion of Clinical Score and Efficacy between the two groups. Post-stratification chi-square test was applied. For stratification, duration of effect modifiers such as lesion duration and type of oral lichen planus was used. A *p*-value of < 0.05 was denoted as significant

RESULTS

All patients experienced burning sensations, intolerance to hot and spicy foods and had bilateral Wickham's striations on clinical presentation. Pain was comparable between both groups with a slight predominance in the clobetasol group i.e. 22(73.3%) compared to 19(63.3%) in the Tacrolimus group.

Regarding the evaluation of the primary outcomes, at baseline the mean VAS was 8.1 ± 1.1 in Group A compared to 8.9 ± 0.9 in Group B and this difference was found significant. At the interim assessment following one and four weeks after commencing treatment, the difference in the mean VAS scores turned out to be statistically significant (*p*-value, <0.001) in Group A as opposed to Group B i.e. 6.1 ± 1.3 vs 7.6 ± 1.1 in Group B after 1 week and 3.9±0.9 vs 4.8±0.8 four weeks after commencing treatment. However, at the end of the treatment after 6 weeks, the difference in the mean VAS scores between the two study groups was found to be insignificant with the *p*-value being 0.62. These findings have been summarized in Table 1.

Table I: Mean VAS comparison between the two groups

	Group A (0.1% Tacrolimus) (n=30)	**Group B (0.05% Clobetasol) (n=30)**	***p*-value**
Pain score VAS (mean ± SD)			
At baseline (pre treatment)	8.1 ± 1.1	8.9 ± 0.9	0.001
At 1 week	6.1 ± 1.3	7.6 ± 1.1	<0.001
At 4 weeks	3.9 ± 0.9	4.8 ± 0.8	<0.001
At 6 weeks	1.4 ± 0.5	1.5 ± 0.5	0.62

The mean lesion size according to the Clinical Score (CS) was 3.8 ± 0.8 cm^2 in tacrolimus group and 4.2 ± 0.9 cm^2 in clobetasol group at baseline. After one week of therapy, there was a statistically significant decrease in the mean lesion size in both interventional groups, with Tacrolimus 2.8 ± 0.6 cm^2 and Clobetasol 3.5 ± 0.5 cm^2 respectively. Similarly, after 4 weeks of initiation of therapy the mean lesion size was 1.8 ± 0.4 cm^2 in the Tacrolimus group as compared to 2.2 ± 0.4 cm^2 in the Clobetasol group, and this difference was also found to be significant as clinically evident in Figure 2 and 3.

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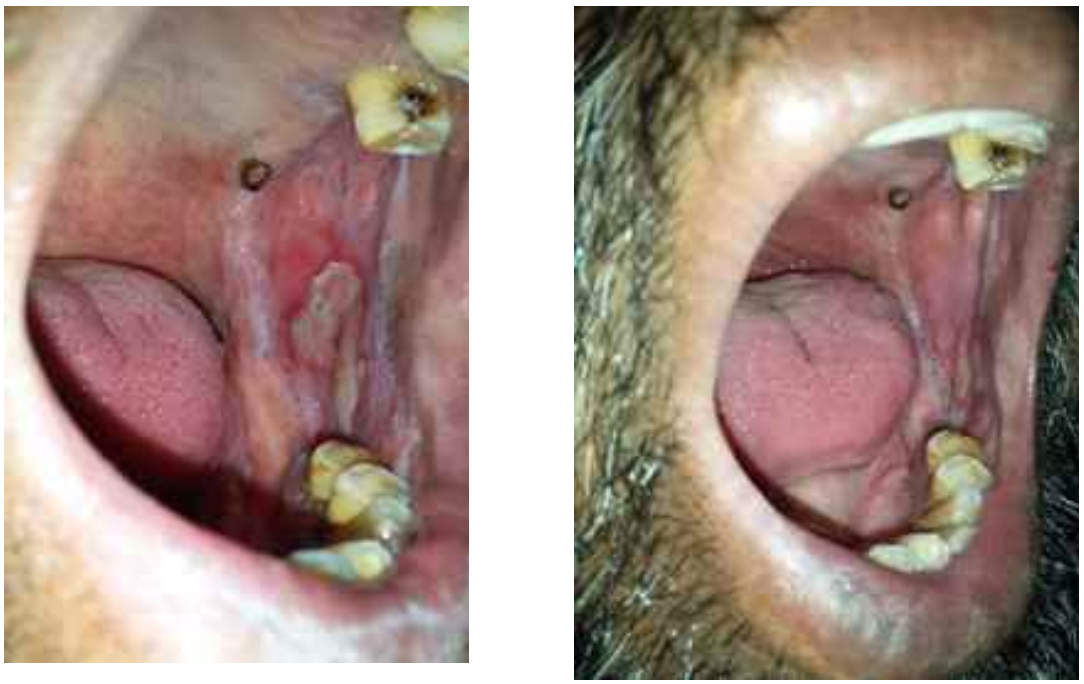

Figure 2: Clinical photographs before and after application of topical tacrolimus 0.1%

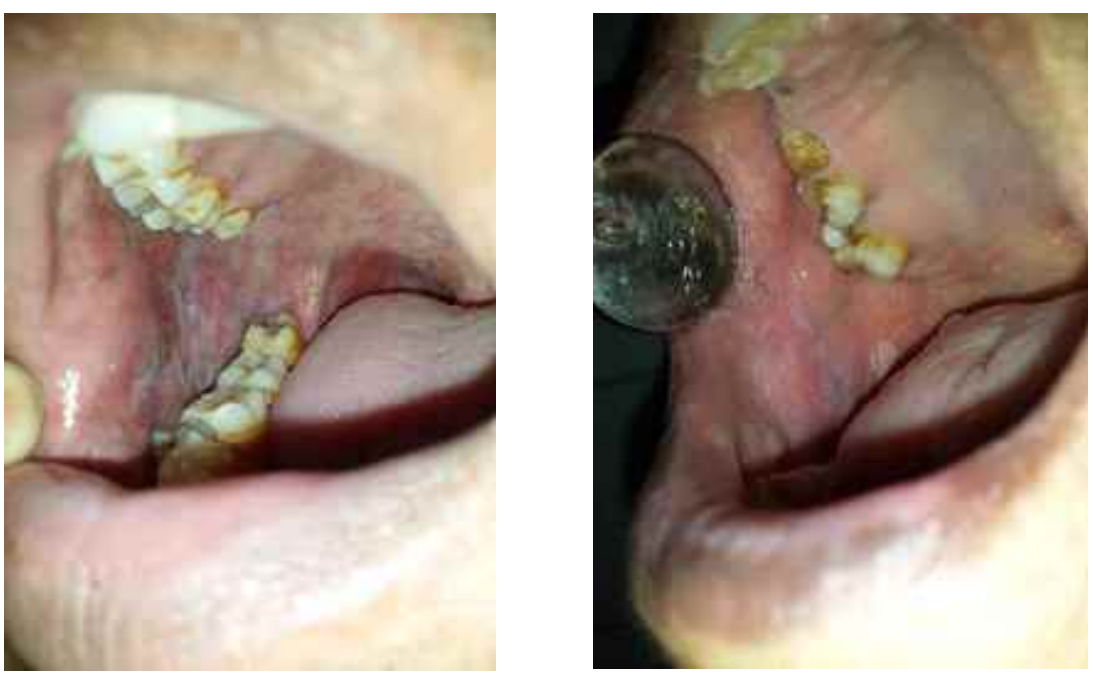

Figure 3: Clinical photographs before and after application of topical clobetasol 0.05%

Towards the end of the treatment, although the mean lesion size showed a significant reduction from the baseline in both groups, the cumulative reduction was found to be insignificant i.e. 1 ± 0.6 (Tacrolimus) vs 0.9 ±0.8(Clobetasol) as shown in Table II with the p-value being 0.61.

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Table 2: Comparison of mean lesion size according to clinical score between the two groups

	Group A (0.1% Tacrolimus) (n=30)	Group B (0.05% Clobetasol) (n=30)	*p*-value
Lesion size per clinical score (mean ± SD)			
At baseline (pre- treatment)	3.8 ± 0.8	4.2 ± 0.9	0.08
At 1 week	2.8 ± 0.6	3.5 ± 0.5	<0.001
At 4 weeks	1.8 ± 0.4	2.2 ± 0.4	<0.001
At 6 weeks	1.0 ± 0.6	0.9 ± 0.8	0.61

DISCUSSION

The treatment of Oral Lichen Planus presents a unique challenge to both the treating doctors and affected patients alike as it is a chronic, debilitating, immune mediated condition and no single treatment modality till date has been effective in offering a radical cure. While steroids are considered as a gold standard in the treatment of Oral Lichen Planus, side effects like candidiasis, xerostomia, sore throat, hirsutism and adrenal insufficiency leading to Cushing disease preclude their long- term usage. [15]

Alternatively immune suppressive agents like calcineurin inhibitors that directly intercept the causative pathways in OLP are being explored. Tacrolimus, commonly known as FK506, is a macrolide immunosuppressive drug that was first authorized for the treatment of atopic dermatitis and works by preventing the generation of IL-2 by T lymphocytes. [16]

The patients who participated in our study shared demographic traits with studies of a similar nature. OLP shows a female predilection with females being twice as commonly affected[17], and in our study the percentage of females was 58% with 35 females and 25 males in both interventional groups. This can be attributed to the fact that OLP has an auto immune pathogenesis and hence is more prevalent in females. Our patients had both erosive and reticular OLP, whereas most prior reports focused on erosive OLP alone. In addition, the most common sub-site for OLP was buccal mucosa in our study which was in line with the established findings.

Our observation indicates that the mean VAS in the Tacrolimus group exhibited a greater initial improvement compared to Clobetasol i.e. from 8.1±0.9 to 6.1±1.3 after 1 week of treatment. A similar result was observed in the study conducted by Hettiarachchi et al who also compared mean VAS scores on both sides of the oral cavity.[18] The mean VAS dropped from 1.91±0.87 to 0.71±0.76 on right side and from 1.85±0.78 to 0.32±0.73 on the left side three weeks after commencing treatment. A complementary study by Vente et al. have also demonstrated promising initial therapeutic results of topical tacrolimus in patients suffering from severe recalcitrant erosive mucosal LP.[19]

Regarding subjective assessment, the Clinical Score in terms of lesion size decreased from 3.8±0.8cm^2 to 1.8±0.4 cm^2 in the Tacrolimus group and from 4.2±0.9 cm^2 to 2.2±0.4 cm^2 in the Clobetasol group four weeks after starting treatment. In the study by Hettiarchchi et al. the mean lesion size decreased from a baseline value of 2.71 to 1.53 on the right side and from 2.56 to 1.56 on the left side in the Tacrolimus group. In the clobetasol group a reduction from 2 to 1.5 on the right and from 2 to 1.74 on the left side was observed respectively.

In our study, at the end of the treatment i.e. six weeks, though the mean lesion size decreased significantly from the pretreatment values, the difference in the lesion size was found to be comparable between the two groups with the p value of 0.61. This observation was paralleled to the randomized double-blind study conducted by Radfar et al. comparing tacrolimus 0.1%

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ointment with clobetasol 0.05% ointment who concluded that although tacrolimus induced a better initial therapeutic response than clobetasol, mean lesion sizes and mean pain measures did not differ significantly between the two treatment groups post treatment.

The main limitations of this study include its small sample size, lack of placebo and lack of assessment of plasma levels of tacrolimus. However, small sample sizes and short observation periods have also been found to be limitations in all the previously reported trials. Although many patients in the present study were followed up beyond the 6-week study period, a significant proportion of patients failed to report for review beyond 8 weeks on average, and thus, further meaningful analysis of the outcome was not realistic for the reasons stated earlier. Nevertheless, this limitation does not invalidate the results already obtained. However, future studies should focus on achieving larger sample sizes and longer follow-up periods.

CONCLUSION

Our clinical investigation's results showed that topical Tacrolimus 0.1% was just as successful in treating symptomatic OLP as Clobetasol 0.05%. Although topical Tacrolimus exhibited a better initial therapeutic response compared to Clobetasol, cumulatively the overall response at the end of the treatment period was similar. Topical Tacrolimus can be considered as an alternative to steroids in patients having recalcitrant OLP not responsive to potent corticosteroids and patients at risk of developing candidiasis.

DISCLAIMER

None to declare.

CONFLICT OF INTEREST

There is no conflict of interest among the authors.

ETHICAL STATEMENT

This study was conducted and submitted for publication after taking approval from ethical review board of Shaheed ZulfqarAli Bhutto Medical University Islamabad, ERB No.F-1/2015/ERB/SZABMU/177

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AUTHORS CONTRIBUTION

Conception and design of the study: S. Zafar,

Acquisition of data: K. Shah, A. Iftikhar, Z.A. Rana

Analysis and interpretation of data: S. Zafar, A. Iftikhar

Drafting of the manuscript: S. Zafar

Critical review of the manuscript: S.A. Khokhar, F. N. Akhter

Approval of the final version of the manuscript to be published: S. Zafar, A. Iftikhar, Z.A. Rana, F. N. Akhter, S.A. Khokhar, K. Shah

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