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A Triple-Blind Randomized Clinical Trial To Compare The Efficacy Of Topical Triamcinolone, Beclometasone And Clobetasole In The Treatment Of Oral Lichen Planus.

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ABSTRACT
Purpose: Oral lichen planus (OLP) is a common chronic mucosal lesion in the oral cavity. There are many treatment options to treat OLP, but most common and effective treatment option is topical corticosteroids. The aim of our study is to compare the efficacy of three commonly used corticosteroids, namely triamcinolone (0.1%), clobetasole (0.05%) and beclometasone (0.025%).
Methods: Total 30 OLP patients were included in our study. They were randomly divided into three groups and were recruited to receive 0.05% clobetasole, 0.1% triamcinolone and 0.025% beclometasone ointments respectively 4 times daily for 6 weeks. Burning sensation and lesion size was recorded at day 1. Follow up was done at day 21 and day 42 and that time burning sensation and lesion size were recorded and compared with day 1.
Results: Beclometasone more significantly reduced burning sensation as compared to clobetasole and triamcinolone. Moreover, clobetasole showed better result than triamcinolone to reduce burning sensation. Clobetasole and beclometasone showed almost same effectiveness to reduce size of lesion as compared to triamcinolone.
Conclusion: We can conclude that topical beclometasone and clobetasole are almost equally effective to treat OLP than topical triamcinolone and among beclometasone and clobetasole, the former is more effective than the later.
Key Words: Beclometasone, Clobetasole, Oral lichen planus, Steroids, Triamcinolone.

I. INTRODUCTION

Lichen planus, described first by Erasmus Wilson in 1869, is a chronic, mucocutaneous, psychosomatic, autoimmune disease which can affect any part the oral cavity, skin, genital mucosa, scalp and nails [1-3]. Lichen planus most commonly occurs in 3rd and 4th decade female individuals. Children are rarely affected. Oral lichen planus (OLP) clinically present as white straie (Wickham's straie), papules, plaque, erythema, erosion or blisters and buccal mucosa, tongue and gingiva are the most common sites in oral cavity. Mainly six clinical variants are found in the oral cavity, such as reticular, papular, plaque type, erosive, atrophic and bullous. More than one variant can co-exist in the same patient [2,4,5]. Lichen planus is a T-cell mediated autoimmune disease in which autocytotoxic $CD8^+$ T-cells trigger the apoptosis of epithelial cells. Dense subepithelial lympho-histocytic infiltrate, intra-epithelial lymphocytes and degeneration of basal keratinocytes (civatte bodies) are present histopathologically [2,5,6].

There are various types of treatment modalities for OLP as it is a chronic and recalcitrant type of lesion and thus its treatment is a challenge for dermatologist as well as oral physician. Treatment of choice depends on severity of lesion, site of lesion in oral cavity and overall health condition of patient [1,4,6]. Corticosteroids are most common and effective modality for treatment of OLP. Steroids have anti-inflammatory effect as well as antiimmunologic property which help to suppress T cell function and for this, they are most effective to treat OLP. Steroids can be used topically, systemically and intralesionally. However, adverse effects are common in systemic steroids even if that is used for short duration. As OLP has a chronic nature, so it often requires long term and frequent treatment and for this reason, topical preparation is the first line choice of treatment for its poor systemic absorption because of interference of stratum corneum which acts as a rate-limiting barrier to percutaneous drug absorption leading to minimal side effects [3,4,7,8]. Though there are other treatment modalities also for OLP, such as retinoids, cyclosporine, azathioprine, dapsone, photodynamic therapy etc, but steroids, especially topical steroids are most frequently used to treat OLP. Clobetasole, betamithasone, beclometasone, triamcinolone,

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fluocinolone are commonly used topical steroids [4,6,9].

This study aimed to investigate the efficacy of three steroid ointments for treatment of OLP. In our study, we have used clobetasole (0.05%), triamcinolone (0.1%) and beclometasone (0.025%) to treat patients with symptomatic OLP. To best of our knowledge, no study has been done till now to compare these three potent steroid ointments on treatment efficacy for OLP.

II. MATERIALS AND METHODS

This study was conducted during the period of July 2022 to March 2023 in the department of Oral Medicine and Radiology. A total 30 adult patients with symptomatic OLP were selected for this study who felt the problem first time or were not received any treatment for OLP in last one year. They were randomly divided into three groups.

Group I- Randomly selected 10 patients with symptomatic OLP subjects were recruited to receive topical clobetasole (0.05%) 4 times daily for 6 weeks

Group II- Randomly selected 10 patients with symptomatic OLP subjects were recruited to receive topical triamcinolone (0.1%) 4 times daily for 6 weeks

Group III- Randomly selected 10 patients with symptomatic OLP subjects were recruited to receive topical beclometasone (0.025%) 4 times daily for 6 weeks

All three groups were instructed to apply ointments topically on lesion sites 4 times daily. They were instructed to keep the ointment 15 minutes in the oral cavity and then spit out, not to swallow (to avoid systemic absorption). They were also instructed not to eat or drink for 30 minutes after application of ointment.

Patients who had received any treatment for OLP in last one year, pregnant women and lactating mother, taking systemic steroids for any systemic illness, any clinicopathological signs of epithelial dysplasia and use of any drug or dental restorations responsible for lichenoid reactions were excluded from this study.

A formal informed written criteria was obtained from all the subjects. A detailed case history was recorded for all patients. Nature of the lesion, its duration and associated any skin lesion history were recorded for all patients. General physical examination and oral examination were done.

Clinical diagnostic criteria used in this study was as follows: [1,10]

1. The presence of keratotic, pinhead-sized, white, slightly elevated papules called as papular lichen planus. If that keratotic structures are discrete or arranged in reticular pattern defined as reticular lichen planus and when those are arranged in plaque-like defined as plaque-like lichen planus.

2. Atrophic lichen planus is characterized by thinning of the epithelium leading to the appearance of atrophic red areas within the white lesions.

3. If ulceration is present within the above described variety, then that is defined as erosive (ulcerative) lichen planus.

4. When bullae are present within the any of the above mentioned variety, then that is defined as Bullous lichen planus.

Histopathological diagnosis was performed whenever there was any doubt about clinical diagnosis. Routine histopathological test was not performed as many patients do not want to give consent for any invasive procedure.

On day 1, burning sensation was recorded for each subject according to VAS score (Visual analogue scale having 0-10 scoring, where 0 is no burning sensation and 10 is severe burning sensation). Lesion size in all sites of oral cavity was informed to patient's attendant.

On day 21, follow up was done. On that day, % of reduction of size of lesion was recorded according to the patient's attendant who had seen the lesion size on first day. Remission of burning sensation was also recorded according to VAS score. On day 42, second follow up was done. On that day also, reduction of size of lesion and remission of burning sensation were again recorded like on day 21. Follow up of all patients were done after 4 months from day 42. No side effect of any ointment is noted. No recurrence of lesion was noted in completely cured cases.

The baseline characteristics were expressed descriptively. Comparison between the variables was performed by one way analysis of variance (ANOVA) followed by Sidak's multiple comparison test. A p-value of <0.05 was considered as statistically significant. The data were analysed by using SPSS version 21 for windows (SPSS, Inc, Chicago).

III. RESULTS

A total 30 OLP patients were included in this study. Both male and females were included.

Demographic characteristics:

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The median age with minimum and maximum and percentage of male and female patients enrolled in this study are presented in Table 1 and Figure 1. The incidence of this lesion was most predominant in females compared to male in this study. The Median age of the patients participated in this study were 41, 39, and 43 years in Group 1 (G1), Group 2 (G2) and Group 3 (G3) respectively with a minimum age being 20 and maximum age being 69 years.

Lesion type and incidence in the studied population:

Three major type of lesion were treated in the studied population. The erosive and reticular types of lesions were most common in all the three treatment groups (Table 2 and Figure 2). Besides, erosive and reticular lesions were predominant in females compared to male patients in our studied population. In G1, 40%, 30% and 0% of females presented with erosive, reticular, and plaque type lesions respectively. Similarly, 30%, 30%, and 20% of females in G2 reported to have erosive, reticular and plaque lesions correspondingly. In the same fashion, G3 reported to have 40%, 20%, and 10% of female patients with erosive, reticular and plaque type lesions.

Comparison of VAS score in three groups:

The mean VAS score on day 1 was 7.4, 6.9, and 7.3 for treatment groups G1, G2, and G3 respectively (Table 3). Upon continuation of the treatment, the VAS score decreased significantly on day 21 with a score of 4.7, 5.5, and 3.7 for G1, G2, and G3 correspondingly. On day 21, G3 shows better prognosis as compared to other two groups. Similarly, on day 42 the VAS scores were noted to be 0.6, 2.0, and 0.3 for G1, G2, and G3 respectively. The most significant difference in the mean of VAS score between the groups was observed in day 42. There was a significant decrease in VAS score in G3 treatment compared to other two groups (Table 4). If we compare between G1 and G2, VAS score was significantly decreased in G1 as compared to G2 in day 42.

Comparison of percentage reduction of lesion size (PRLS):

One way ANOVA followed by Sidak's multiple comparison tests (Table 5) was performed to check whether there was significant difference in the mean of percent reduction in lesion size between the three treatment groups. The test result revealed a significant difference in the percentage reduction in the lesion size in G3 on day 21 as compared to other groups. On day 21, reduction of lesion size 50% and above from day 1 were 90% and 60% cases in G1 and G2 respectively. In G3, on day 21, lesion size was reduced 60% and above in all cases from day 1. On day 42, completely healed lesion (100% reduction) occurred in 60%, 30% and 80% cases in G1, G2 and G3 respectively. The statistical analysis revealed there was a significant difference between G1 and G2; G3 and G2 as G2 group had less percent reduction in the lesion size on day 42 compared to other two treatment groups. Statistically no significant difference was observed in G3 and G1 ensuring that these treatment groups had similar percent reduction in lesion size on day 42 with similar prognosis.

IV. DISCUSSION

Lichen planus is a T-cell mediated chronic, inflammatory, autoimmune, mucocutaneous, psychosocial disease [1,11]. Oral lichen planus (OLP) is more commonly affected middle aged females [1,9]. In our study, 18 to 75 years patients were included where median age of the patients were 41, 39, and 43 years in Group 1 (G1), Group 2 (G2) and Group 3 (G3) respectively which is concordant with the studies of Ingafou et al. [10] and Lacy et al. [12]. In our present study, females are more commonly affected as compared to male (Table 1, Figure 1). The similar observations were found in the study of Ingafou et al. [10], Lacy et al. [12] and Ravi Prakash S Mohan et al [1]. Middle aged female predominance may be due to greater psychological stress as OLP is a psychosocial disease [1].

OLP may present in many clinical form, such as erosive, reticular, plaque type, papular, atrophic and bullous [1,10]. In our studied population, three clinical forms were found: erosive, reticular and plaque type. Among these types, erosive and reticular type were more frequently found than plaque type (Table 2), but most of the other studies, reticular type is most common [1,10,12]. This observation may be found due to small sample size. Moreover, erosive and reticular types were most common in females in our study.

To record burning sensation, we have used VAS (Visual Analog Scale) score in our study. The mean VAS score on day 1 was 7.4, 6.9, and 7.3 for treatment groups respectively (Table 3). On day 21, reduction of VAS score was more in G3 who were using beclometasone 0.025% ointment as compared to other two groups. Beclometasone gave more relief from burning sensation than clobetasole 0.05% and triamcinolone 0.1% on day 21. Similar result was found in day 42 also where VAS score

was significantly reduced in G3 as compared to other two groups. In G3, only 2 of 10 patients have very mild burning sensation and in G1, 4 patients have very mild burning sensation on day 42 whereas in G2, only 3 patients got complete relief from burning sensation. In our study, beclometasone was more effective for reducing burning sensation as compared to clobetasole and triamcinolone which is in contrast in the study of Shahla Afshar et al [13] where they found triamcinolone was more effective then beclometasone in relieving irritation symptoms. On day 42, G1 showed more reduction of VAS score than G2. Clobetasole showed more effectiveness than triamcinolone in our study which is in consistent with the study of P-O Rodstrom et al [14] where they used clobetasole propionate and triamcinolone acetonide to treat erosive OLP and they observed that clobetasole propionate provided more immediate clinical response than triamcinolone acetonide. In another studies done by Lorenzo Lo Muzio et al [7] and M Carbone et al (8), the researchers concluded that topical clobetasole is an effective drug for treating OLP.

Anti-inflammatory and antiimmunologic properties of corticosteroids help to suppress T lymphocytes which is beneficial to reduce OLP lesion [4,15,16]. Steroids help to reduce the exudation of leukocytes as well as plasma constituents and form soluble inflammatory mediators, thus help to maintain cellular membrane integrity, reduction of phagocytosis and prevention of lysosomal release from granulocytes. Steroids help to stabilize the membrane of lysosomes which contain hydrolytic enzyme. Steroids inhibit those hydrolytic enzymes, thus it decreases cell damage and prevents progression of inflammatory tissue destruction of adjacent area [3,5,7,17].

Based on efficacy of topical steroids, they are classified into four potency: class I (mild potent), class II (moderately potent), class III (potent) and class IV (very potent). Triamcinolone is moderately potent (type II) steroid [3,4]. Beclometasone dipropionate and clobetasole propionate are categorized as high potent steroids [15,18]. In our study, triamcinolone is used 0.1% whereas beclometasone and clobetasole are used 0.025% and 0.05% respectively. Potency may be the reason why beclometasone and clobetasole show better result in our study as compared to triamcinolone, though it is used more amount per unit volume as compared to other two steroids.

On day 21, reduction of lesion size was more in G3 as compared to other two groups. On day 42, lesion size reduction was significantly less in G2 as compared to other two groups. In our study, triamcinolone was less effective to treat OLP as compared to beclometasone and clobetasole which is in contrast with the study of Shahla Afshar et al where they observed that there was no significant difference between triamcinolone and beclometasone in reducing extend and severity of erosive type OLP, but pain and irritational symptoms were more effectively reduced by triamcinolone than beclometasone [13]. A study was done by P-O Rodstrom et al. [14] about the efficacy of clobetasole and triamcinolone on OLP where they found that clobetasole was more effective than triamcinolone for treating OLP which is in consistent with our present study. Sivakumar Sivaraman et al also found the similar result about the comparison between clobetasole and triamcinolone in treating OLP [11]. In our study, there was no statistically significant difference in G3 and G1 for lesion size reduction on day 42. Beclometasone and clobetasole showed similar efficacy in reducing extend of OLP, though beclometasone had greater efficacy in reducing burning sensation in the present study. To best of our knowledge, no such study was done about the comparative efficacy between beclometasone and clobetasole on OLP.

V. CONCLUSION

In our study, it is concluded that overall 0.025% beclometasone and 0.05% clobetasole have almost similar efficacy and better than 0.1% triamcinolone for the treatment of OLP, though beclometasone shows slightly better efficacy than clobetasole in reducing burning sensation. Recurrence for completely healed cases was not reported in any group after 4 months follow up.

Study limitation:

This study concluded that the G1 and G3 treatment cohorts have better clinical outcome and prognosis compared to G2. However, Sidak's multiple comparisons test revealed G3 treatment outcome was most significant among three groups. Based on the above outcome we further tried to test which ointment is best for what type of lichen planus by one way ANOVA. The outcome of this test was not significant due to lower sample size. Hence, further investigation with higher sample size may solve this concern in the future.

In our study, no patient has complaint about any side effect. Corticosteroids cause hypothalamic-pituitary-adrenal axis suppression. Though systemic corticosteroids mainly cause this side effect, but it should be evaluated whether there is any effect on pituitary-adrenal axis of topical steroids by doing a study taking large sample size.

Furthermore, a detailed blinded randomized trial should be done in future with large sample size and long term follow up to conclude the comparative efficacy of beclometasone and clobetasole for the treatment of oral lichen planus, a very common and chronic lesion in oral cavity.

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Table 1: Demographic Characteristics

Descriptive statistics						
	N	Median age	Minimum	Maximum	Sex (n, %)	
Group 1	10	41	20.00	62	M= 3, (30)	F=7, (70)
Group2	10	39	25.00	65	M=4, (40)	F=6, (60)
Group 3	10	43	20.00	69	M=5, (50)	F=5, (50)

Figure 1: Demographic Characteristics

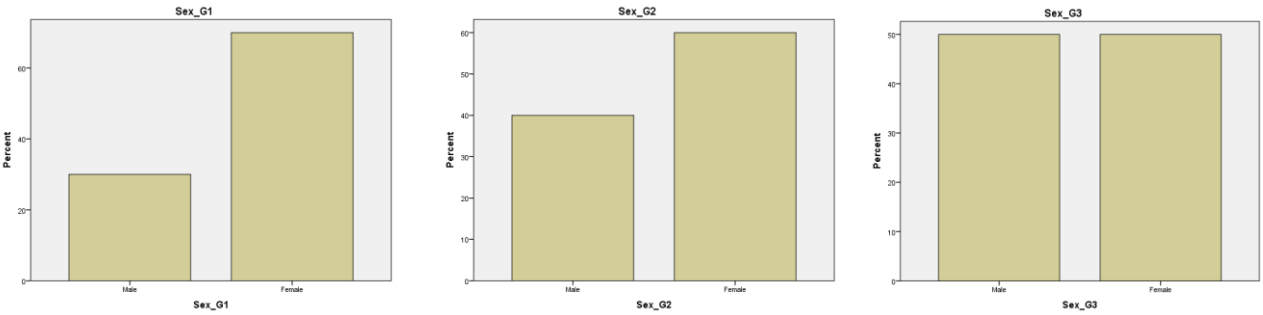

Table 2: Lesion type and incidence in the studied population

Lesion Type	Group-1			Group-2			Group-3		
Erosive (n, %)	5, 50	M	F	4, 40	M	F	4, 40	M	F
		1	4		1	3		0	4
Reticular (n, %)	4, 40	1	3	4, 40	2	2	4, 40	2	2
Plaque (n, %)	1, 10	1	0	2, 20	0	2	2, 20	1	1
Total (n, %)	10 (100)			10 (100)			10 (100)		

Figure 2: Lesion type and incidence in the studied population

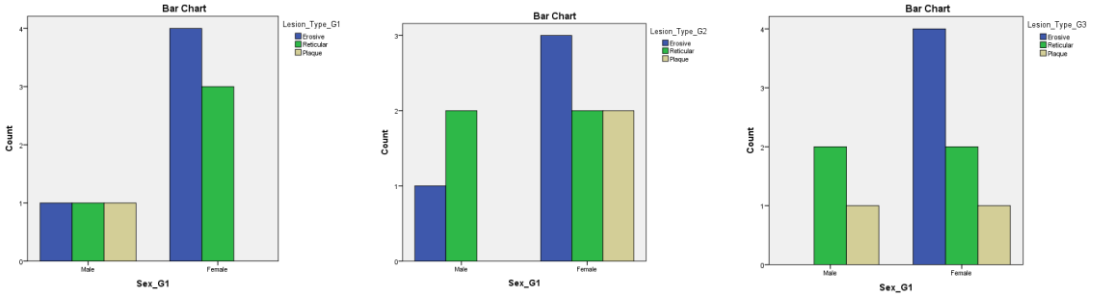

Table 3: Mean of VAS score (day wise)

N= 10	Minimum	Maximum	Mean ± SD
VAS_D1_G1	5.00	9.00	7.4 ± 1.2
VAS_D21_G1	3.00	6.00	4.7 ± 1.2
VAS_D42_G1	.00	2.00	0.6 ± 0.84
VAS_D1_G2	6.00	8.00	6.9 ± 0.99
VAS_D21_G2	4.00	7.00	5.5 ± 0.84
VAS_D42_G2	.00	4.00	2.0± 1.6
VAS_D1_G3	5.00	9.00	7.3 ± 1.3
VAS_D21_G3	2.00	5.00	3.7 ± 0.94
VAS_D42_G3	.00	2.00	0.3 ± 0.6

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Table 4: ANOVA table with multiple comparison test result

Sidak's multiple comparisons test	Mean ± SE Diff.	P Value
VAS_D1_G1 vs. VAS_D21_G1	2.700±0.50***	<0.0001
VAS_D1_G1 vs. VAS_D42_G1	6.800±0.50***	<0.0001
VAS_D1_G1 vs. VAS_D42_G2	5.400±0.50***	<0.0001
VAS_D1_G1 vs. VAS_D21_G3	3.700±0.50***	<0.0001
VAS_D1_G1 vs. VAS_D42_G3	7.100±0.50***	<0.0001
VAS_D21_G1 vs. VAS_D42_G1	4.100±0.50***	<0.0001
VAS_D21_G1 vs. VAS_D42_G2	2.700±0.50***	<0.0001
VAS_D21_G1 vs. VAS_D1_G3	-2.600±0.50***	<0.0001
VAS_D21_G1 vs. VAS_D42_G3	4.400±0.50***	<0.0001
VAS_D42_G1 vs. VAS_D1_G2	-6.300±0.50***	<0.0001
VAS_D42_G1 vs. VAS_D21_G2	-4.900±0.50***	<0.0001
VAS_D42_G1 vs. VAS_D1_G3	-6.700±0.50***	<0.0001
VAS_D42_G1 vs. VAS_D21_G3	-3.100±0.50***	<0.0001
VAS_D1_G2 vs. VAS_D42_G2	4.900±0.50***	<0.0001
VAS_D1_G2 vs. VAS_D21_G3	3.200±0.50***	<0.0001
VAS_D1_G2 vs. VAS_D42_G3	6.600±0.50***	<0.0001
VAS_D21_G2 vs. VAS_D42_G2	3.500±0.50***	<0.0001
VAS_D21_G2 vs. VAS_D1_G3	-1.800±0.50*	0.0211
VAS_D21_G2 vs. VAS_D21_G3	1.800±0.50*	0.0211
VAS_D21_G2 vs. VAS_D42_G3	5.200±0.50***	<0.0001
VAS_D42_G2 vs. VAS_D1_G3	-5.300±0.50***	<0.0001
VAS_D42_G2 vs. VAS_D21_G3	-1.700±0.50*	0.0397
VAS_D42_G2 vs. VAS_D42_G3	1.700±0.50*	0.0397
VAS_D1_G3 vs. VAS_D21_G3	3.600±0.50***	<0.0001
VAS_D1_G3 vs. VAS_D42_G3	7.000±0.50***	<0.0001
VAS_D21_G3 vs. VAS_D42_G3	3.400±0.50***	<0.0001

Table: 5 ANOVA followed by Sidak's multiple comparison test to compare percentage reduction of lesion size (PRLS)

Groups	Mean ± SD, N=10	
G1	95.30 ± 6.21	
G2	81 ±14.87	
G3	98.50 ± 3.37	
Sidak's multiple comparisons test		
	Mean ± SE Diff.	P Value
PRLS_D42_G1 Vs G2	14.30 ± 4.25	.007
PRLS_D42_G3 Vs G1	3.20 ± 4.25	.841
PRLS_D42_G3 Vs G2	17.50 ± 4.25	.001