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Research Article

AN OPEN-LABEL RANDOMIZED CLINICAL STUDY OF TOPICAL NANOPARTICULATE ANTIPSORIATIC POLYHERBAL CREAM

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ABSTRACT

Objective: Objective of the study was to investigate the safety, efficacy, and antipsoriatic activity of topical cream enriched with Nanostructured Lipid Carriers (NLC) of *Azadirachta indica*, *Lawsonia inermis*, and *Mallotus philippensis* through the controlled clinical study.

Methods: The randomized controlled trial was performed for 12 months on 65 adult patients between the age group 20 and 60 years of either sex of diagnosed, uncomplicated cases of psoriasis Vulgaris. The Test group received a local application of the herbal antipsoriatic NLC enriched cream, while the Control group was treated with Clobetasol propionate 0.05% cream twice daily for 3 months. Both groups were assessed for parameters of skin and nail examinations, lab investigation, and Psoriasis Area and Severity Index (PASI) score. The data were analyzed and interpreted statistically.

Results: Significant improvement in itching and PASI score was seen during successive visits in both groups. However, recurrence of mild itching and erythema in a few patients of the control group was seen after 2 weeks, whereas no such recurrence is seen in the test group. Statistically significant reduction in eosinophilia in the control group was observed before and after treatment. The efficacy of clobetasol in the control group and the prepared formulation in the test group both show statistical efficacy at par.

Conclusion: The data suggest that the NLC enriched cream exhibited significant relief in all the symptoms of psoriasis and therefore can be used as a potent antipsoriatic agent due to the easy availability of the drugs and cultural affinity for herbal formulations.

Keywords: Psoriasis, Nanostructured lipid carriers, Cream, Clinical trial.

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INTRODUCTION

Psoriasis (Taqashshur-e-Jild) is a chronic inflammatory skin disorder characterized by red, scaly, and raised patches. Several attempts have been made in overcoming psoriasis with prolonged treatment duration and high cost. The oral antipsoriatic agents though quite effective are associated with renal, hepatic, and hematological toxicities [1,2]. Hence considering the high prevalence of the disease, and safe, economic topical application is the need. Attempts to use topical allopathic treatments such as corticosteroids, calcipotriene, retinoids, coal tar, anthralin, clobetasol propionate, methotrexate, and cyclosporines have failed due to their toxicities and inappropriate formulation design of the conventional dosage forms [3]. The literature survey supports an anti-inflammatory activity of *Azadirachta indica* leaves, *Lawsonia inermis* leaves, and fruit of *Mallotus philippensis* and has been used in combination in traditional medicine in the treatment of psoriasis [3]. The antipsoriatic potential of the *A. indica* leaves extract (AE), *L. inermis* leaves extract (LE) and fruit extract of *M. philippensis* (ME) enriched Nanostructured Lipid Carriers (NLCs) and their cream formulation has been reported and discussed in our previous work [3-5]. With positive outcomes from the preclinical studies, we further focused on the validation of the clinical efficacy of Nano-particulate antipsoriatic cream to that of the Clobetasol propionate 0.05% cream. It is noteworthy that the topical safety of NLCs has been reported in the literature [6-8]. Through this research, the authors have investigated the safety, efficacy, and antipsoriatic activity of topical cream enriched with NLC of *A. indica, L. inermis,*and *M. philippensis* through a randomized controlled trial was performed for 12 months on 65 adult patients between the age group 20 and 60 years of either sex of diagnosed, uncomplicated cases of psoriasis Vulgaris.

MATERIALS AND METHODS

Materials

Dried herbs of *A. indica* leaves, *L. inermis* leaves, and *M. philippensis* powder were purchased from local vendors and authenticated (Ref No.: Bot/10/2017) from the Department of Botany, SavitribaiPhule University of Pune, India. The solid lipids were obtained as gift samples from Gattefosse, France. Rest all chemicals were of AR grade and were purchased from Sigma Aldrich.

i. Test drug: Topical Nanoparticulate antipsoriatic herbal cream was prepared in collaboration with the Department of Pharmaceutics of Allana College of Pharmacy, Azam Campus, Camp, and cleared by animal testing and cell line studies
ii. Standard drug: Clobetasol Propionate 0.05% cream.

Methods

The study protocol was approved by the Member Secretary Ethics Committee of MCE Society vide letter dated 30/9/2014, MCES/EC/2014/01. In the present study, 65 patients of diagnosed, uncomplicated cases of psoriasis, between the age group 20 and 60 years of either sex enrolled in the test as well as in the control group. The sample size was estimated based on an estimated average 4% prevalence of psoriasis in India. The sample size was calculated using principles of statistics [9], using the formula:

$$(N) = 4pq / x^2$$

Where, N=Sample size, p=prevalence (4%), q=1-p (100-4=96), x is the permissible error (5%).

Substituting the above values we get

$$N = (4 \times 4 \times 96) \div 25$$

N=61.4=62

Therefore, a sample size of 32 in each group, that is, control and test groups was included with a total of 65 patients for an open-labeled, randomized controlled clinical study with a duration of 12 months at skin outpatient department of Z. V.M. Unani Medical College and Hospital Pune. The Inclusion criteria were diagnosed, uncomplicated cases of psoriasis not suffering from any other illness, age between 20 and 60 years of either sex. Moreover, the exclusion criteria included (1) complicated cases of psoriasis, (2) patients with secondary infection, (3) pregnant and lactating women, (4) immuno-compromised patients, and (5) diabetes mellitus, cancer. The withdrawal criteria were (1) fail to follow-up for more than two visits, (2) any adverse effects observed during treatment, and (3) progression of the disease. The patients were clinically evaluated for General, Systemic and Local Examination.

General examination

The parameters such as pallor, cyanosis, edema, and patients built; blood pressure and pulse rate; general examination of clubbing, tongue, lymphadenopathy, nails, teeth and gums, eyes, nose, mouth, and throat.

Systemic examination

Cardiovascular system, respiratory system, gastrointestinal tract, central nervous system, obstetric.

Local examination

Examination of skin to assess site, shape, color, and scaling, and the border of lesions in the regions of Head/Trunk/Arms/Legs.

- Color: Red, White, Whitish
- Scaling: Present/Absent
- Border: Ill-defined/well defined
- Erythema: Present/Absent
- Surface: Smooth/Rough/Thin/Thick
- Plaques Formation: Present/Absent.

Examination of the nails

Pitting/brittle/sub fungal growth, Candle Grease Sign, Auspitz Sign, Koebner's phenomenon.

Study protocol

A local application of the Unani antipsoriatic nanoparticulate-based cream was given to the Test group of 32 patients twice daily for 3 months, while the Control group of 33 patients received Clobetasol propionate 0.05% cream twice daily for 3 months after obtaining their written consents. A detailed medical history of all patients was recorded. The symptomatic evaluation was performed using the Psoriasis Area and Severity Index (PASI) index (As per Performa). The total symptom score was based on body parts involved (head, trunk, arms, and legs) and on severity parameters such as itching, erythema, scaling, and thickness. All patients were randomly divided into two groups (standard group and test group). Laboratory Investigations of Patients were performed to record their hemogram, blood sugar level, urine routine, and urine microscopic examination. The patients were followed up for 3 months at 0 days and intervals of 15, 30, 60 and after completion of 90 days. The therapeutic response of the patients was assessed according to PASI score before, during follow-up and after completion of treatment. A general clinical checkup was performed during each follow-up visit. All adverse events reported or observed by the patients or investigator were recorded along with information about the date of onset, duration and severity, and action taken regarding the topical applications. Patients were allowed to withdraw voluntarily from the study. Such five patients had withdrawn from the study due to irregular follow-ups and progression of itching in one patient. Data thus obtained were presented in the form of tables and graphs by the use of MS-Excel and SPSS software version 20. Quantitative parameters (PASI score) were analyzed using a t-test and qualitative parameters (symptoms) were analyzed using the Chi-square test. The Chi-square test involves the use of parameters to test the statistical significance of the observations understudy and determines whether or not a relationship exists between the two variables. Probability (p)<0.05 would be considered significant.

RESULTS AND DISCUSSION

An open-label, randomized controlled clinical trial was conducted to evaluate the safety and efficacy of UnaniAntipsoriatic lipid-based cream for topical application in Taqashshur-e-Jild. Intending to evaluate clinical safety and efficacy of classical Unani medicines prescribed by Hakims and to formulate Lipid-Based Nano-particulate Topical Drug Delivery System in the treatment of Taqashshur-e-Jild (Psoriasis) using various modern scientific parameters, the objective of the present study was to: assess the efficacy and safety of Unani Anti-Psoriatic cream in uncomplicated cases of psoriasis, controlled clinical study of topical nanoparticulate antipsoriatic Unani formulation with that of Clobetasol propionate 0.05% cream was performed on the human volunteers with the statistical presentation, analysis, and interpretation after applying appropriate tests of significance to compare the safety and efficacy of nanoparticulateUnani antipsoriatic formulation and Clobetasol propionate 0.05% cream. In the present study, 65 patients of diagnosed, uncomplicated cases of psoriasis, between the age group 20 and 60 years of either sex were included. The Test group received a local application of the Unani antipsoriatic nanoparticulate-based cream twice daily for 3 months, while the Control group received Clobetasol propionate 0.05% cream twice daily for 3 months after obtaining written consent from the patients. The duration of the study was 12 months. The allotment of patients was random. 32 patients each were enrolled in the test as well as in the control group. Five patients were lost to follow-up (2 patients of the test group complained of itching, hence they withdrew from the study, and 3 patients of the control group withdrew based on irregular follow-ups). Observations were based on clinical assessment of the patients. Age Distribution in the control group, out of 32 patients, 19 patients (59.38%) were between the age group of 25 and 35, 11 (34.38%) were between the age group of 36 and 46 and 02 patients (6.25%) were between the age group of 47 and 57. Whereas, in the test group, out of 32 patients, 12 patients (37.60%) were between the age group of 25 and 35, 11 patients (34.38%) were between the age group of 36 and 46, 09 patients (28.13%) were between the age group of 47 and 57. Statistically not significant (p<0.05 is considered statistically significant). Thus, the control group and test group are comparable. Most of the patients in both groups belong to 25–35 years of age, with a predominance of females from the middle class. Thus, the control group and test group are comparable. Addiction wise distribution in the control group indicates that 15 patients (46.88%) with smoking habits, 04 patients (12.50%) were alcoholics, 01 patients (03.13%) with tobacco, and 02 patients (06.25%) with chewing pan habits; finally, 14 patients (43.75) without any addiction. Whereas in test group, 09 patients (28.13%) were smoking, 02 patients (06.25%) were drinking alcohol, 02 patients (06.25%) were chewing tobacco, and 07 patients (21.88) were chewing pan; finally, 16 patients (50.00) having no addiction. The Chi-square value of 5.411 with p=0.247 indicates the test is statistically not significant (p<0.05 is considered statistically significant). Thus, the control group and test group are comparable. Table 1 shows the demographic data for the completion of treatment control and test groups.

From Table 1, it can be interpreted that both the groups have completed the treatment reasonably, that is, in the test group, PASI scores touched zero in two cases at visit three. One patient was lost to follow-up after visit three, with a score of 0.3. The Chi-square value of 3.148 with p=0.076, indicating that the results were not statistically significant (p<0.05 is considered statistically significant).

As expected and can be predicted from Table 2, itching was most commonly seen in both groups (100%). The frequency of other symptoms was comparable in both the groups, and the difference

Table 1: Data on completion of treatment

Completion of treatment	(Control Group) n=32		(Test Group) n=32		p-value
	No.	%	No.	%	
Treatment completed	32	100	29	90.63	0.076
Treatment not completed	0	0.00	3	9.38	
Total	32	100	32	100	

Table 2: Chief complaints of patients on first visit

Complaints	(Control Group) n=32		(Test Group) n=32		p-value
	No.	%	No.	%	
Itching	32	100	32	100	0.943
Scaling	25	78.13	28	87.50	
Chronicity	0	0.00	0	0.00	
Erythema	0	0.00	0	0.00	
Psoriatic Arthopathy	0	0.00	0	0.00	
Thickness of Skin	25	78.13	18	56.25	

Table 3: Trigger history for the onset of psoriasis

Trigger of psoriasis	(Control Group) n=32		(Test Group) n=32		p-value
	No.	%	No.	%	
Chemical	1	3.13	0	0.00	0.568
Cold	6	18.75	2	6.25	
Detergent	3	9.38	2	6.25	
Dust	1	3.13	1	3.13	
Heat	5	15.63	2	6.25	
Hot weather	1	3.13	0	0.00	
Smoking	1	3.13	1	3.13	
Stress	6	18.75	11	34.38	
Summer	1	3.13	1	3.13	
Sweat	0	0.00	1	3.13	
Washing Powder	1	3.13	0	0.00	
Soap	0	0.00	1	3.13	
Water	2	6.25	2	6.25	
Winter	2	6.25	2	6.25	
Rains	0	0.00	1	3.13	
Dry skin	0	0.00	2	6.25	
Unknown	2	6.25	3	9.38	

Table 4: General examination

General examination	(Control Group) n=32		(Test Group) n=32		p-value
	No.	%	No.	%	
Built					
Thin	16	50.00	16	50.00	0.596
Average	16	50.00	15	46.88	
Obese	0	0.00	1	3.13	
Pallor					
Yes	0	0.00	0	0.00	1.000
No	32	100	32	100	
Cyanosis					
Yes	0	0.00	0	0.00	1.000
No	32	100	32	100	
Edema					
Yes	0	0.00	0	0.00	1.000
No	32	100	32	100	

was not statistically significant at the initiation of treatment as can be predicted from the Chi-square and p=1.21 and 0.943, respectively.

Table 5: Examination of skin

Skin examination	(Control Group) n=32		(Test Group) n=32		p-value
	No.	%	No.	%	
Site of Lesion					
Trunk	3	9.38	6	18.75	0.444
Legs	8	25.00	9	28.13	
Head	2	6.25	2	6.25	
Arms	14	43.75	14	43.75	
Head, Trunk	5	15.63	1	3.13	
Shape of Lesion					
Regular	2	6.25	0	0.00	0.470
Irregular	24	75.00	26	81.25	
Rounded	5	15.63	4	12.50	
Rounder Irregular	1	3.13	2	6.25	
Color					
Red	27	84.38	29	90.63	0.864
White	2	6.25	1	3.13	
Red, White	2	6.25	1	3.13	
Whitish	1	3.13	1	3.13	
Scaling					
Present	25	78.13	25	78.13	1.000
Absent	7	21.88	7	21.88	

Table 6: Examination of the skin

Skin examination	(Control Group) n=32		(Test Group) n=32		p-value
	No.	%	No.	%	
Border of lesions					
Ill Defined	31	96.88	29	90.63	0.301
Well Defined	1	3.13	3	9.38	
Erythema					
Absent	29	90.63	31	96.88	0.301
Present	3	9.38	1	3.13	
Surface					
Smooth	4	12.50	7	21.88	0.494
Rough	5	15.63	9	28.13	
Thick	17	53.13	11	34.38	
Thin	2	6.25	2	6.25	
Rough, Thick	4	12.50	3	9.38	
Plaque Formation					
Present	1	3.13	1	3.13	1.000
Absent	31	96.88	31	96.88	

Table 7: Examination of nails

Examination of nails	(Control Group) n=32		(Test Group) n=32		p-value
	No.	%	No.	%	
Koebner's Effect	30	93.75	27	84.38	0.401
Candle Grease sign	2	6.25	4	12.50	
Auspitz sign	0	0.00	1	3.13	

The symptom of itching, which was seen in 100% of patients, has not been included in the PASI score. Table 3 depicts the demographic data about the trigger history for the onset of psoriasis in both groups. The Chi-square value of 7.666 and probability p=0.568 indicates statistical insignificance. Thus, the control group and test group are comparable. However, it was interesting to note that, as expected, stressors were the most important triggers to initiate and exaggerate the symptoms (in the control group 18.75% and test group 34.38%).

The patients were assessed clinically through general examinations (Table 4 and Fig. 1 and Fig. 3) and systemic examinations (Tables 5-7 and Fig. 4 for the parameters such as skin examination that includes

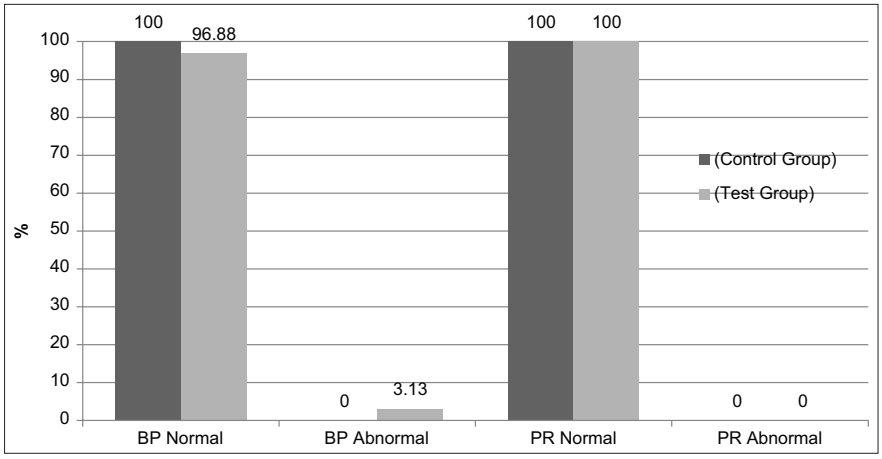

Fig. 1: General examination of blood pressure and pulse rate

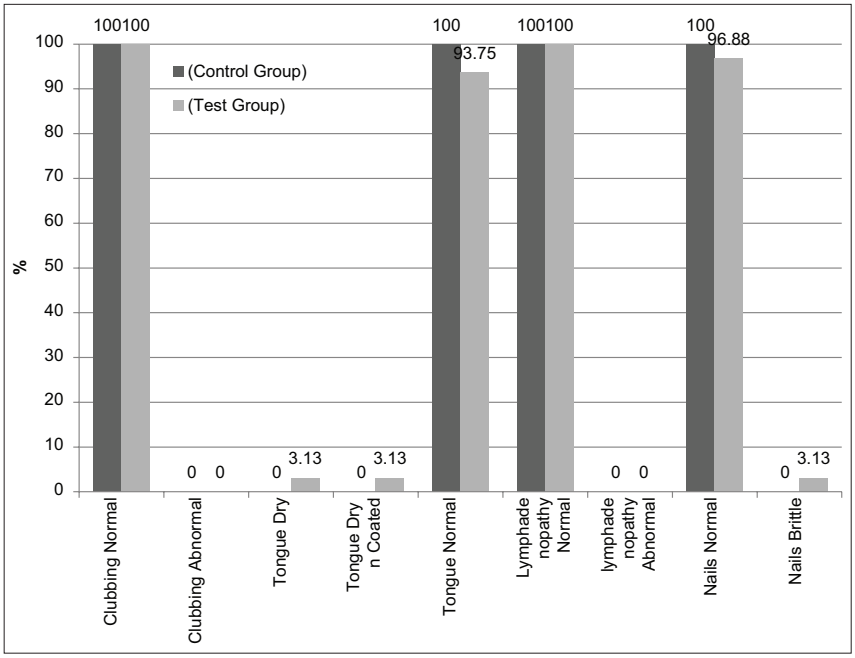

Fig. 2: General examination of clubbing, tongue, lymphadenopathy, and nails

Table 8: Laboratory investigations of patients

Laboratory Investigations	(Control Group) n=32				(Test Group) n=30			
	Before		After		Before		After (n=30)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
HB%	12.87	1.20	12.47	0.90	12.31	1.33	12.49	1.40
Total WBC count	6512.50	1301.05	6518.75	1072.36	6287.50	1346.14	6420.00	1316.84
Lymphocytes	14.22	16.82	13.13	15.51	18.56	14.44	17.86	15.21
Eosinophils	2.28	0.81	1.88	0.55	2.56	0.72	2.17	1.02
Basophils	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Monocytes	1.69	0.54	1.50	0.51	1.87	0.50	1.60	0.77

site, shape, color and scalings, surface, erythema, and border of lesions; plug formation, an examination of nails to detect Koebner's Effect, Candle Grease Sign and Auspitz Sign).

As evident from Table 4, none of the parameters such as pallor, cyanosis, edema, and patients built show any significant difference between the two groups. Statistically not significant. Thus, the control group and test group are comparable.

Statistically not significant ($p<0.05$ is considered statistically significant). Thus, the control group and test group are comparable.

As evident from Tables 5-7, scalings and thickness of skin were observed in both groups. Stress triggered exaggerated the symptoms. The most common lesion involved the arms followed by legs, trunk, and head. The shape of the lesions was irregular and red. Scaling was present in most of the patients, plaque formation was absent in most of the patients.

Table 9: Laboratory investigations of patients

Laboratory investigations	(Control Group) n=32				(Test Group) n=32			
	Before		After		Before		After	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
Blood sugar Level	102.13	16.32	100.27	10.15	99.92	14.39	102.14	20.18
Urine Routine	-	-	-	-	-	-	-	-
Urine Microscopic	-	-	-	-	-	-	-	-

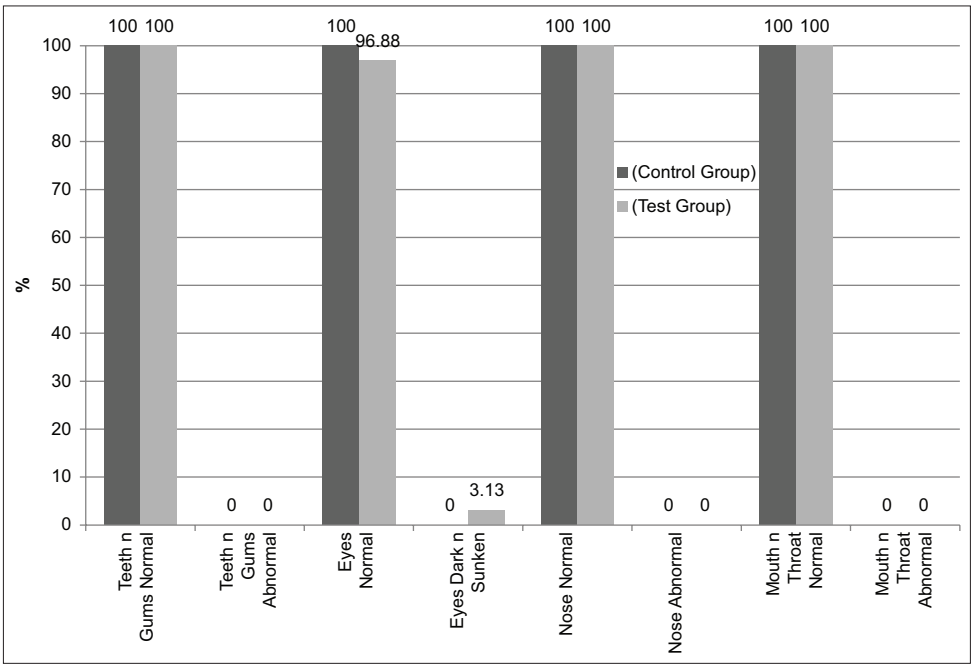

Fig. 3: General examination of teeth and gums, eyes, nose, mouth, and throat

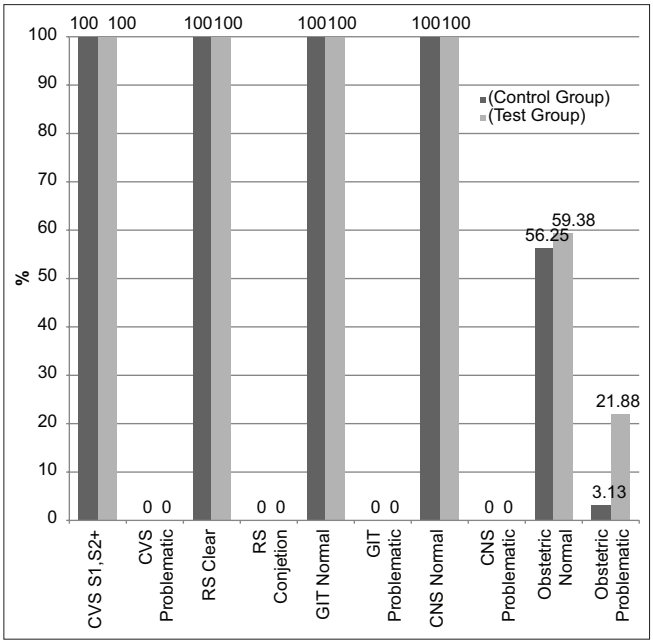

Fig. 4: Systemic physical examination of patients

Koebner's effect was also seen in the majority of the patients. Follow-up was done after every 15 days.

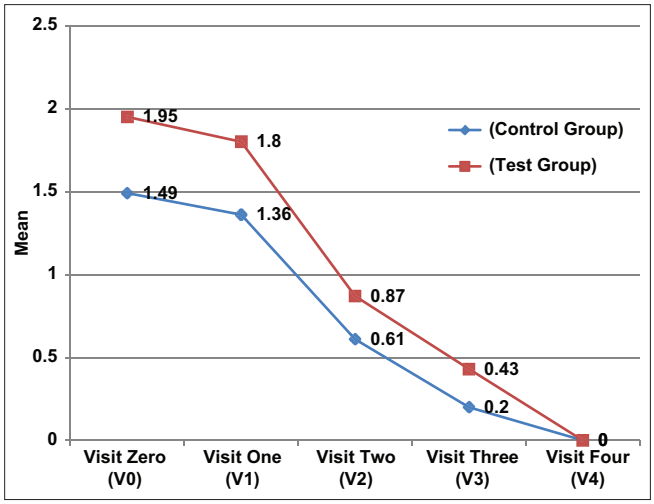

Fig. 5: Psoriasis area and severity index scores

The data of the Lab investigation are shown in Tables 8 and 9, statistically significant reduction in eosinophilia in the control group was observed before and after treatment. Fig. 5 presents visit-wise PASI score. Psoriasis was triggered in the rainy and winter season. The itching was present in 100% of patients at the first visit. Significant improvement in itching and PASI score was seen during successive visits in both groups, that is, control group and test group. However,

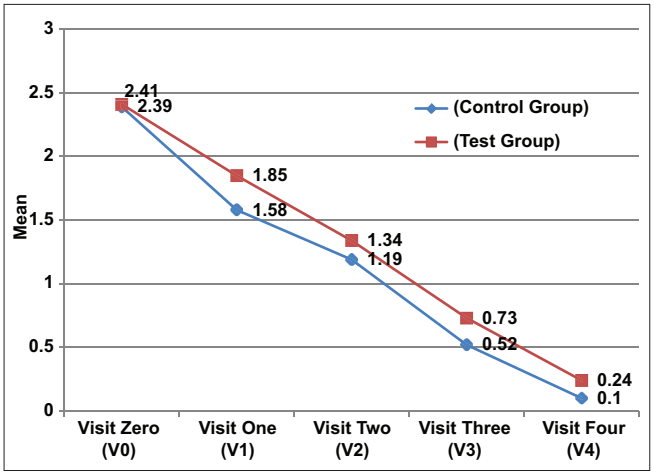

Fig. 6: Itching scores

recurrence of mild itching and erythema in a few patients of the control group was seen after 2 weeks, whereas no such recurrence is seen in the test group. Fig. 6 depicts the Itching scores in patients. The itching was controlled in the control group during the second visit, whereas significant improvement in itching was observed in the third visit in the test group.

FUTURE DIRECTION AND CONCLUSION

In the present study, according to the collected data, it can be concluded that AE, LE, and fruit extract of ME loaded NLC-based cream show significant relief in all the symptoms of Taqashshur-e-Jild (Psoriasis). Esthetically, also the prepared NLC-based cream containing the above-mentioned drugs is highly impressive and acceptable. The efficacy of clobetasol in the control group and the prepared formulation in the test group both show statistical efficacy at par. Therefore, AE, LE and fruit extract of ME loaded NLC-based cream can be used as a potent antipsoriatic agent due to the easy availability of the drugs and cultural affinity for herbal formulations.

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AUTHOR CONTRIBUTION

The authors formulated and evaluated the dosage forms required for conducting the study, conducted, collected, and processed the data in detail, including statistical analysis, and further interpreted the data and prepared the manuscript.

CONFLICT OF INTEREST

None declared.

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