NEEM

A clinical study to evaluate the efficacy and safety of Neem caplets in Acne Vulgaris: A double blind placebo controlled study

INVESTIGATOR

Dr. Uma Agarwal

Skin, Hair, Allergy & Cosmetology Specialist

Srirampore, Hooghly

Himalaya™

WELLNESS SINCE 1930

OBJECTIVES OF THE STUDY

To evaluate the safety and efficacy of a pure herb Neem (Azadirachta indica) in patients suffering from acne vulgaris.

STUDY DESIGN

Double blind placebo controlled study.

PRIMARY ENDPOINTS

The primary end point was clinical recovery from the signs and symptoms of Acne vulgaris

SECONDARY ENDPOINTS

Incidence of adverse effects and overall compliance to the drug.

INCLUSION CRITERIA

- Adult patients of both sex suffering from mild to moderate acne vulgaris.
- Both male and female patients aged more than 18 years of age.
- Patients willing to give written informed consent and comply with the study procedures.

EXCLUSION CRITERIA

- Patients with below eighteen years of age
- Patients presenting with severe acne-vulgaris,
- Pre-existing systemic disease necessitating long-term medications, genetic and endocrinal disorders,
- subjects with known history or present condition of allergic response to any cosmetic/herbal products, toiletries or its components or ingredients in the test products
- Pregnant and lactating women.
- Patients not willing to give written informed consent.

STATISTICAL ANALYSIS

The values are expressed as Mean ± SD. Statistical analysis was carried out using Fisher's Exact Test using GraphPad Prism, Version 4.03 for windows, Graphpad Software, San Diego, California, USA. for presence or absence of various signs and symptoms. Repeated measures of ANOVA followed by Dunnett's Multiple Comparison Posthoc Test were used for the analysis clinical parameters.

METHODOLOGY

Ninety six subjects aged between 18 to 34 years suffering from mild to moderate acne vulgaris and who were willing to give informed written consent were included in the study. After obtaining informed consent baseline history was obtained which include personal data, a description of symptoms and details of past medical history, family history of acne, history of possible exacerbating factor/s, etc. Thereafter all patients underwent a clinical examination and thorough skin examination. The grading of acne vulgaris was as follows:

Grade I: Mild acne with only papules;

Grade II: Moderate acne with papules and comedones;

Grade III: Severe acne with papules and pustules;

Grade IV: Very severe acne with papules, pustules and cysts.

GRADING OF ALS WAS AS FOLLOWS

GRADE	% REDUCTION IN ALS
0	No reduction in ALS.
1	< 25% reduction in ALS.
2	25-49% reduction in ALS.
3	50-74% reduction in ALS
4	> 75% reduction in ALS.

Patients were randomly treated with either Neem caplet or a similar looking placebo at a dose of 1 caplet once daily for a period of 6 weeks. Patients were instructed not to use any other medication for acne. The response to therapy was evaluated at intervals of two weeks up to the six weeks by calculating the ALS and the efficacy was determined by the percentage reduction in the ALS at the end of six weeks of treatment. Improvement in the form of reduction in the ALS was graded.

During each follow-up visit, local skin examination was done and observations were recorded in the case report form. In addition, patients were also evaluated for control of local inflammation (erythema and telangiectesia), new comedone (black and white) formation, relief of pruritus and pain in inflamed acne lesions, soothing and moisturizing effects and healing without hyperpigmentation or scarring were also considered for the overall response to the treatment. In case any adverse effects were reported, or observed by the subjects were recorded with information about severity, date of onset, duration and action taken regarding the study drug. Relation of adverse events to study medication was predefined as *"Unrelated"* (a reaction that does not follow a reasonable temporal sequence from the administration of the drug), *"Possible"* (follows a known response pattern to the suspected drug, but could have been produced by the subject's clinical state or other modes of therapy administered to the subject), and *"Probable"* (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the subject's clinical state).

Subjects were allowed to voluntarily withdraw from the study, if they had experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For subjects withdrawing from the study, efforts were made to ascertain the reason for dropout. Non-compliance (defined as failure to take less than 80% of the medication) was not regarded as treatment failure, and reasons for non-compliance were noted.

RESULTS

The demographic details of both the groups neem caplet and placebo namely are listed in table 1. All subjects completed the study as planned. Data of all the patients was available for analysis.

Table 1

DEMOGRAPHIC DATA OF PATIENTS ON ENTRY (n=96)

PARAMETERS		NEEM CAPLET (n=25)	PLACEBO (n=48)
Age in years (mean ± SD)		27.38 ± 08.06	24.72 ± 07.56
Weight in Kg (mean ± SD)		64.10 ± 12.35	56.60 ± 18.70
Sex ratio/ M:F		22:26	20: 28
H/o smoking (No. of cases)		6	4
H/o alcohol consumption (No. of cases)		2	2
Diet (veg/mixed)		24/24	28/20
H/o acne-vulgaris (years)		1.2 ± 0.9	1.44 ± 0.89
SKIN TYPE	Normal to dry skin (No. of patients)	12	15
	Dry skin (No. of patients)	4	2
	Normal to oily skin (No. of patients)	13	14
	Oily skin (No. of patients)	19	17

The results of subjects treated with Neem caplet is as follows. Most patients started responding to the therapy at the end of 2 weeks of treatment. At 4th week follow up, 16 patients showed moderate response (25-49% reduction in acne lesions), 10 patients showed good response (50-74% reduction). At the end of 6 weeks treatment, 8 patients showed excellent response, 15 patients showed a good response, 14 patients showed moderate response and 04 patients showed poor response.

There was significant reduction in black and white comedones after treatment Significant reduction in black comedones was observed from 10.11 ± 8.01 at entry to 7.30 ± 4.85, 4.20 ± 4.06 and 2.08 ± 0.16 at the end of 2, 4 and 6 weeks of treatment, respectively with significance of $p<0.001$. There was also a significant reduction in white comedones from 7.71 ± 4.04 at entry to 5.21 ± 3.02, 3.37 ± 1.01 and 1.27 ± 0.30 at the end of 2, 4 and 6 weeks of treatment, respectively with significance of $p<0.001$ (Table 3). Significant reduction in papules was obsereved from 16.08 ± 7.40 at entry to 12.60 ± 7.34, 9.80 ± 6.35 and 5.25 ± 2.54 at the end of 2, 4 and 6 weeks of treatment, respectively with significance of $p<0.001$.

Table 2

ACNE LESION SCORE OBSERVED AT THE INTERVAL OF TWO WEEKS (n=96)

ACNE LESION SCORE	CASES					
	NEEM CAPLET (n=48)			PLACEBO (n=48)		
	Week 2	Week 4	Week 6	Week 2	Week 4	Week 6
0 (No reduction in acne lesion score)	18	10	04	28	19	15
1 (< 25% reduction in acne lesion score)	20	12	07	10	18	16
2 (25-49% reduction in acne lesion score)	10	16	14	10	11	12
3 (50-74% reduction in acne lesion score)	-	10	15	-	-	05
4 (> 75% reduction in acne lesion score)	-	-	08	-	-	-

In addition, The mean baseline score for erythema significantly reduced from 1.08 ± 1.00 to 0.98 ± 0.64, 0.38 ± 0.18 and 0.24 ± 0.14 at the end of 2, 4 and 6 weeks, respectively. The mean baseline score for telangiectesia significantly reduced from 0.34 ± 0.12 to 0.23 ± 0.11, 0.14 ± 0.04 and 0.12 ± 0.05 at the end of 2, 4 and 6 weeks, respectively. Good response was also noted in reduction in inflammation and pruritis. Majority of the patients experienced a soothing effect with neem caplet. There was no hypersensitivity or flaring of lesions seen during the treatment. None of the patients reported any adverse effects during the entire period of the trial. No worsening of acne infection was observed in any patient during the trial. There were no significant clinical improvement in patients treated with placebo.

Table 3

OVERALL RESPONSE AT THE INTERVAL OF TWO WEEKS (n=96)

	NEEM CAPLET (n=48)				PLACEBO (n=48)			
Overall Response (score)	At entry	Week 2	Week 4	Week 6	At entry	Week 2	Week 4	Week 6
Black comedones	10.11 ± 8.01	7.30 ± 4.85*	4.20 ± 4.06**	2.08 ± 0.16**	10.21 ± 8.14	09.30 ± 3.87	8.20 ± 2.16	7.88 ± 0.16
White comedones	7.71 ± 4.04	5.21 ± 3.02*	3.37 ± 1.01**	1.27 ± 0.30**	7.79 ± 3.84	7.21 ± 3.11	6.87 ± 1.22	7.02 ± 1.33
Papules	16.08 ± 7.40	12.60 ± 7.34*	9.80 ± 6.35**	5.25 ± 2.54**	15.67 ± 7.30	15.60 ± 5.34	15.11 ± 7.35	14.25 ± 2.88
Erythema	1.08 ± 1.00	0.98 ± 0.64	0.38 ± 0.18	0.24 ± 0.14	1.58 ± 0.89	1.49 ± 0.54	1.38 ± 0.22	1.40 ± 0.14
Telangiectesia	0.34 ± 0.12	0.23 ± 0.11	0.14 ± 0.04	0.12 ± 0.05	0.36 ± 0.32	0.33 ± 0.11	0.24 ± 0.14	0.24 ± 0.05
Pruritis	0.76 ± 0.54	0.36 ± 0.25	0.20 ± 0.14	0.04 ± 0.02	0.76 ± 0.56	0.75 ± 0.55	0.58 ± 0.44	0.54 ± 0.32
Hyper-pigmentation	1.68 ± 0.90	1.02 ± 0.47	0.88 ± 0.58	0.62 ± 0.30	1.98 ± 0.90	1.62 ± 0.32	1.48 ± 0.88	1.29 ± 0.80

Values are expressed in mean ± SD. *p<0.01 as compared to "At entry" values,
**p<0.001* as compared to "At entry" values.

DISCUSSION & CONCLUSION

Acne is a common disease of the pilosebaceous units of the skin and it is an end result of the interplay of multiple factors. Various treatment modalities are adapted to treat acne. These include locally applicable antibacterial agents like erythromycin and various systemic drugs.