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Comparison Betwen Therapeutic Effects of Low Molecular Weight Heparin and Oral Steroids in the Treatment of Lichen Planus

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ABSTRACT

Objective: To compare the therapeutic effects of low molecular weight heparin versus oral steroids in patients being treated for Lichen Planus.

Study Design: Quasi-experimental study.

Place and Duration of Study: Department of Dermatology, Ghurki Trust Teaching Hospital Lahore, Pakistan, from Apr 2021 to Jan 2022.

Methodology: A total of 96 patients with biopsy-proven Lichen Planus between the ages of 21 and 60 years of both genders were divided into two equal groups of 48 patients each. Patients in Group-A (n=48) were treated with low molecular weight heparin while those in Group-B (n=48) were treated with oral corticosteroids for 2 months. All patients followed in dermatology outpatient weekly for first month and then fortnightly there after till 3 months of treatment for remission of the disease and any adverse effects. Independent sample T-test and Chi square were applied to different variables, taking p value ≤0.05 as statistically significant.

Results: The mean age of patients included in the study was 35.83±9.06 years. The study sample comprised of 58 female patients (60.42%). Complete remission was achieved in 36 patients (37.5%) in Group-A, and 60 patients (62.5%) in Group-B, the difference being statistically significant (p<0.001). The overall frequency of complications was 3(6.3%) in Group-A and 17 (35.4%) in Group-B with the difference being statistically significant (p<0.001).

Conclusion: Oral corticosteroids are better than low molecular weight heparin in the treatment of Lichen Planus, albeit the increased frequency of dyspeptic symptoms associated with steroid use.

Keywords: Lichen Planus, Low Molecular Weight Heparin, Steroids.

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INTRODUCTION

Lichen planus (LP) is an inflammatory papulosquamous idiopathic skin eruption that presents as a pruritic, noninfectious dermatosis that has a characteristic clinical and histological appearance. It commonly affects the cutaneous surfaces and mucous membranes such as oral mucosa, and less commonly the hair and nails.[1-3]

The exact prevalence of LP is not known however it has been reported to range between 0.22% to 5% globally, with a similar frequency in Pakistan.[4,5] LP has multiple variants which include the most common classic variety, followed by hypertrophic, atrophic, actinic, erosive, bullous, ulcerative, and LP pigmentosus variants to name a few.[4,6] Classical lesions of LP presents as characteristic purple, polygonal, pruritic papules, and plaques interspersed by white lines formed as a result of hypertrophy of the granular layer of epidermis known as the "Wickham striae." The most common site of involvement include the flexor surfaces around the wrists and ankles.[7]

The management of LP is not simple as the treatment protocols may change on case to case basis. It is pertinent to mention that few patients may achieve spontaneous remission with a year.[8] Therefore the therapeutic plan is sometimes individualized based on severity, variety, location and pattern of the dermopathy.[9] The main aim of treatment is to reduce the symptomology of the disease especially pruritus, early diagnosis of the exact variety and achieving rapid resolution of the skin lesions as early as possible.[4] The various options available for management of LP include corticosteroids, low molecular weight heparin (LMWH), methotrexate, retinoids, calcineurin inhibitors, phototherapy, vitamin D derivatives, biologics, and anti fungals to name a few.[9,10]

The primary objective of this study was to identify the better therapeutic option in patients

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presenting with symptomatic LP by comparing outcomes of the disease as well complications encountered during treatment.

METHODOLOGY

This Quasi-experimental study was carried out at the Department of Dermatology, Ghurki Trust Teaching Hospital Lahore, Pakistan, from April 2021 to January 2022, after obtaining prior approval from Hospital Ethical Review Board (ERC approval letter no. LMDC/17032-33).

Inclusion Criteria: Patients between the ages of 21 to 60 years belonging to either gender with biopsy proven Cutaneous LP (papular, annular, linear, hypertrophic and atrophic varieties) affecting the skin, scalp, and nails were included.

Exclusion Criteria: Patients with known allergies or contraindications to any of the treatment options, liver dysfunction, uncontrolled hypertension, deranged renal profile, pregnancy, lactation, coagulopathies, LP affecting the mucous membranes and history of drug induced Lichen Planus were excluded.

The sample size was determined using the WHO sample size calculator taking anticipated population proportion 1 of 88.8% and anticipated population proportion 2 of 75.0%,[11] which came to 48 patients in each group making a total sample size of 96 patients.[11] Non-probability consecutive sampling technique was used, and informed consent was taken from all study participants.

A total of 110 patients were initially enrolled in the study but 14 patients were lost to follow up while 96 patients completed the study (Figure).

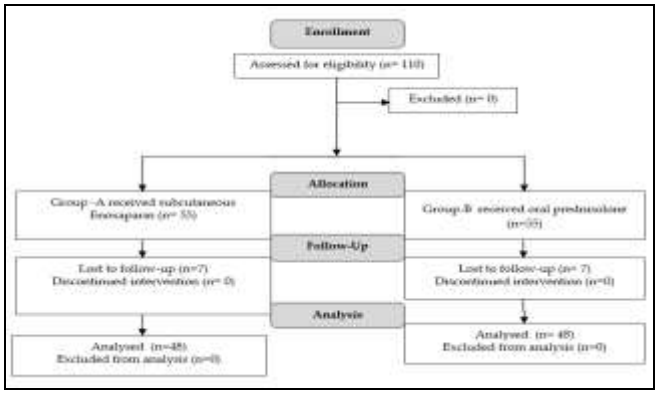

Figure: Patient Flow Diagram (n= 96)

The demographic details of all patients were recorded. Patients in Group-A received 5mg of low molecular weight heparin (Enoxaparin) subcutaneously per week for 8 weeks while patients in Group-B were started on oral prednisolone 0.5mg/Kg per day with the dose gradually tapered off by decreasing it 5 mg weekly for a total duration of 8 weeks of treatment. After 8 weeks of treatment the administration of oral corticosteroids was completely stopped.

Visual Analogue Score (VAS) was used to determine the severity of pruritus by calculating the itch score on a linear scale from 1-10. Patients were asked to describe severity of itching, with 1 being the lowest itch score and 10 being the highest itch score. The severity of pruritus was then divided into 3 grades, including mild (VAS=1-3), moderate (VAS=4-6) and severe pruritus (VAS=7-10) respectively. Itching score was calculated at the start and completion of treatment after 8 weeks.

All patients were followed in Dermatology OPD weekly for first month after completion of treatment and then fortnightly till 3 months of completion of treatment for remission of the disease and any adverse effects. The adverse effects that were followed included dyspepsia, facial puffiness/flushing, and relapse of the disease. The final result was compiled at 3 months of completion of treatment and patients were grouped into complete remission, partial remission and no remission. During this time, seven patients from each group were lost to follow-up.

Remission was defined as the reduction or total disappearance of pruritus as well as the disappearance of lesions of LP. Complete disappearance of LP lesions as well as pruritus was labeled as complete remission while partial reduction in the LP lesions such as flattening or change in color of the lesion, as well as partial improvement in pruritus was labelled as partial remission. No remission implied that the treatment had no effect on the lesions of LP. Relapse was defined as the reappearance of symptoms after achieving complete remission. In this study we followed the patients for relapse till 3 months of completion of treatment.

Data was analyzed using Statistical Package for the Social Sciences (SPSS) version 25. For quantitative variables like age and itching score, Mean±SD were calculated. Qualitative variables like gender, grade of pruritus, thickness of lesions, complications and result of treatment were presented as frequency and percentage. Independent sample t-test was used to compare itching score before and after treatment between the two groups. Chi-square test was applied

comparing the two groups in terms of post treatment complications and treatment results taking *p*-value ≤0.05 as statistically significant.

RESULTS

A total of 96 patients were included in the study. The overall mean age of patients was 35.83±9.06 years. The study revealed a female gender preponderance with 58 patients (60.42%) and 38 male patients (39.58%). The male to female ratio was 1:1.53. The distribution of patients according to age and gender is given in Table-I.

Table-I: Distribution of Patients According to Age and Gender (n=96)

Variable	Variable Groups	Group-A n (%)	Group-B n (%)
Age Groups (Years)	21-40	35 (72.9%)	33 (68.8%)
	41-60	13 (27.1%)	15 (31.2%)
Gender	Male	16 (33.3%)	22 (45.8%)
	Female	32 (66.7%)	26 (54.2%)

The overall mean itch score at the start of study was 7.20±0.96 while it was 1.91±1.18 at completion of treatment. The distribution of patients according to mean itch score at the start of treatment and at completion of treatment after 8 weeks between the two groups is given in Table-II below. There was a statistically significant difference in the patient's itch score before and after treatment (p<0.001).

Table-II: Comparison of the Two Groups in Terms of Mean itch Score (n=96)

Variable	Group-A Mean±SD	Group-B Mean±SD	*p*-value
Itch Score at the start of treatment	7.19±0.96	7.21±0.96	0.916
Itch Score at completion of treatment	2.63±1.00	1.19±0.89	<0.001

At presentation, 12 patients (25.0%) in Group-A and 10 patients (20.8%) in Group-B had moderate pruritus, while 36 patients (75.0%) in Group-A and 38 patients (79.2%) in Group-B had severe pruritus. The difference between the two groups was insignificant (p=0.627). At the completion of treatment, 39 patients (81.3%) in Group-A and 48 patients (100%) in Group-B had mild pruritus while 9 patients (18.7%) in Group-A and 0 patients in Group-B had moderate pruritus respectively. The difference between the two groups was significant (p=0.002).

The frequency of complete and partial remission in Group-A was 44(91.7%) while it was 47(97.9%) in Group-B, the difference between the two groups being statistically significant (p=0.035). The results of treatment in both groups is shown in Table-III.

Table-III: Comparison of the Treatment Results Across Groups (n=96)

Result	Group-A n (%)	Group-B n (%)	*p*-value
Complete Remission	18(37.5%)	30(62.5%)	0.035
Partial Remission	26(54.2%)	17(35.4%)	
No Remission	4(8.3%)	1(2.1%)	

In Group-A, only 3 patients (6.25%) developed disease relapse. The overall complication rate was considerably higher in Group-B (17 patients, 35.4%), with one patient in Group-B developing both face swelling and relapse of disease.

DISCUSSION

Historically, corticosteroids were considered as the gold standard for the management of Lichen Planus (LP) because of their immune-modulatory and anti-inflammatory properties but over the turn of the 21st century, various newer modalities and treatment options have been tried due to the adverse effects profile of steroids.[12] Although the exact mechanism of development of LP is not known, it has been postulated that CD8+ T lymphocytes play a significant role as the main component of the infiltrate that damages the keratinocytes in the skin.[13] LWMH in low doses is believed to have immunomodulatory and anti-proliferative properties with suppression of release of cytokines which might prove beneficial in the treatment of LP.[11]

A research protocol by Patel *et al*. published in 2018 highlighted inconsistencies and conflicting results amongst various studies.[14] Therefore we conducted this study to compare LWMH with oral corticosteroids in our setup. The mean age of patients included in our study was 35.83±9.06 years. A study by Iraji *et al*., from Iran reported a comparable mean age of 38.8±14.4 years in the LMWH group and 36.7±13.7 years in the oral corticosteroids group respectively.[15] Another study by Saeed *et al*., reported a mean age of 44.43±11.93 years.[16] Our study sample showed a female predominance with a male to female ratio of 1:1.53. Comparable findings were reported by Gajula *et al*., with a male to female ratio of 1:2.15.[11]

With regards to the treatment results, the oral corticosteroids group fared better than Enoxaparin group in terms of remission. The frequency of complete or partial remission in LMWH group was

91.7% while that in oral corticosteroids group was 97.9%, the difference being statistically significant (p=0.035). Similarly, Gajula *et al*., also reported a good-to-excellent treatment response in 88.8% patients treated with oral corticosteroids versus 75% patients managed with LMWH (p<0.05).[11] Iraji *et al*., also reported that complete or relative remission was achieved in 72% patients in LMWH group versus 95.6% patients in the oral corticosteroids group, the difference also being statistically significant (p=0.005).[14] Another study reported remission rate of 90% with LMWH.[17]

Enoxaparin group was found to have a significantly lower overall complication rate of 6.3% versus a complication rate of 35.4% for oral corticosteroids group, the difference was highly significant (p<0.001). However the relapse rate was slightly higher in LMWH group (6.3%) versus oral corticosteroid group (4.2%), the difference being statistically non-significant (p=0.646). A study from 2021 reported that the remission rate of LP after treatment with LMWH was significantly higher (33.3%) versus only 6.7% in oral steroids group (p<0.01). The study reported that facial puffiness occurred in 31.57% patients and gastric irritation was reported in 42.1% patients treated with oral steroids, while none of the patients in enoxaparin group reported these side effects.[18]

On the contrary, another study reported that the relapse rate following oral corticosteroid therapy was 39.13% at 6 months follow-up versus 33.3% relapse rate in the LMWH group respectively.[11] This relapse rate was considerably higher but the duration at which relapse was assessed was also 6 months, as compared to our assessment, which was at 3 months after treatment.

LMWH does appears to be a promising treatment option for LP with lesser side effects and can be offered to selected patients. This study will serve as a trigger for further research on comparative treatment results for LP in the Pakistani population as it is only the second study from the country on this topic.

LIMITATIONS OF STUDY

The limitations of our study was that the sample size was comparatively small and the cost benefit analysis was not done in this study. We also only followed up the patients for relapse till 3 months. Longer follow-up may have exposed further complications and side effects of either treatment regimen.

CONCLUSION

Oral corticosteroids were found to be better than low molecular weight heparin in achieving rapid and effective remission of LP albeit the increased frequency of dyspeptic symptoms and facial puffiness associated with steroid use. However low molecular weight heparin does appear to be a promising treatment option with better safety profile.

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Authors' Contribution:

Following authors have made substantial contributions to the manuscript as under:

BJB & SH: Conception, study design, drafting the manuscript, approval of the final version to be published.

HN & TA: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

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Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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