# **Original Research Article**

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# Comparative evaluation of oral corticosteroids versus low molecular weight heparin in the treatment of lichen planus

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#### **ABSTRACT**

**Background:** Lichen planus (LP) is an immunologically mediated inflammatory disorder involving the skin, nails, hair follicles and mucous membranes. Though several drugs and phototherapy are tried and mentioned in the literature, dermatologists are still depending on corticosteroids, which have various serious side effects on long term usage. Thus, in search for an alternative therapy, the present study is conducted to compare the efficacy of systemic corticosteroids and low dose low molecular weight heparin in management of lichen planus.

**Methods:** 60 patients with biopsy proven LP were selected and divided randomly into two groups with 30 patients each. Group 1 was treated with oral corticosteroids and group 2 was treated with low molecular weight heparin for 8 weeks. Follow up was done for a period of 6 months, at monthly intervals in all patients and any relapses if any were noted.

**Results:** 60 patients with biopsy proven LP were selected and divided randomly into two groups with 30 patients each. Group 1 was treated with oral corticosteroids and group 2 was treated with low molecular weight heparin for 8 weeks. Follow up was done for a period of 6 months, at monthly intervals in all patients and any relapses if any were noted.

**Conclusions:** Low dose enoxaparin in the treatment of lichen planus could be considered as an alternative to oral corticosteroids because of equal efficacy and fewer side effects.

**Keywords:** Lichen planus, Low molecular weight heparin, Oral corticosteroids

# **INTRODUCTION**

Lichen planus is an immunologically mediated inflammatory disorder involving the skin, nails, hair follicles and mucous membranes. The term lichen planus is derived from the Greek *Leichen*, meaning "tree moss", from Latin *planus* meaning "flat". The term lichen was coined to denote diseases in which the primary lesions had a resemblance to scurfy, finely furrowed, dry excrescences of the symbiotic vegetation known as Lichen. In 1869, Erasmus Wilson published the first well documented series on lichen planus.

In Indian series, the skin alone was affected in 70%, skin &mucous membranes in 19.1% and mucous membranes alone in 10%. Females are usually affected in their 50s and 60s, whereas males develop lichen planus at a somewhat earlier age<sup>3</sup>. Lichen planus affects both sexes. Females appear to be more commonly affected than men. 4

Lichen planus is characterized by features of a cell mediated attack on the epidermis by activated T-lymphocytes. It has been suggested that an unknown antigen is processed by Langerhans cells, which activates T-lymphocytes that subsequently destroy the basal layer.

These lymphocytes produce an endoglycosidase (heparinase), which allows them to penetrate in to the sub epithelial basal lamina. Heparin inhibits T-lymphocyte heparinase, resulting in the prevention of T-cell hypersensitivity.<sup>5</sup> Cell-mediated immunity, plays the major role in triggering the clinical expression of the disease. Both CD4+ and CD8+ T cells are found in lesional skin of lichen planus. The epithelium-lymphocyte interaction can be divided into three major stages: (1) antigen recognition, (2) lymphocyte activation, and (3) keratinocyte apoptosis.<sup>5</sup> T-cell becomes activated by antigen presenting cells and produce interferon - γ (IFNγ) and interleukin–2 (IL-2), which modulate the immune function. IFN- y induces keratinocytes to express HLA -DR antigen and basal keratinocytes to express inter cellular adhesion molecule-1 (ICAM -1) thus increasing interaction with the helper T-cells. These helper T-cells induce keratinocytes to produce cytokines. Cytotoxic Tcells and cytokines mediate basal cell liquefaction and keratinocyte apoptosis.<sup>1</sup>

The classic cutaneous lesion of lichen planus is characterized by a faintly erythematous to violaceous, flat-topped, polygonal papule. Papules are frequently grouped and tend to coalesce to form plaques a thin, transparent and adherent scale may be discerned atop the lesion. Fine, whitish puncta or reticulated networks referred to as Wickham's striae, are present over the surface of many well developed papules due to focal increase in the thickness of the granular layer along with dermal infiltrate.<sup>6</sup> These are considered to be highly characteristic and are readily visible after application of oil, xylene or water with a magnifying lens or a hand held dermatoscope.<sup>1</sup> The lesions are usually distributed symmetrically and bilaterally over the extremities, usually the flexural areas of the wrists, arms, legs and at times the lumbar region. Lichen planus (LP) tends to be quite pruritic, although 20% of patients are largely asymptomatic.<sup>3</sup> The degree of pruritus is generally related to the extent of involvement, with more intense pruritus in generalized case.

Apart from the classic presentation, LP has many variants which can be categorized by- configuration of lesions (annular LP, linear LP), morphology of lesions (hypertrophic LP, atrophic, vesicobullous LP, erosive and ulcerative LP, actinic LP, follicular LP, lichen planus pigmentosus), site of involvement (LP of scalp, mucosal LP, oral LP, genital LP, anal LP, palmo-plantar LP, Inverse LP, LP of nails), other variants (guttate lichen planus, perforating lichen planus, exfoliative lichen planus, invisible lichen planus)

In LP of scalp, patches of atrophic cicatricial alopecia develop over the scalp. It results from follicular destruction by the inflammatory infiltrate; with scarring cutaneous lichen planus does not carry any increased risk of malignant transformation of the lesions or internally. However, there is an increased risk of oral cancer (squamous cell carcinoma) particularly in men. 9

Management of LP can be challenging and discouraging for both the patient and physician. Due to chronicity and relapses, various drugs have been proposed for the treatment of cutaneous and oral lichen planus.

Corticosteroids are time tested mainstay of dermatologic therapy because of their potent immunosuppressive and anti-inflammatory properties. Topical glucocorticoids are typically used for limited cutaneous disease. Potent topical glucocorticoids like fluocinonide 0.05% and clobetasol propionate 0.05%, with or without occlusion, are beneficial in cutaneous lichen planus. Intralesional triamcinolone acetonide (5 to 10 mg/ml) is effective in treating oral and hypertrophic lichen planus. Systemic corticosteroids like oral prednisolone (0.5-1 mg/kg/body weight) for 4-6 weeks is found to be useful.

Phototherapy (narrow band UVB/PUVA/Bath PUVA) have been used in the treatment of LP with good effect. Narrow band UVB therapy is the preferred mode of phototherapy with improvement and remission of disease in up to 85% of patients in a recent series. Extracorporeal photopheresis has been used as a monotherapy in a patient in recalcitrant, severe erosive cutaneous LP. 12

Dapsone has been found to be successful in the treatment of bullous LP and erosive oral LP in children and adults at a dose of 200 mg/day for 4 months. Hydroxychloroquine at 200-400 mg/day have been reported to be particularly useful in actinic lichen planus. 14

Patients with widespread LP with or without concomitant amoebiasis or giardiasis improved when treated with metronidazole 250 mg twice daily for 2-3 weeks. <sup>15</sup> Cyclosporine-both low (1-2.5mg/kg) and high doses (3-6 mg/kg) have been used but mucosal and genital cases are slow to respond to cyclosporine. <sup>16</sup> The high cost of treatment is a deterrent.

Low molecular weight heparin in low doses has lymphoid antiproliferative and immunomodulatory properties. At a dose of 3 mg weekly, heparin injections have been reported to significantly improve the symptoms of pruritus and activity of the disease. Four to six injections of heparin induced complete regression of lesions within 4 to 10 weeks.

Oral antihistamines like promethazine hydrochloride, trimeprazine tartrate, hydroxyzine hydrochloride are beneficial for the symptomatic relief of itching.<sup>7</sup>

Azathioprine has been used successfully for the treatment of erosive and generalized lichen planus.<sup>18</sup> Cyclophosphamide, methotrexate, and phenytoin reportedly are useful but should be reserved for cases refractory to less-toxic drugs though the several drugs and phototherapy are tried and mentioned in the literature, dermatologists are still depending on

corticosteroids, which have various serious side effects on long term usage. Hence an attempt to search for another effective alternative medicine is made. Thus this study is taken up to compare the efficacy of systemic corticosteroids and low molecular weight heparin in patients suffering from LP.

### **METHODS**

The study was carried out on patients between 11-60 years of age of both genders with clinical features suggestive of LP, attending the outpatient department of Dermatology, Venereology and Leprosy, Chalmeda Anand Rao Institute of Medical Sciences, Karimnagar from December 2014 to October 2016.

We included 60 patients with biopsy proven LP. We excluded the patients with any contraindications for heparin and it's derivatives, liver and renal dysfunction, contraindication for oral prednisone, past history for use of drugs that can cause drug induced LP like reaction, pregnancy and lactation.

The details of the patients i.e. age, sex, occupation, duration of the symptoms, past history, personal history, family history, drug history were recorded in proforma.

A complete dermatological examination was done noting morphology, configuration and distribution of lesions with special reference to intensity of pruritus and thickness of lesion. They were given grades (0, 1, 2, 3) depending on the intensity of pruritus and thickness and were assessed according to a four point scale and were rated on scale (0-3).

Pruritus- Grade 0: no -pruritus, Grade 1: minimal pruritus, Grade 2: moderate pruritus, Grade 3: severe pruritus.

Thickness- Grade 0: no thickness, Grade 1: slight thickness, Grade 2: moderate thickness, Grade 3: very thick.

Routine blood investigations like total WBC count, Differential count, ESR, Haemoglobin, random blood sugar, renal function tests, liver function tests were done in each patient. Histopathological examination was done in all the cases patients were randomly divided in to two groups with 30 patients in each group. Special investigations like platelet count, bleeding time, clotting time were done for patients under group 2.

1<sup>st</sup> group of patients were treated with oral corticosteroids i.e. prednisolone 40 mg/day. Prednisolone tapered 5 mg every week. 2<sup>nd</sup> group of patients were treated with low molecular weight heparin (enoxaparin) subcutaneously in dose of 3 mg weekly.

The duration of therapy was 8 weeks in both the groups. The clinical response was noted once in 2 weeks while on treatment and side effects if any were recorded. Follow up was done for a period of 6 months, at monthly intervals in all patients and any relapses if any were noted.

Grading of clinical response was done as follows- Grade 0: no improvement, Grade I: poor-0-25%, Grade II: fair-26-50%, Grade III: good-51-75%, Grade IV: excellent-76-100%.

# Ethics approval

The study was reviewed and approved by the Institute Ethics Committee, CAIMS, Karimnagar. Informed consent was taken from the patients.

# Statistical analysis

Study tools and data analysis were used to record the information. Data was tabulated in Microsoft Excel 2010 Worksheet. Data analysis was done using IBM SPSS 23.0 (Chicago, IL, USA).

### **RESULTS**

The maximum number of lichen planus cases (25) was detected in the age group of 31-40. The least number of cases (3) was observed in 51-60 years age group, between 10-30 sizeable number (20) of patients were present (Table 1). In our study females are more affected than males with a ratio of female:male= 2.15:1.

Table 1: Age distribution.

| Age (in years) | No. of cases | Percentage (%) |
|----------------|--------------|----------------|
| 11-20          | 5            | 8.30           |
| 21-30          | 15           | 25.00          |
| 31-40          | 25           | 41.60          |
| 41-50          | 12           | 20.00          |
| 51-60          | 3            | 5.00           |
| Total          | 60           | 100            |

Out of total 60 patients 58.3% had classical lichen planus, whereas the incidence of classical lichen planus with mucosal involvement and linear lichen planus were 26.6% and 3.3% respectively. Only three cases each of classical lichen planus with hypertrophic lichen planus and hypertrophic lichen planus were reported. One case of classical with follicular lichen planus was reported (Table 2).

By the end of trials complete response (Grade IV) in Oral corticosteroid group of patients was observed in 15 out of 26 cases i.e. 57.69% and 8 out of 26 patients showed Grade III response i.e. 30.76% (Figure 3A and B). A total of 88.80% of patients showed good to excellent response (Table 3).

Table 2: Distribution of various types of LP.

| Clinical type                           | No of patients | Percentage (%) |
|---|----------------|----------------|
| Classical LP                            | 35             | 58.30          |
| Classical LP with mucosal involvement   | 16             | 26.60          |
| Linear lichen planus                    | 2              | 3.30           |
| Classical LP with hypertrophic LP       | 3              | 5.00           |
| Hypertrophic lichen planus              | 3              | 5.00           |
| Classical with follicular lichen planus | 1              | 1.66           |
| Total                                   | 60             | 100            |

Table 3: Degree of response in relation to duration of treatment.

|                 |                        | 2nd week | 4th week | 6th week  | 8th week |
|-----------------|------------------------|----------|----------|-----------|----------|
|                 |                        |          | N (%)    | N (%)     | N (%)    |
| Corticosteroids | Partial response (III) | -        | -        | -         | 7 (26.9) |
|                 | Complete response (IV) | -        | 3 (11.5) | 10 (38.4) | 3 (11.5) |
| LMWH            | Partial response (III) | -        | -        | -         | 4 (16.6) |
|                 | Complete response (IV) | -        | 5 (20.8) | 6 (25)    | 3 (12.5) |

Table 4: Response of the disease in relation to duration of therapy and modality of treatment.

|                             | Duration of treatment in weeks |                       |                 |     |   |     |                 |     |          |       |       |
|-----------------------------|--------------------------------|-----------------------|-----------------|-----|---|-----|-----------------|-----|----------|-------|-------|
| Modality Total no. of No. o |                                | No. of patients       |                 |     | <b>4</b> <sup>th</sup> <b>6</b> <sup>th</sup> |     | 8 <sup>th</sup> |     |          | Total |       |
| of treatment patients tried | •                              | complete<br>treatment | 2 <sup>nd</sup> | No. | %   | No. | %               | No. | <b>%</b> | No    | %     |
| Steroids                    |                                |                       |                 |     |   |     |                 |     |          |       |       |
| Oral                        | 30                             | 26                    |                 | 3   | 11.53   | 10  | 38.46           | 10  | 38.46    | 23    | 88.80 |
| corticosteriods             |                                |                       |                 |     |   |     |                 |     |          |       |       |
| LMWH                        | 30                             | 24                    | -               | 5   | 20.80   | 6   | 25.00           | 7   | 29.10    | 18    | 75.00 |

Table 5: Relapse rate during follow up after treatment.

|                 | 2nd month       |   | 4 <sup>th</sup> month |     | 6 <sup>th</sup> month |       |  |
|-----------------|-----------------|---|-----------------------|-----|-----------------------|-------|--|
|                 | No. of patients | % | No. of patients       | %   | No. of patients       | %     |  |
| Corticosteroids | 0               |   | 1                     | 4.3 | 9                     | 39.13 |  |
| LMWH            | 0               |   | 1                     | 5.5 | 6                     | 33.3  |  |

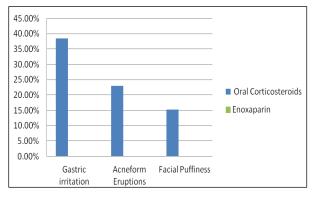


Figure 1: Comparison of side effects.

In LMWH group, 14 out of 24 showed excellent response (58.3%) (Figure 2 A and B) and 4 patients showed good response (16.6%) (Figure 3A and B). A total of 18 out of 24 patients i.e. 75% showed good to excellent response. The difference observed among different treatments was

statistically significant as chi-square value more than 5.99 with degree of freedom 2 and p is <0.05.



Figure 2: (A) Before treatment with LMW heparin; (B) excellent (Grade-4) response after treatment with LMW heparin at 8 weeks.

On the whole, 4 in group 1 and 6 in-group 2 dropped the treatment in the middle of the study in spite of the

counseling. After 4 weeks of treatment, response was observed in 3 cases i.e. 11.53% in Group 1 and 5 cases i.e. 20.8% in Group 2. After 6 weeks of treatment response was observed in 10 cases i.e. 38.46% in Group 1 and 6 i.e. 25% cases in Group 2 (Table 4).



Figure 3: (A) Before treatment; (B) good response after treatment with LMW heparin at 6 weeks.



Figure 4: (A) Before treatment with oral corticosteroids; (B) good response after treatment with oral corticosteroids after 8 weeks.

By the end of the trail i.e. of 8 weeks, response was observed in 10 (38.46%) and 7 (29.10%) with oral corticosteroids and low molecular weight heparin respectively.

No side effects were observed with low dose low molecular heparin. With oral corticosteroid gastric irritation in 10 (38.4%) cases, puffiness of face in 4 (15.3%) and acneiform eruption in 6 (23%) was observed respectively.

During the follow up period of six months, 4.3% and 5.5% of patients developed relapse in 4<sup>th</sup> month and 39.13% and 33.3% developed relapse in 6<sup>th</sup> month of oral corticosteroids, and low molecular weight heparin therapy respectively (Table 5).

The best response was observed in younger age group (100%) in both the groups and in older age group response rate was significantly low.

#### **DISCUSSION**

For LP, corticosteroids were the gold standard of therapy for the past few decades. Now, due to serious side effects encountered during long term use of corticosteroids, many different alternative therapies are tried; one among them being low dose low molecular weight heparin (LMWH) (Enoxaparin.)

Activated T lymphocytes have the ability to negotiate through vascular barriers, penetrate the extra cellular matrix and migrate to target tissues. Stability is related to their expression of enzyme. <sup>19</sup> Heparinase that degrades the heparin sulphate moiety of the proteoglycan of the extracellular matrix. <sup>20</sup>

In vitro and in vivo studies in animals showed that low dose heparin suppressed the expression of T-lymphocyte heparinase activity and concurrently inhibited T-cell migration and delayed type hypersensitivity.<sup>21</sup>

The immunomodulatory molecules in heparin inhibit the production of key proinflammatory cytokine- tumour necrosis factor-  $\alpha$  (TNF- $\alpha$ ). In humans, low dose low molecular weight heparin has also shown to inhibit the elicitation of allergic contact dermatitis.<sup>22</sup>

Out of 60 patients 40 patients i.e. 66.6% of lichen planus cases were detected in age group of 30-60 years. This is consistent with statement made in Fitzpatrick's text book of dermatology in general medicine i.e. at least two thirds of cases were between age group of 30-60 years. The mean age in the present study was 33.51 years which was consistent with the findings in Yusuf et al (34.26) and Salah et al (39.7). 23,24

In children, the incidence was 8.3% (total of 5 patients). This was in consistent with the statement made in Kumar et al, Luis-Montoya et al i.e., while LP is generally considered an adult disease, 5 to 10% of cases do occur in children. <sup>25,26</sup> In this study female patients outnumbered the men in ratio of 2.15:1, consistent with the one in Bolognia dermatology i.e. studies have found that women were affected approximately twice as often as men.

In the present study majority of patients were affected by classical lichen planus i.e. 58.3% (35 out of 60 patients). This was consistent with Kachhava et al study i.e. 52%.<sup>2</sup> On the other hand the incidence of classical lichen planus with mucosal involvement was 26.6% (16 out of 60 patients) in the present study which is almost near to the incidence of Kachhava et al, study that is 19 (Table 10).

Among 60 patients, finally 50 patients completed treatment modality. 26 patients were treated with oral

prednisolone and 24 patients were treated with low molecular weight heparin. The mean age of the group treated with oral prednisolone was 33.3 years and the group treated with low molecular weight heparin was 33.8 years. Total patients were 19 males and 41 females, 9 males and 21 females in the oral corticosteroid group and 10 men and 20 women were in subcutaneous enoxaparin group i.e. 88.8%.

The best results of response were observed in oral corticosteroid group of patients. Complete remission was seen in 59.69% (15 of 26 patients) and relative remission in 30.76% (8 of 26) patients. This is consistent with statement given in IADVL text book of dermatology i.e. that systemic steroids in gradually tapering doses are more helpful in treating lichen planus.<sup>27</sup>

In low dose low molecular weight heparin group clinical response achieved was in 75% cases i.e., complete clearance in 58.33% and relative remission in 16.66%. This is consistent with Hodak et al, study (80%); Pacheco et al study (71.3%) and Stefanidou et al study 61%. Whereas Hodak et al study claims complete regression of lesions in 4-10 weeks, this study got complete clearence in 8 weeks in 58.33% of cases. 3.28,29

By the end of six weeks 49.9% cases responded with oral corticosteroids, where as 45.8% responded with low dose low molecular weight heparin. But by end of eight weeks response rates were 88.8% and 75% in oral corticosteroids and low dose mow molecular weight heparin respectively.

During the follow up period of six months relapse were observed in 43.47% and 38.8% of patients on oral corticosteroids and low molecular weight heparin group respectively.

The important side effects reported with oral corticosteroids in the literature are proximal myopathy, psychological disturbances, peptic ulceration, hypertension, diabetes mellitus, purpura and striae. In the present study patients developed gastric irritation in 38.4%, puffiness of face in 15.3% and acneform eruption in 23% respectively. These subsided during follow up period thus there was no permanent damage. The Side effects reported with low dose mow molecular weight heparin are bleeding, thrombocytopenia, osteoporosis and allergic reactions to heparin. However, in the present study no side effects were reported. This is consistent with Hodak et al, study where none of the patients developed the above side effects.<sup>3</sup> This may be because; the dose of heparin is too low to produce side effects (Figure 1).

As expected it was the oral corticosteroids which gave relatively significant side effects. Among patients treated with oral corticosteroids patients in age group of 51-60 years responded less when compared to younger age patients.

As age advanced patients showed low response to treatment with low dose low molecular weight heparin. Response rates with oral corticosteroids as well as low dose low molecular weight heparin decreases as age advanced. Relapse rate is highest with oral corticosteroids and comparatively less with low dose low molecular weight heparin.

### **CONCLUSION**

Low dose low molecular weight heparin has not caused any side effects, oral corticosteroids have caused relatively significant gastric irritation in addition to puffiness of face and acneiform eruption. Thus, Low dose low molecular weight heparin in the treatment of lichen planus could be considered because of safety and effectiveness, however, oral prednisone therapy is important in certain cases, especially in cases requiring a rapid, more effective and reliable treatment.

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