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Research Article

EVALUATION OF EFFICACY OF TOPICAL APPLICATION OF 5% AMLEXANOX ORAL PASTE AND 0.1% TRIAMCINOLONE ACETONIDE ORO-MUCOSAL PASTE IN THE TREATMENT OF ORAL LICHEN PLANUS

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ABSTRACT

Aims: The aim of the present study was to evaluate the efficacy of topical application of 5% Amlexanox oral paste and 0.1% Triamcinolone Acetonide oro-mucosal paste in the treatment of Oral Lichen Planus. Objectives: The objectives were to assess the clinical symptoms , burning sensation or pain, erythematous change ,to assess the response to the treatment of Oral Lichen Planus by assessing reduction in burning sensation or pain, erythematous areas and white striae with size of the lesion and to compare the overall treatment response of two drugs – 5% Amlexanox oral paste and 0.1% Triamcinolone Acetonide oro-mucosal paste. Materials and Methods: 60 patients with Oral Lichen Planus were included in the study. After histopathological confirmation, the selected patients were divided into two groups – group A and group B. Patients in group A received 5% Amlexanox Oral Paste (n=30) and patients group B received 0.1% Triamcinolone Acetonide Oro-mucosal Paste (n=30) and their responses to the treatment were recorded. Results: Both the groups were asymptomatic at the end of the treatment course. But the rate of reduction of clinical sign stage was better in group B compared to group A. Group A showed 60% reduction in the clinical sign stage were as the group B showed 98% reduction at the end of 3 months. Conclusion: Topical application of 0.1% Triamcinolone Acetonide is more effective than Topical application of 5% Amlexanox in the treatment of Oral Lichen Planus. However Amlexanox can be used effectively for reducing the pain/burning sensation and erythematous area, devoid of the usual adverse effects associated with the use topical steroids, in patients for whom topical steroids are contraindicated.

Key words:- Amlexanox, Oral Lichen Planus, Triamcinolone Acetonide, Topical steroids.

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INTRODUCTION

Oral Lichen Planus (OLP) is a chronic inflammatory mucocutaneous disease with prevalence

Corresponding Author **Dr. Vidhya Kalanjiam Email: -** vidhya.kalanjiam@gmail.com rates varying from 0.5% to 2.2%. The proportion of women affected by it is higher when compared to men and it is found rarely in children. The typical age of presentation of this lesion is between 30 to 60 years [1].

The etiology of OLP is unknown, but from the evidences OLP is viewed as a T-cell-mediated

immunological response to an antigen expressed at the basal layer of the oral mucosa. Oral Lichen Planus can cause symptoms ranging from burning sensation to severe pain, especially during the intake of hot and spicy foods thereby reducing quality of life and causing difficulty in eating, speaking and/ or brushing the teeth and ulcerations [2].

Treatment is palliative, aimed at relieving pain among patients from painful, erosive and ulcerative forms of the disease; not curative [3]. Wide spectrum of topical and systemic therapies, surgery, Psoralen therapy with Ultraviolet light A (PUVA) and Laser are being used in managing OLP. It is considered a potentially malignant condition and long-term close surveillance is recommended.

Complete cure is very difficult to achieve because the exact cause for OLP is still not clear. Topical Corticosteroids are conventionally used and have proved to be effective in the treatment of OLP because of its anti-inflammatory and immunosuppressive action. But because of chronicity many patients need to apply topical steroid repeatedly to keep the condition stable. Long term steroid therapy may cause serious side effects such as Pseudomembranous Candidiasis, thinning of epidermis, mucocutaneous atrophy, hypopigmentation, delayed wound healing and adrenal insufficiency [4]. In addition, the use of corticosteroids are contraindicated in patients with hypertension, diabetes, peptic ulcer, renal and immunosuppressive cardiac failure, pregnancy, conditions and in Tuberculosis [5].

Amlexanox ($C_{16}H_{14}N_2O_4$) is a topical antiinflammatory drug, anti-allergic, immunomodulator that has been developed as an oral paste (containing 5% Amlexanox) for the treatment of patients with recurrent aphthous ulcerations. Amlexanox can inhibit the formation and release of histamine, TNF- α and leukotrienes from the mast cells, neutrophils, and mononuclear cells through increasing intracellular Cyclic Adenosine Monophosphate content and also has membrane stabilizing effect [6]. Therefore the strong anti-inflammatory effects with few adverse reactions in recurrent aphthous ulceration and several inflammatory diseases make Amlexanox a very strong treatment option for OLP.

Materials and methods:

After selecting the patients with the clinical criteria white and /or red lesions with very fine radiating grayish-white lines with symptoms of pain/burning sensation, erythematous areas and satisfying the inclusion criteria, socio-demographic-economic characteristics, past history and informed consent were obtained from the patient after explaining the complete detail about the study. Inclusion criteria of the study was patients with symptomatic OLP (pain and or burning sensation) who were willing to undergo biopsy and apply the medication given to them. Patients who had a history of malignancy,

immunocompromised diseases, current systemic or generalized infections, history of pregnancy or breast feeding and those who have received topical or systemic immunosuppressants, retinoids or any other systemic therapies known to cause or suspected to have an effect on OLP within the last 4 weeks and patients allergic to the drugs used in the study were excluded from the study

To evaluate the efficacy of topical application of two drugs on Oral Lichen Planus, the patients were divided into two groups - group A and group B, after histopathological confirmation. Both groups had 30 patients each. The allocation of patients was done randomly. Patients in group A received 5% Amlexanox Oral Paste and patients group B received 0.1% Triamcinolone Acetonide Oral Paste. Both the groups were asked to apply the oral paste four times daily after food by the means of a finger on the lesion. Patients were advised not to rinse, eat or drink anything for the next half an hour after the application of the oral paste. And were instructed to come to the hospital for the evaluation of progression of the treatment for 3 months (follow up was done on the first week, second week, fourth week, sixth week and third month of treatment period).

The overall response of the treatment was studied by observing the reduction in burning sensation or pain, erythematous areas, white striae with size of the lesion(clinical sign stage) in patients treated with Topical application of 0.1% Triamcinolone acetonide oral paste and patients treated with 5% Amlexanox oral paste.

The intensity of pain/burning sensation was determined using a Visual Analogue Scale recorded by clinically examining the patient. During each periodic visit for the period of 3 months the presence /absence were recorded for each patient.

Clinical sign stage response to the topical application of two drugs was recorded according to the criteria given by Thongprasom et al [7]. This criteria has been commonly used to assess the response of the oral lichen planus over the course of the treatment. The criteria has six scores spread between 0-5 based on the presence/absence of the white striae and the size of the lesion. By clinically examining the lesion for the presence of the white /red lesion with the Wickham striae and measuring the size of the lesion along the longest diameter of the lesion scoring was done. The size of the lesion was measured using a divider and scale. The criteria for scoring are given below.

Score 5 = white striae with erosive area more than 1 cm

Score 4 = white striae with erosive area less than 1 cm

Score 3 = white striae with atrophic area more than 1 cm

Score 2 = white striae with atrophic area less than 1 cm Score 1 = mild white striae, no erythematous area

Statistical analysis of the data was performed using Statistical Package for Social Science (SPSS) for Windows version 17 software. For analysing the relation a non-parametric method Mann Whitney Test and Chi square test was used. Statistical significance was considered to be 5% or p < 0.05 level.

RESULT:

A total of 60 patients with OLP satisfying the inclusion criteria were included in the study to evaluate the efficacy of 0.1% Triamcinolone Acetonide and 5% Amlexanox Oral Paste in OLP. The distribution of age group among 60 patients included in the study were 3 patients (5%) in the 10-19 age group, 13 patients (22%) in the 20-29 age group, 14 patients (23%) in 30-39 age group, 13 patients (22%) in 40-49 age group, 12 patients (20%) in 50-59 age group and 5 patients (8%) > 60 age group.

Out of 60 patients 33 patients were female (55%) and 27 patients were male (45%).Regarding the distribution of clinical types in the 60 patients, 39 patients (65%) had reticular type of OLP, 15 patients (25%) had erosive type, 2 patients (3.3%) had bullous type, 3 patients (5%) had papular, 1 patient (2%) had plaque-like and none had atrophic type of OLP.

The total number of individual sites that were affected in the 60 patients was 90 because some patients had lesions in multiple sites. 38 patients (63%) had lesion only at single site and 22 patients (37%) had lesions in multiple sites. Among the 90 sites that were treated in the 60 patients, 58 lesions (64%) were present on buccal mucosa/buccal vestibule, 10 lesions (11%) were on labial mucosa/ labial vestibule. 13 lesions (14%) were on tongue, 3 were on gingiva (3%), 2 lesions each on retromolar trigone (2%), palatal mucosa (2%) and floor of the mouth (2%). buccal mucosa was clearly the predominately affected site among the 60 patients.

Based on the nature of the lesion, 57 patients (95%) had bilateral presentation and 3 patients (5%) had unilateral presentation of the lesion intraorally.

Comparing the response of OLP to the treatment using 5% Amlexanox oral paste and 0.1% Triamcinolone Acetonide by assessing reduction in burning sensation or pain, erythematous areas and clinical sign stage (white striae with size of the lesion), we found that patients in group A had mean \pm standard deviation value for pain or burning sensation VAS score during pre-treatment as 5.73 ± 1.68 . This value remained the same for Day 1 but for during 1st week, 2nd week, 4th week, 6th week and 3rd month the mean \pm standard deviation values were observed as 4.43 ± 1.45 , 2.5 ± 1.38 , 0.83 ± 1.02 , $0.07 \pm$ 0.25 and 0 ± 0 respectively. For group B the values at the same time interval was 5.63 ± 1.47 at pre-treatment and 4.03 ± 1.35 , 2.06 ± 1.31 , 0.5 ± 1.14 , 0.16 ± 0.91 and 0.03± 0.18 for 1st week, 2nd week, 4th week, 6th week and 3rd month respectively. (Table 1,Graph 1)

The mean reduction in pain/burning sensation in group A patients over the treatment course compared with the pre-treatment pain/burning sensation score (pre-treatment score -1^{st} week score, pre-treatment -2^{nd} week score, pre-treatment -3^{rd} week score and so on)

were 1.3 ± 0.99 , 3.23 ± 1.41 , 4.9 ± 1.54 , 5.67 ± 1.65 and 5.73 ± 1.68 for the 1st week, 2nd week, 4th week, 6th week and 3rd month. (Table 2,Graph 2)

Compared to the mean pre-treatment pain/burning sensation score of 5.73, these values corresponds to 22.67%, 56.40%, 85.47%, 98.84% and 100% reduction in pain/burning sensation. For group B, the mean reduction in pain/burning sensation score during the treatment period was 1.6 ± 0.97 , 3.53 ± 1.25 , 5.13 ± 1.36 , 5.47 ± 1.48 and 5.6 ± 1.43 for 1st week, 2nd week, 4th week, 6th week and 3rd month. The percentage reduction from the mean pre-treatment pain score of 5.63 was 28.40%, 63.31%, 91.12%, 97.04% and 99.40% respectively.

Analysing the pre-treatment VAS score with the course of treatment using Mann-Whitney non-parametric test, the p values observed were - 0.24, 0.386, 0.536, 0.623 and 0.742 for the 1st week, 2nd week, 4th week, 6th week and 3rd month. Since the p value was greater than 0.05, there was no significant difference between the two groups. From this data, it can be inferred that both the drugs were equally effective in reducing the pain/burning sensation.

Analysing the effect of Topical application of two drugs on erythematous areas over the course of the treatment, group A had 16 patients with erythematous areas before the beginning of treatment. As the treatment proceeded, the number of patients during 1st week, 2nd week, 4th week, 6th week and 3rd month reduced as 16, 14, 7, 0 and 0 respectively. Compared to group A, group B had 15 patients with erythematous areas initially which reduced as 15, 10, 3, 0 and 0 respectively. From this data, it can be seen that by 6th week no patients had erythematous area in both the groups. Thus it was inferred that both the drugs were equally effective in reducing erythematous area.(Graph 5)

To analyse the effect of Topical application of the two drugs on clinical sign stage response (white striae and size of the lesion), individual site were taken into consideration because some patients had lesions at multiple sites. Total number of sites were 90 of which group A had 44 and group B had 46.

While the mean and standard deviation value for group A before starting the treatment was 2.82 ± 1.13 , the values reduced over the course of the treatment into 2.70 ± 1.15 , 2.36 ± 1.22 , 1.84 ± 1.01 , 1.5 ± 0.79 and 1.11 ± 0.78 during 1st week, 2nd week, 4th week, 6th week and 3rd month. The mean and standard deviation for pretreatment scores for group B was 2.91 ± 1.05 which reduced into 2.63 ± 1.08 , 1.87 ± 0.96 , 1.37 ± 0.90 , 0.41 ± 0.62 and 0.04 ± 0.21 during 1st week, 2nd week, 4th week, 4th week, 6th week and 3rd month. (Table 3,Gragh 3)

The mean and standard deviation of reduction in score in group A during 1^{st} week was 0.11 ± 0.32 which is 4.03% reduction and increased to 0.45 \pm 0.59, 0.98 \pm 0.51, 1.32 \pm 0.60 and 1.70 \pm 0.79 during 2^{nd} week, 4th

week, 6^{th} week and 3^{rd} month corresponding with 16.13%, 34.68%, 46.77% and 60.48% reduction of score. In group B the mean and standard deviation of reduction of score at week 1 were 0.28 ± 0.46 which increased to 1.04 ± 0.70 , 1.54 ± 0.78 , 2.5 ± 0.98 and 2.87 ± 1.07 during 2^{nd} week, 4^{th} week, 6^{th} week and 3^{rd} month. This value when expressed in percentages is 9.70% reduction during 1^{st} week, 35.82% reduction during 2^{nd} week, 52.99% reduction during 4^{th} week, 85.82% reduction during 6^{th} week and 98.51% reduction at 3^{rd} month.(Table 4,Graph 4)

A simple comparison with group A data shows that group B had greater reduction in the score during the

course of the treatment. Analysing the pre-treatment score with the course of treatment using Mann-Whitney non-parametric test, the p values observed were - 0.046, 0.00, 0.00, 0.00 and 0.00 for the 1st week, 2nd week, 4th week, 6th week and 3rd month. Since the p value was less than 0.05 starting 2nd week, there is significant difference between the two groups. From this data, it can be inferred that in reducing the white striae and size of the lesion (clinical sign stage), 0.1% Triamcinolone Acetonide oral paste had better effect than 5% Amlexanox oral paste starting from 2nd week till the end of treatment at 3rd month.

	Pre treatment	1 day	1 week	2 weeks	4 weeks	6 weeks	3 months
Group A mean ± std dev	5.73 ± 1.68	5.73 ± 1.68	4.43 ± 1.45	2.5 ± 1.38	0.83 ± 1.02	0.07 ± 0.25	0 ± 0
Group B mean ± std dev	5.63 ± 1.47	5.63 ± 1.47	4.03 ± 1.35	2.06 ± 1.31	0.5 ± 1.14	0.16 ± 0.91	0.03 ± 0.18
Group A Difference using Mean			1.30	3.23	4.90	5.67	5.73
Group B Difference using Mean			1.60	3.57	5.13	5.47	5.60

Table 1: Mean	pain/burning	sensation score d	luring course o	of treatment
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Table 2: Mean Reduction in	pain/ burning sensation sco	re between pretreatment and i	the course of treatment.

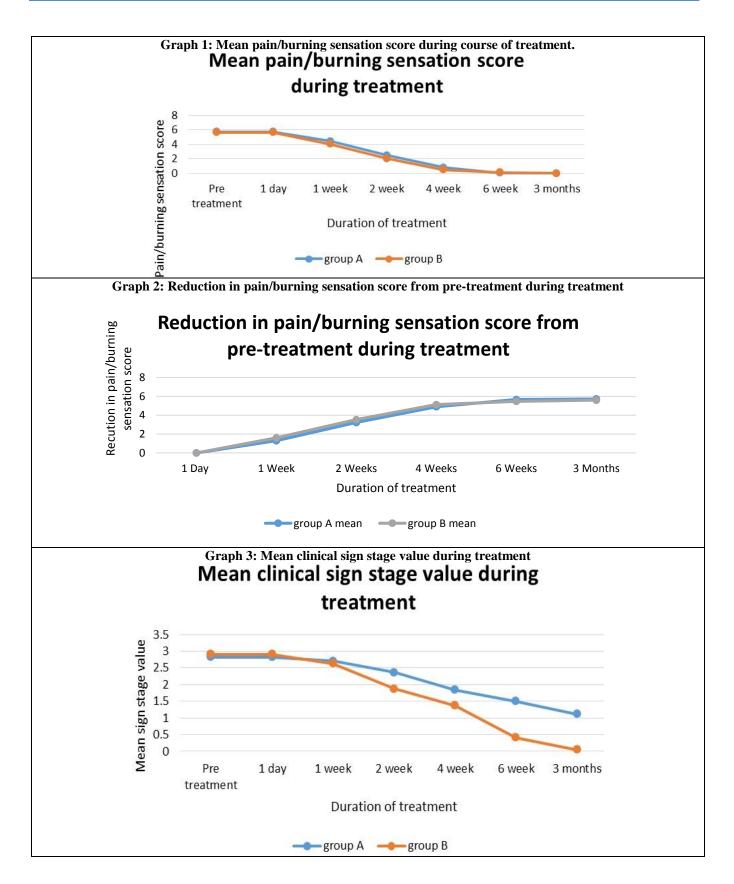
	1 Day	1 Week	2 Weeks	4 Weeks	6 Weeks	3 Months
Group A mean ± std dev	0 ± 0	1.3 ± 0.988	3.23 ± 1.406	4.9 ± 1.539	5.67 ± 1.647	5.73 ± 1.68
Group B mean ± std dev	0 ± 0	1.6 ± 0.968	3.53 ± 1.252	5.13 ± 1.358	5.47 ± 1.479	5.6 ± 1.429
group A percentage of reduction		22.67	56.40	85.47	98.84	100.00
group B percentage of reduction		28.40	63.31	91.12	97.04	99.40
p value		0.24	0.386	0.536	0.623	0.742

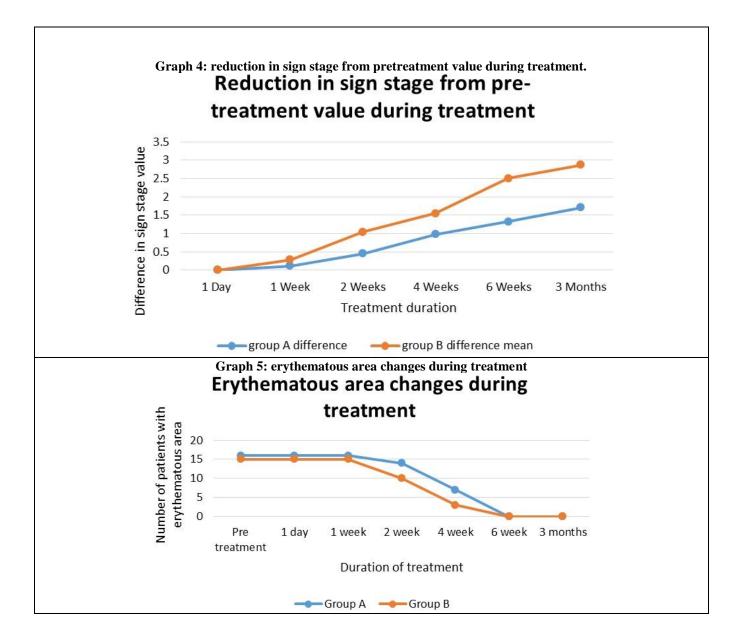
Table 3: Mean clinical sign stage during course of treatment.

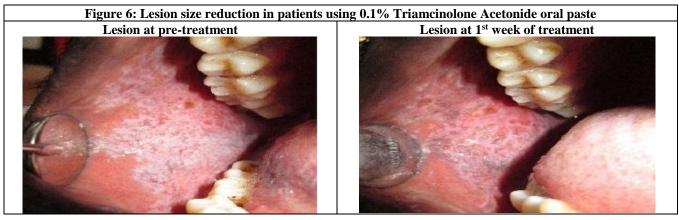
	Pre treatment	1 day	1 week	2 Weeks	4 Weeks	6 Week	3 months
Group A mean ± Std dev	2.82 ± 1.13	2.82 ± 1.13	2.70 ± 1.15	2.36 ± 1.22	1.84 ± 1.01	1.5 ± 0.79	1.11 ± 0.78
Group B mean ± Std dev	2.91 ± 1.05	2.91 ± 1.05	2.63 ± 1.08	1.87 ± 0.96	1.37 ± 0.90	0.41 ± 0.62	0.04 ± 0.21
Group A Difference using Mean		0	0.11	0.45	0.98	1.32	1.70
Group B Difference using Mean		0	0.28	1.04	1.54	2.5	2.87

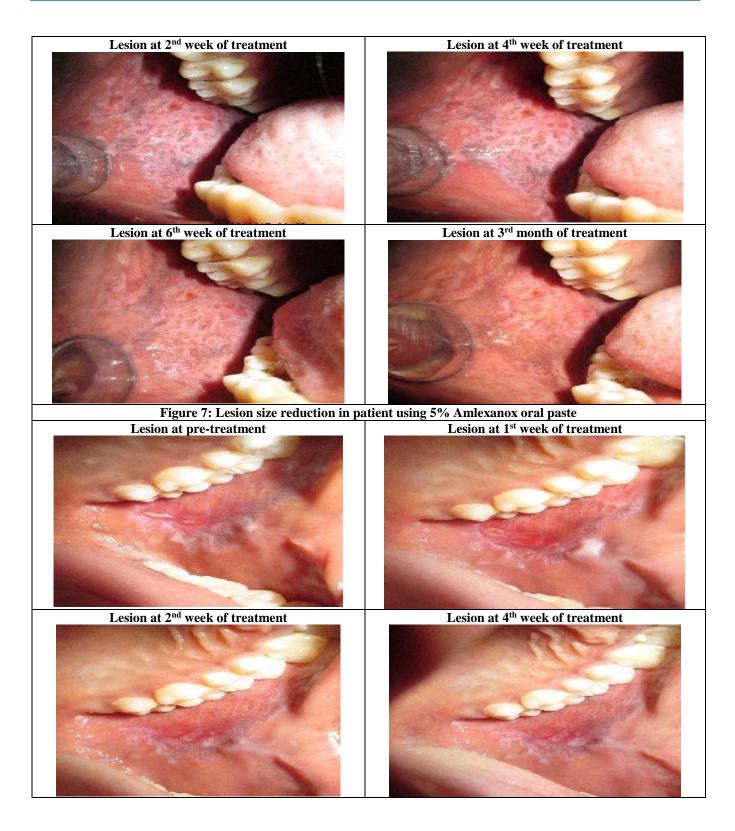
Table 4: Mean sign stage difference between pre-treatment and course of treatment.

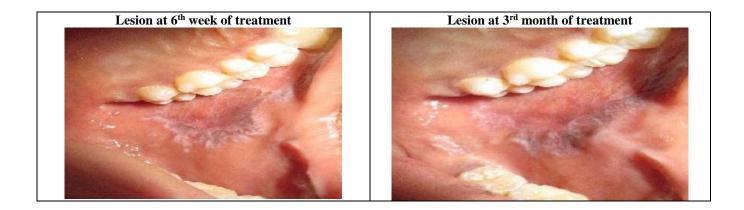
	1 Day	1 Week	2 Weeks	4 Weeks	6 Weeks	3 Months
Group A mean ± Std dev	0 ± 0	0.11 ± 0.32	0.45 ± 0.59	0.98 ± 0.51	1.32 ± 0.60	1.70 ± 0.79
Group B mean ± Std dev	0 ± 0	0.28 ± 0.46	1.04 ± 0.70	1.54 ± 0.78	2.5 ± 0.98	2.87 ± 1.07
Group A percentage of reduction	0	4.03	16.13	34.68	46.77	60.48
Group B percentage of reduction	0	9.70	35.82	52.99	85.82	98.51
p value		0.046	0.00*	0.00*	0.00*	0.00*











DISCUSSION:

Only few studies are present regarding the efficacy of Topical Amlexanox on OLP. Moreover the earlier studies had small sample size and were short term studies. So for a detailed analysis, we compared the efficacy of 5% Amlexanox oral paste with that of 0.1% Triamcinolone acetonide oral paste which is readily available for intraoral application.

Regarding the distribution of age group in our study, out of 60 patients, 52 were between 20-60 years age group, in that maximum number to about 14 patients were in 30-39 years age group. In this aspect, our sample set was different from the studies of Axéll et al [8], who have reported the peak of incidence of OLP in 50-57 years age group.

Among 60 patients, 33 were female and 27 were male. In our gender distribution, females outnumbered males by 55% to 45%. This distribution is consistent with the findings of Nagao et al [9] and Pakferat et al [10] in their studies females were 64.9% and males were 35.1% of their population.

According to Xue et al ^[11] the most common clinical type of OLP was reticular type (51.3%). Axéll et al ^[8] and Nagoa et al ^[9] have also reported reticular type as the most common clinical type of OLP with distribution of 77.3% and 91.6% respectively. In this study, about 39 out of 60 patients amounting to 65% had reticular type of OLP followed by erosive type which is comparable with the previous studies.

Regarding the distribution of site that is commonly affected by OLP, buccal mucosa was the predominantly affected site in this study at 63%, followed by tongue at 14%. Similar findings have been reported from the studies of Axéll et al [8] and Nagao et al [9] to support the fact that buccal mucosa is the commonly affected site.

Ali et al [12] in a study published in 2011, which was conducted on sample set similar to this study, reported the results of application of topical Triamcinolone Acetonide on patients with OLP. In their study conducted with sample set with mean age of 45.9 ± 9.91 consisting of 66% female patients they found that the mean pain score (recorded on a VAS) reduced from 5.20 ± 1.13 to 1 ± 0.47 within 4 weeks (reduction of 78.27%) and to 0.40 ± 0.51 (reduction of 92.37%) at the end of the treatment course. The results obtained for group B which received 0.1% Triamcinolone Acetonide in this study showed reduction of mean pain/burning sensation score based on VAS to be from 5.63 ± 1.47 to 0.50 ± 1.41 at 4 weeks (91.1% reduction) and 0.03 ± 0.18 (reduction of 99.47%) at the end of the treatment which are consistent with the previous study.

Fu et al [13] in a study conducted in 2012 on a comparably similar sample set found that Amlexanox oral paste reduced mean pain/burning sensation recorded based on VAS by 77%. The results obtained for patients in group A which received 5% Amlexanox oral paste in this study, showed a reduction of mean pain/burning sensation score by 85% which is consistent with the previous study. Fu et al also found a 76.58% improvement on the overall response to the treatment in patients that were given Amlexanox oral paste. In this study, the overall response was recorded as an improvement of 60.48% (Amlexanox group).

Within this study, comparing the mean pain/burning sensation score for group A (5% Amlexanox oral paste) with group B (0.1% Triamcinolone acetonide), it is observed that both produce an equally effective reduction at a comparable rate. While the rate of reduction was slightly lagging behind the rate of reduction produced by group B up to 4 weeks, both the groups had almost complete remission in pain/burning sensation symptoms by 3rd month. The p values obtained by Mann-Whitney non-parametric test on the mean reduction in pain/burning sensation had values 0.24, 0.39, 0.54, 0.62 and 0.74 for the 1st week, 2nd week, 4th week, 6th week and 3rd month indicating that they were not significant.

Comparison of the reduction in erythematous area between the two groups also had a similar

observation since both drugs were able to complete resolve the erythematous areas by 6^{th} week. In a similar observation as above, while group A had a slightly laggard rate of reduction compared to group B, both groups had equal responses at the end of the course of treatment.

However, observations on the reduction of clinical stage data (white striae and size of the lesion) were very different compared to the symptomatic changes. While group B had a higher rate of reduction of clinical sign stage and also achieved better results by reducing the value up to 98% by 3^{rd} month, group A had a comparatively slow rate of reduction and only achieved 60% reduction by 3^{rd} month. This has led us to infer that while 5% Amlexanox oral paste is as effective as 0.1% Triamcinolone acetonide in treating the symptoms like pain/burning sensation and erythematous areas it is not as

effective in reducing the sign stage. None of the patients in Amlexanox group developed any adverse effects during the treatment course but one patient in 0.1%Triamcinolone acetonide group developed oral candidiasis during the 6th week of the therapy.

CONCLUSION:

Though Amlexanox is equally effective in reducing the pain/burning sensation and the erythematous area, it is not as effective as 0.1% Triamcinolone acetonide in reducing the clinical sign stage (white striae with the size of the lesion). So despite the fact that Amlexanox is not effective in reducing clinical sign stage of the lesion, it can be used as an effective treatment for reducing the symptoms in those patients where topical steroids are contraindicated.

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