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A prospective cohort study to determine the reduction of Itch Severity Score (ISS) in Lichen Planus treated with low molecular weight heparin in a tertiary care centre

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Introduction

Lichen planus (LP) is a T cell mediated disorder[(6)] that affects the skin and mucosa, exhibiting distinct morphologic and histopathological features.[(10)] The term Lichen is derived from Greek word (Leichen),[(6)] which means tree moss.[(20)] It is a self-limiting disease that affects mostly middle-aged people.[(13)] It can involve the skin, mucous membrane, hair and nails.[(6)] Oral lichen planus[(38)] can occur with or without skin lesions. The typical lesion of lichen planus is pruritic, polygonal, faintly erythematous to violaceous flat topped papule distributed over the flexors. Other morphological types[(9)] include hypertrophic, atrophic, vesicular and bullous lesions.[(13)] Koebner's phenomenon may be seen. Many causes have been implicated. Although spontaneous regression can occur in a few patients itching can be very troublesome. Various treatment options are available in the form of topical[(48)] and systemic therapy.[(46,47)] Low dose of low molecular weight heparin (Enoxaparin) was first used by Hodak et al[(1)] in 1988 at the dose of 3 mg in the treatment of lichen planus. Enoxaparin[(7)] is a disaccharide[(43)] moiety derived from heparin by a method of polymerization.[(37)] Unlike heparin it is devoid of anticoagulant property. Its immunomodulatory[(42)] and anti proliferative properties enables its use in lichen planus. Enoxaparin[(19)] inhibits the expression of heparanase enzyme (endoglycosidase) that is synthesized by CD4 cells. T lymphocytes heparanase[(44)] cleaves the heparin sulfate side chains of the extracellular matrix allowing the T cell to penetrate into subendothelial[(47)] basal lamina of the epidermis to reach the target tissues. Enoxaparin also inhibits delayed type hypersensitivity response.[(33,39)] It also acts by inhibiting the key pro- inflammatory cytokine tumour necrosis factor alpha.[(36,21)] Its anti-pruritic effect[(33)] is evident within a week of onset of the treatment. In our study Enoxaparin was given at a dose of 4mg subcutaneously every week to 100 patients for 9 weeks and the reduction in ISS was determined. The percentage of reduction was also analysed.

Study design: It is a prospective cohort study to determine the reduction in itch severity score in patients with generalized lichen planus and to calculate the percentage of reduction in itch severity score in male and female patients.

Patient selection: Study population of 100 patients aged between 18 and 60 years with generalized cutaneous lichen planus were included based on the inclusion and exclusion criteria. Study was started after getting clearance from the ethical committee.

Inclusion criteria:

1. Male and non pregnant non –lactating females between 18 and 60 years of age and who were willing to give consent.
2. Patients willing for follow up and being photographed.

Exclusion criteria:

1. Congenital or acquired haemostatic defects.
2. Uncontrolled hypertension, renal or hepatic insufficiency
3. H/O peptic ulcer, haemorrhagic stroke, hypersensitivity to enoxaparin, heparin or its derivatives.
4. History of intake of drugs inducing lichenoid reactions

Drug administration: After a complete basic investigation profile and specific tests like PT INR, APTT TO R/O any hemostatic defects, Enoxaparin was administered subcutaneously using prefilled syringes in the antero lateral or postero lateral abdominal wall, alternately on the left and the right side at a dose of 4 mg every week for 9 weeks. ISS was measured at 3, 6 and 9 months and serial photographs were taken. The percentage of reduction in ISS was also calculated.

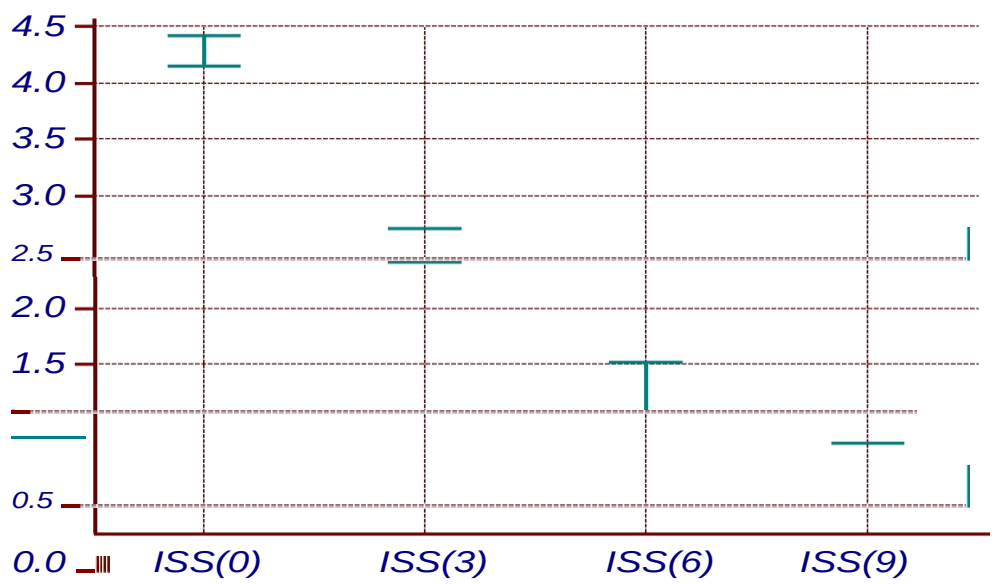
Clinical assessment: The efficacy of Enoxaparin was assessed by the following clinical parameter

1. Itch severity score (ISS):

Grade '0' -No itch
Grade '1' - Mild itch
Grade '2' - Moderate itch
Grade '3' - Severe itch
Grade '4' - Very severe itch
Grade '5' - Worst possible itch that interferes with daily activity.

Itch severity score was assessed periodically at 3, 6 and 9months after the beginning of the treatment.

Statistical analysis: The Statistical test was done using repeated measures ANOVA to determine the association between variables. The data obtained was represented as mean+/-SEM and percentages as applicable. A difference was considered as significant if the p value was <0.05.



Number of subjects		**100**				
Sphericity						
Method	Epsilon					
Greenhouse-Geisser	0.821					
Huynh-Feldt	0.843					
Test of Within-Subjects Effects						
Source of Variation		**Sum of Squares**	**DF**	**Mean Square**	**F**	**P**
Factor	Sphericity assumed	776.200	3	258.733	574.32	<0.001
	Greenhouse-Geisser	776.200	2.462	315.226	574.32	<0.001
	Huynh-Feldt	776.200	2.530	306.804	574.32	<0.001
Residual	Sphericity assumed	133.800	297	0.451		
	Greenhouse-Geisser	133.800	243.774	0.549		
	Huynh-Feldt	133.800	250.466	0.534		

Trend analysis

Trend	**t**	**DF**	**Significance**
Linear	-40.1030	99	P < 0.0001
Quadratic	7.3944	99	P < 0.0001
Cubic	0.4290	99	P = 0.6688

Within-subjects factors

Factor	**Mean**	**Std. Error**	**95% CI**
ISS_0_	4.2800	0.06679	4.1475 to 4.4125
ISS_3_	2.5600	0.07564	2.4099 to 2.7101
ISS_6_	1.3000	0.1106	1.0806 to 1.5194
ISS_9_	0.6200	0.09404	0.4334 to 0.8066

Pairwise comparisons

Factors			**Mean Difference**	**Std. Error**	**P [a]**	**95% CI**
ISS_0_	-	ISS_3_	1.720	0.0604	<0.0001	1.557 to 1.883
	-	ISS_6_	2.980	0.105	<0.0001	2.696 to 3.264
Group Statistics						
	Sex	**N**	**Mean**	**Std. Deviation**	**Std. Error Mean**	
% of reduction	M	42	80.79	23.232	3.585	
	F	58	90.86	16.334	2.145	

Independent Samples Test					
% of reduction	Equal variances assumed	**Levene's Test for Equality of variance**		**t-test for Equality of Means**	
		F	**Sig.**	**T**	**df**
		26.125	.000	-2.546	98
	Equal variances not assumed			-2.410	69.224

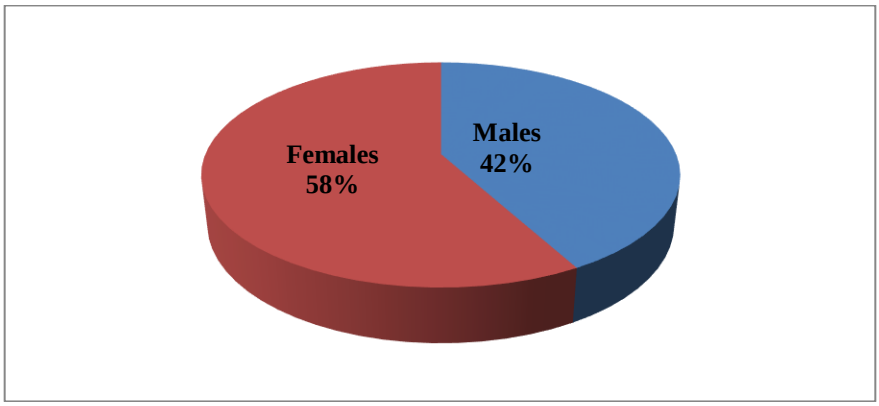
Independent Samples Test				
% of reduction	Equal variances assumed	**t-test for Equality of Means**		
		Sig. (2-tailed)	**Mean Difference**	**Std. Error Difference**
		.012	-10.068	3.955
	Equal variances not assumed	.019	-10.068	4.177

Independent Samples Test			
% of reduction	Equal variances assumed	**t-test for Equality of Means 95% Confidence Interval of the Difference**	
		Lower	**Upper**
		-17.916	-2.220
	Equal variances not assumed	-18.402	-1.735

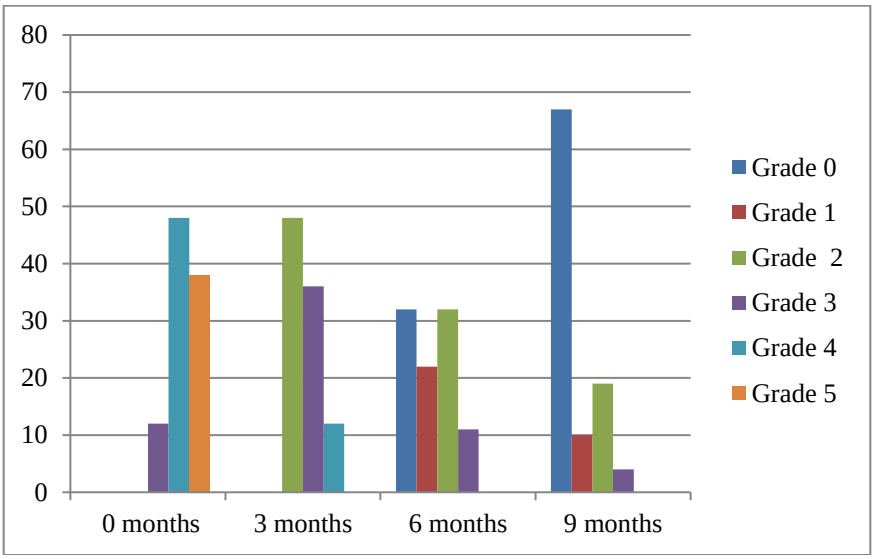
Results

100 patients with generalized lichen planus were given 4 mg of Enoxaparin sc every week for 9 weeks and the reduction in itch severity score was analysed. There were 42 males and 58 females in the study. The average age of the patients was 28.76 yrs. The duration of the disease in the study population was between 6 and 9 months. 48 patients had ISS score of grade 5, 34 had ISS score of grade 4 and 18 had ISS score of grade 3 during the beginning of the study. Clinical improvement was noticed in the form of decrease in ISS within 1 to 3 weeks of commencement of the drug. 25% and 64% of the patients showed complete disappearance of itch in 6 and 9 weeks respectively. There was a statistically significant reduction in itch severity score at 3, 6 and 9 months both within and between groups. The percentage of reduction was also found to be statistically significant with p value=0.012. The Mean, Std deviation and Std error of male and female population was 80.79, 23.232, 3.585 and 90.86, 16.334 2.145 respectively. Further it was found that the percentage of reduction was higher in females than in males.

Sex distribution



Reduction in ISS



Discussion

Lichen planus is one of the common dermatological diseases that can affect any age group. It affects both sexes equally. Although the exact cause of lichen planus is unknown, evidence show that cell-mediated immune response to surface antigens of keratinocytes is altered. T-Cell Lymphocyte attack the keratinocytes during the process and lymphocytotoxic cytokines are released from the keratinocytes and cause more damage to lymphocytes. Tumor necrosis factor (TNF) α is the pro-inflammatory cytokine[(16)] reported to play a role in the pathogenesis and inflammatory process of lichen planus. It has been reported that heparin inhibits the production of TNF. Various studies have been done to assess the efficacy of low molecular weight heparin in lichen planus. In many studies they used 3 mg of Enoxaparin subcutaneously for a period of 6 to 20 weeks. In our study, Enoxaparin 4 mg (20mg/0.2ml)[1] was given for 9 weeks. The common age group affected was between 20 – 40 yrs (78%) that was significantly higher than the study by Sehgal et al (46%)[(2)] and Kacchawa et al (47%).[(3)] There was a female preponderance in this study, which correlated with the study by Lodi et al[(4)] and Daramola et al.[(5)] Most of the cases included were with duration between 6 to 9 months, the range is greater than that reported by Sehgal et al[(2)] and Kacchawa et al[(3)] study (2 to3 months). All the patients had ISS of 3 or more during the beginning of the study.

Thus in our study there was complete disappearance of the itch in 67% with 15 reporting mild to moderate itch at the end of 9 months. In our study we also found the reduction in percentage to be statistically significant. And it was also found that the percentage of reduction was higher in females when compared to males.

Conclusion

As evidenced by 38% of females and 29% of males had complete disappearance of itch at the end of 9 months**.** Almost all the patients showed significant reduction in ISS at 3 months follow up. We conclude that Enoxaparin can be effectively used as monotherapy in the reduction of ISS in lichen planus. Larger studies are warranted to prove it further.

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