

COMPARATIVE STUDY TO EVALUATE THE EFFICACY OF LOW-DOSE ISOTRETINOIN TO STANDARD DOSE ISOTRETINOIN IN MODERATE-TO-SEVERE GRADES OF ACNE VULGARIS

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ABSTRACT

BACKGROUND

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit characterised by comedones, papules, pustules, nodules and cysts, which may later on develop into scarring. This disease occurs worldwide and usually starts in adolescence and resolves in the mid 20s. Initially, isotretinoin was used only for severe grades of acne, but in recent years, this drug has been increasingly prescribed in moderate cases of acne unresponsive to the conventional treatment. Isotretinoin is the most dependable acne treatment and maybe justified in moderate grades of acne where scarring is imminent or acne associated with psychological diseases. Though the recommended dose produces good results, it causes many side effects, cheilitis being most common. To overcome these side effects, lower doses of isotretinoin are being tried in various clinical trials.

MATERIALS AND METHODS

The study was conducted on 80 patients of acne attending the Outpatient Department of Dermatology at a tertiary care hospital. The patients fulfilling the inclusion and exclusion criteria were enrolled or excluded. The assessment of effectiveness was done using 'total acne load' and follow up of patients were done after 2nd, 4th, 8th, 12th week and 16th of initiation of treatment.

RESULTS

On comparison of group 1 with group 2 with Student's t-test, p value was 0.10 at 2 weeks of therapy indicating there was no difference between the efficacies of these two treatment groups at 2 weeks. However, the p value calculated for 4 weeks, 8 weeks, 12 weeks and 16 weeks were 0.01, 0.00, 0.00 and 0.00. This indicated that therapy with standard dose was more effective.

CONCLUSION

The results from this study indicate that on comparing total acne load at end of 16 weeks therapy, low-dose isotretinoin therapy is slightly less in efficacy (87.31%) than standard dose isotretinoin therapy (94.45%), but they are comparable. Taking into account, the side effect profile, they are significantly less in incidence and severity in low-dose therapy than the standard-dose therapy.

KEYWORDS

Isotretinoin; Low Dose; Standard Dose.

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BACKGROUND

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit, characterised by comedones, papules, pustules, nodules and cysts, which may later on develop into scarring.¹ This disease occurs worldwide and usually starts in adolescence and resolves in the mid 20s.²

Although, acne is not an inherited condition, there is an inherited predisposition. Several genes are believed to be involved of which only the gene for Cyt P450 1A1 and the

gene for steroid 21-hydroxylase are documented. Positive family history is obtained in 40% of patients.³

Acne has a variable impact on the quality of life. Besides anxiety and depression, acne patients are more prone to low self-esteem, low confidence and social inhibition.

The primary pathognomonic lesion of acne is 'microcomedone.' The formation of microcomedone requires a complex interplay of multiple factors-

1. Altered follicular keratinisation.
2. Hyperplasia of sebaceous glands.
3. Over colonisation of sebaceous follicles with P. acne.

Acne is classified by Indian Acne Alliance in 3 grades.⁴
Grade 1 (Mild)- Predominance of comedones, occasional papules.
Grade 2 (Moderate)- Predominance of papules, few pustules.

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Grade 3 (Severe)- Predominantly pustules, nodules and abscess.

Isotretinoin (13-cis-retinoic acid) is a derivative of retinol (vitamin A). It is the most potent antiacne agent available today and the only one that addresses all the pathogenic mechanisms.⁵ It is a FDA approved drug for the treatment of severe nodular acne that has proven unresponsive to conventional therapy including systemic therapy since 1982. The conventional recommended dose is 0.5 to 1 mg/kg/day in two divided doses after meals for 16-32 weeks with maximum cumulative dose of 120 mg/kg.^{6,7}

Initially, isotretinoin was used only for severe grades of acne, but in recent years, this drug has been increasingly prescribed in moderate cases of acne unresponsive to the conventional treatment. Isotretinoin is the most dependable acne treatment and maybe justified in moderate grades of acne where scarring is imminent or acne associated with psychological diseases.^{8,9} Though the recommended dose produces good results, it causes many side effects, cheilitis being most common.

To overcome these side effects, lower doses of isotretinoin are being tried in various clinical trials. Low-dose isotretinoin (0.3-0.5 mg/kg/day) was attempted for severe acne also with or without combining other agents and it proved equally effective as standard dose.¹⁰

MATERIALS AND METHODS

A total of 70 patients visiting the OPD of Department of Dermatology, Venereology and Leprology at a tertiary care centre with moderate-to-severe acne were assigned into two groups. Every alternate patient was put in either of the two groups.

Inclusion Criteria-

1. Males and non-pregnant, non-nursing females having severe grades of acne.
2. Males and non-pregnant, non-nursing females having moderate grades of acne, unresponsive to conventional line of management or associated with psychological disturbance.
3. Age more than 12 years.

Exclusion Criteria-

Following patients were excluded from the study-

1. Use of vitamin A supplements in excess of US-recommended daily allowances.
2. Hypersensitivity to vitamin-A or its derivative.
3. Recent history of alcohol abuse.
4. Weight less than 30 kg.
5. Any clinically significant elevation of laboratory values before starting treatment.
6. Treatment with isotretinoin in the past leading to severe depression, or insomnia to a degree that affected the ability to work or perform normal daily activities.
7. Sexually active young females, not adopting any contraceptive measures or whose family was not completed.

8. Patients having family or personal history of hyperlipidaemia or diabetes.

Patients fulfilling the above mentioned criteria were enrolled. After enrolling, informed and written consent was taken. All the patients were subjected to meticulous history taking. Similarly detailed clinical assessment of the acne and any other signs and symptoms, if significant, was done and finding recorded on the pro forma. Out of the 70 patients 35 (50%) were assigned to group 1 and 20 mg of oral isotretinoin alternate day as single dose after meal was given. Rest 35 patients (50%) were assigned to group 2 and standard dose of oral isotretinoin (0.5-1 mg/kg/day) in two divided doses after meals was given. All the patients were also advised to apply topical 1% clindamycin phosphate gel twice daily.

Calculation of Total Acne Load

"Total acne load" was calculated on the basis of Definition Severity Index as stated below-

- Non-inflamed comedones, open and closed (no erythema) - 0.5.
- Comedones/papules with surrounding erythema - 1.
- Superficial pustules < 2 mm with no or little erythema - 1.
- Pustules with a diameter > 2 mm - 2.
- Pustules with a significant erythema - 2.
- Deep infiltrates with or without pustules/nodules /isolated cysts - 3.

Total acne load can be calculated by multiplying the total number of each type of lesion with its severity index adding them all together.

Complete blood count, liver function test and lipid profile was done before starting treatment and urine pregnancy test was done. Same investigations were repeated during follow up. Score of 1 was given if investigations were within normal limits and 2 was given if deranged. The criteria for discontinuation of treatment was- Blood tests rising above following values in the first two months of follow up- triglycerides more than 400 mg/dL (>4.52 mmol/L), alkaline phosphatase >264/UL (female) and >500 AJL (male), alanine transaminase >62/UL, aspartate aminotransferase >80/UL, cholesterol >300 mg/dL (>7.7 mmol/L).

Follow up- Patients were given date of next scheduled visit. Follow up was done at 2, 4, 8, 12 and 16 weeks after starting treatment.

At every visit, total acne load was calculated. Patients were asked for side effects he or she noticed during treatment period. Various side effects were graded as- none - 0, mild - 1, moderate - 2 and severe - 3.

Results and Statistics- Results of the both study group were reported as both average of total acne load pretreatment and total acne load and adverse effect of treatment at each follow up visit at 2nd week, 4th week, 8th

week, 12th week and 16th week. Results were compared using Student's t-test and Pearson Correlation of Coefficient (r value) for quantitative data and Chi-square test for qualitative data. Statistical significance was set at $p < 0.05$.

RESULTS

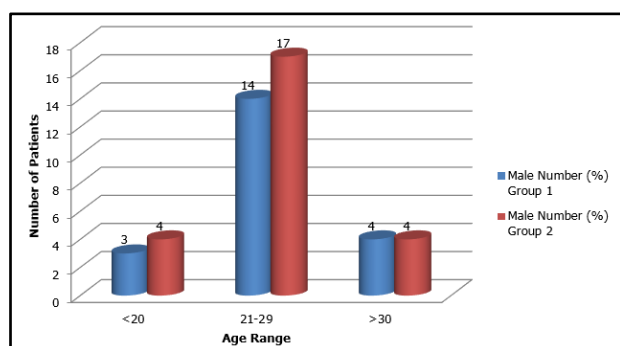
Group 1- The mean age of patients of this group was 25.89 years with SD ± 5.35 and range of 18-38. The mean weight of patients was 53.74 kg with SD ± 8.35 and range of 29-72. The mean age of onset of acne was 21.94 years with SD ± 2.92 and range of 16-29. The mean acne load before starting the treatment was 232.36 with SD ± 85.97 and range of 77-373.50. Out of 35 patients 21 were male patients and 14 were female patients. The mean age of male patients was 26.14 ± 5.50 years and of female patients was 25.5 ± 5.30 . The mean weight of male and female patients was 54.57 ± 8.35 kg and 52.5 ± 5.39 respectively. The mean age of onset of acne for male patients was 21.71 years with SD ± 2.92 and for female patients was 22.29 years with SD ± 2.99 . The mean acne load before starting the treatment for male and female patient was 246.14 ± 84.07 and 211.68

± 87.67 , respectively. Out of 35 patients total acne load was <150 in 8, 150-250 in 12 and >250 in 15 patients.

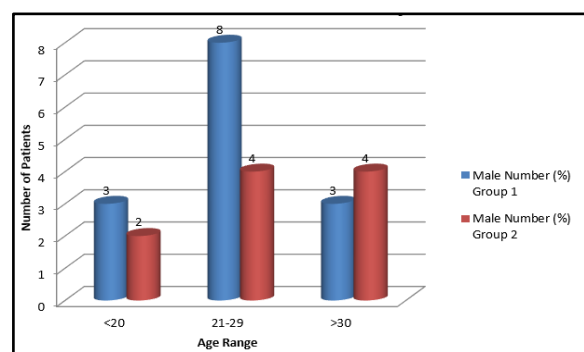
Group 2- The mean age of patients of this group was 25.66 years with SD ± 5.09 and range of 17-35. The mean weight of patients was 54.34 kg with SD ± 8.78 and range of 28-69. The mean age of onset of acne was 21.80 years with SD ± 3.49 and range of 16-29. The mean acne load before starting the treatment was 225.34 with SD ± 78.13 and range of 84-367.50. Out of 35 patients 25 were male patients and 10 were female patients. The mean age of male patients was 24.96 ± 4.62 years and of female patients was 27.4 ± 6.02 . The mean weight of male and female patients was 55.00 ± 9.08 kg and 52.7 ± 8.20 respectively. The mean age of onset of acne for male patients was 21.28 years with SD ± 3.19 and for female patients was 23.10 years with SD ± 4.01 . The mean acne load before starting the treatment for male and female patient was 237.64 ± 76.35 and 194.60 ± 77.73 respectively. Out of 35 patients total acne load was <150 in 8, 150-250 in 13 and >250 in 14 patients.

Age (in Years)	Male Number (%)		Female Number (%)	
	Group 1	Group 2	Group 1	Group 2
<20	3 (8.57)	4 (11.43)	3 (8.57)	2 (5.71)
21-29	14 (40)	17 (48.57)	8 (22.86)	4 (11.43)
>30	4 (11.43)	4 (11.43)	3 (8.57)	4 (11.43)
Total	21 (60)	25 (71.43)	14 (40)	10 (28.57)

Table 1. Age and Gender Distribution of the Patients



Graph 1. Showing Age and Gender (Male) Distribution in Two Groups



Graph 2. Showing Age and Gender (Female) Distribution in two Groups

Sl. No.	Variable	Correlation Coefficient (r)	p value	Significance
1.	Age	0.099	0.569	Not significant
2.	Weight	0.0689	0.694	Not significant
3.	Age of onset	0.019	0.913	Not significant
4.	Total Acne Load	0.048	0.784	Not significant

Table 2. Correlation of Group 1 Vs. Group 2

Group 1 Vs Group 2- Both groups were comparable in terms of age, weight, age of onset of acne and total acne load before starting of treatment with correlation coefficient r was 0.099, 0.068, 0.019 and 0.048, respectively. The p value was more than 0.05 for all the above variable indicating that both the groups were matched and this correlation was not by chance and treatment results could be compared.

Treatment Results of Group 1 Vs. Group 2- The pretreatment mean acne load in group 1 patients was 232.36 ± 85.97 with range of 77.00-373.50, which decreased to 221.10 ± 81.40 with range of 77.50-353.00 at 2 weeks. It decreased to mean acne load of 179.41 ± 66.38 with range of 63.50-331.50 at 4 weeks. It decreased to 130.9 ± 49.91 with range of 48.50-207.50, 86.41 ± 43.27 with range of 28.00-186.00 and 29.41 ± 20.39 with range of 3.50-74.00 at 8 weeks, 12 weeks and 16 weeks,

respectively. The decrease in mean acne load in comparison with pretreatment level in percentage was $4.71 \pm 3.54\%$ (range 0.00-12.18), $22.16 \pm 6.78\%$ (range 8.04-42.03), $42.96 \pm 8.07\%$ (range 27.06-62.01), $63.16 \pm 9.80\%$ (range 42.06-80.13) and $87.31 \pm 7.13\%$ (range 72.73-98.04) at 2,4,8,12 and 16 weeks respectively of therapy.

The pretreatment mean acne load in group 2 patients was 225.34 ± 78.13 with range of 84.00-367.50 which decreased to 191.37 ± 66.70 with range of 71.50-318.00 at 2 weeks. It decreased to mean acne load of 142.07 ± 56.47 with range of 54.50-254.00 at 4 weeks. It decreased to 83.80 ± 38.38 with range of 28.00-166.00, 40.49 ± 21.95 with range of 8.50-87.50 and 12.86 ± 10.69 with range of 0.50-50.00 at 8 weeks, 12 weeks and 16 weeks,

respectively. The decrease in mean acne load in comparison with pretreatment level in percentage was $14.85 \pm 7.34\%$ (range 1.11-29.06), $36.97 \pm 10.09\%$ (range 18.45-61.13), $63.02 \pm 9.79\%$ (range 41.67-80.00), $83.14 \pm 7.17\%$ (range 67.04-93.15) and $94.45 \pm 3.60\%$ (range 84.10-99.83) at 2,4,8,12 and 16 weeks respectively of the therapy.

On comparison of group 1 with group 2 with Student t-test, p value was 0.10 at 2 weeks of therapy indicating there was no difference between the efficacies of these two treatment groups at 2 weeks. However, the p value calculated for 4 weeks, 8 weeks, 12 weeks and 16 weeks were 0.01, 0.00, 0.00 and 0.00. This indicated that therapy with standard dose was more effective.

Sl. No.	Weeks	Group 1 Total Acne Load	Group 2 Total Acne Load	P value
1.	0	232.36	225.34	0.72
2.	2	221.10 (4.71%)	191.37 (14.85%)	0.10
3.	4	179.41 (22.16%)	142.07 (36.97%)	0.01
4.	8	131.19 (42.96%)	83.80 (63.02%)	<0.00
5.	12	86.41 (63.16%)	40.49 (82.14%)	<0.00
6.	16	29.41 (87.31%)	12.86 (94.45%)	<0.00

Table 3. Treatment Results of Group 1 Vs. Group 2

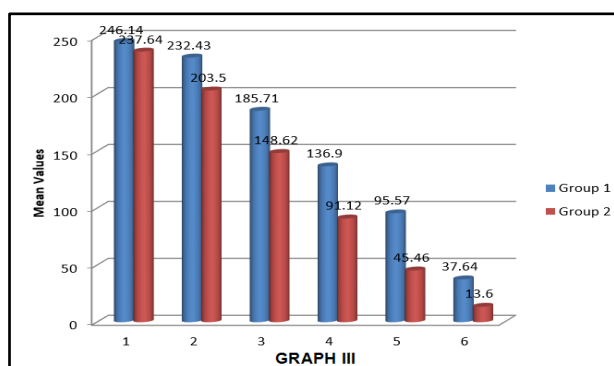
Group 1 males Vs. group 2 males- The pretreatment mean acne load in male patients of group 1 was 246.14 ± 84.07 with range of 82.50-373.50, which decreased to 232.43 ± 80.18 with range of 75.50-353.00 at 2 weeks, while in group 2 males pretreatment mean acne load was 237.64 ± 76.35 with range of 84.00-367.50 which decreased to 203.50 ± 67.02 with range of 71.50-318.00. In group 1 males, mean acne load was decreased to 185.71 ± 65.13 (range 63.50-331.50), 138.98 ± 50.61 (range 50.00-207.50), 95.57 ± 46.03 (range 28.00-186.00) and 37.64 ± 20.85 (range 3.50-74.00) at 4 weeks, 8 weeks, 12 weeks and 16 weeks, respectively. The decrease in mean acne load

in percentage of pretreatment acne load was 5.62 ± 3.62 at 2 weeks, 24.10 ± 7.47 at 4 weeks, 43.21 ± 8.16 at 8 weeks, 61.98 ± 10.05 at 12 weeks and 84.76 ± 6.93 at 16 weeks.

In group 2, males mean acne load was decreased to 148.62 ± 53.90 (range 65.50-254.00), 91.12 ± 36.55 (range 35.00-166.00), 45.46 ± 21.70 (range 12.50-87.50) and 13.60 ± 10.89 (range 1.00-50.00) at 4 weeks, 8 weeks, 12 weeks and 16 weeks, respectively. The decrease in mean acne load in percentage of pretreatment acne load was 14.39 ± 7.76 at 2 weeks, 37.10 ± 9.96 at 4 weeks, 61.23 ± 9.73 at 8 weeks, 80.87 ± 6.50 at 12 weeks and 94.34 ± 3.86 at 16 weeks.

Sl. No.	Weeks	Group 1 Males	Group 2 Males	p value
1.	0	246.14	237.64	0.723
2.	2	232.43 (5.62%)	203.50 (14.39%)	0.197
3.	4	185.71 (24.10%)	148.62 (37.10%)	0.044
4.	8	138.98 (43.21%)	91.12 (61.23%)	0.009
5.	12	95.57 (61.98%)	45.46 (80.87%)	0.000
6.	16	37.64 (84.76%)	13.60 (94.34%)	0.000

Table 4. Treatment Results of Group 1 Males Vs. Group 2 Males



Graph 3. Showing Treatment Results of Groups 1 Versus Group 2 Males at Different Time Intervals

Group 1 females Vs. group 2 females- The pretreatment mean acne load in female patients of group 1 was 211.68 ± 87.67 with range of 77.00-351.00, which decreased to 204.11 ± 83.19 with range of 77.00-326.50 at 2 weeks, while in group 2, females pretreatment mean acne load was 194.60 ± 77.73 with range of 89.50-308.00, which decreased to 161.06 ± 58.29 with range of 80.0-225.55 at 2 weeks. In group, 1 female mean acne load was decreased to 169.96 ± 69.56 (range 65.50-276.50), 119.50 ± 48.25 (range 48.50-193.50), 72.68 ± 36.04 (range 31.50-136.50) and 17.07 ± 12.04 (range 4.50-42.00) at 4 weeks, 8 weeks, 12 weeks and 16 weeks, respectively. The decrease in mean acne load in percentage of pretreatment acne load was 3.33 ± 3.03 at 2 weeks, 19.26 ± 4.41 at 4 weeks, 42.59 ± 8.23

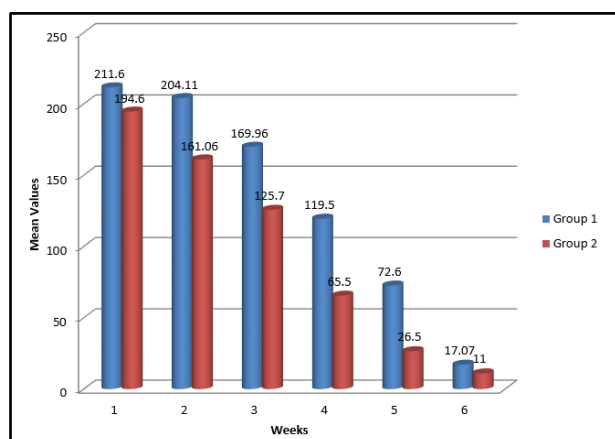
at 8 weeks, 64.94 ± 9.49 at 12 weeks and 91.14 ± 5.76 at 16 weeks.

In group 2 females, mean acne load was decreased to 125.70 ± 62.32 (range 54.50-240.00), 65.50 ± 38.49 (range 28.00-141.50), 28.05 ± 18.03 (range 8.50-64.50) and 11.00 ± 10.48 (range 0.50-33.00) at 4 weeks, 8 weeks, 12 weeks

and 16 weeks, respectively. The decrease in mean acne load in percentage of pretreatment acne load was 16.01 ± 6.39 at 2 weeks, 36.65 ± 10.97 at 4 weeks, 67.50 ± 8.87 at 8 weeks, 85.31 ± 8.14 at 12 weeks and 94.71 ± 3.55 at 16 weeks.

Sl. No.	Weeks	Group 1 Females	Group 2 Females	p value
1.	0	211.68	194.60	0.620
2.	2	204.11 (3.33%)	161.06 (16.01%)	0.150
3.	4	169.96 (19.26%)	125.70 (36.65%)	0.117
4.	8	119.50 (42.59%)	65.50 (67.50%)	0.006
5.	12	72.68 (64.94%)	28.05 (85.31%)	<0.000
6.	16	17.07 (91.14%)	11.00 (94.71%)	0.202

Table 5. Treatment Results of Group 1 Females Vs. Group 2 Females



Graph 4. Showing Treatment Results of Groups 1 Versus Group 2 Females at Different Time Intervals

Results as per acne load- Depending upon the pretreatment acne load, patients of group 1 and 2 were further divided into 3 groups.

Pretreatment acne load less than 150- There were 8 patients in group 1 and 2 each with acne load less than 150. The mean acne load in group 1 patients was 107.44 ± 22.68 , which decreased to 102.63 ± 21.52 at 2 weeks. It further decreased to 85.38 ± 15.40 , 61.13 ± 8.81 , 37.56 ± 5.21 and 13.44 ± 7.40 at 4 weeks, 8 weeks, 12 weeks and 16 weeks, respectively. The decrease in mean acne load in percentage of pretreatment acne load was 4.35 ± 4.44 at 2 weeks, 20.00 ± 5.02 at 4 weeks, 42.15 ± 6.60 at 8 weeks, 63.46 ± 9.76 at 12 weeks and 86.76 ± 8.05 at 16 weeks.

In group 2, pretreatment mean acne load was 110.88 ± 19.39 , which decreased to 93.81 ± 19.00 at 2 weeks. It further decreased to 71.13 ± 10.70 , 38.63 ± 7.70 , 19.81 ± 7.92 and 4.75 ± 3.61 at 4 weeks, 8 weeks, 12 weeks and 16 weeks, respectively. The decrease in mean acne load in percentage of pretreatment acne load was 15.45 ± 6.02 at 2 weeks, 34.78 ± 11.35 at 4 weeks, 64.03 ± 11.02 at 8 weeks, 81.54 ± 8.37 at 12 weeks and 95.63 ± 3.13 at 16 weeks.

Pretreatment acne load 150-250- There were 12 and 13 patients in group 1 and 2 respectively with acne load between 150 and 250. The mean acne load in group 1 patients was 215.08 ± 28.05 , which decreased to 205.38 ± 27.62 at 2 weeks. It further decreased to 165.75 ± 20.15 ,

124.08 ± 21.64 , 72.25 ± 21.54 and 27.42 ± 13.56 at 4 weeks, 8 weeks, 12 weeks and 16 weeks, respectively. The decrease in mean acne load in percentage of pretreatment acne load was 4.51 ± 3.32 at 2 weeks, 22.69 ± 5.42 at 4 weeks, 42.02 ± 8.46 at 8 weeks, 66.31 ± 9.15 at 12 weeks and 87.64 ± 5.70 at 16 weeks.

In group 2, pretreatment mean acne load was 217.12 ± 24.53 , which decreased to 187.88 ± 25.12 at 2 weeks. It further decreased to 133.81 ± 31.08 , 81.19 ± 24.83 , 36.15 ± 16.65 and 13.00 ± 5.74 at 4 weeks, 8 weeks, 12 weeks and 16 weeks, respectively. The decrease in mean acne load in percentage of pretreatment acne load was 13.41 ± 6.78 at 2 weeks, 38.84 ± 9.80 at 4 weeks, 63.34 ± 8.30 at 8 weeks, 83.83 ± 6.42 at 12 weeks and 94.14 ± 2.36 at 16 weeks.

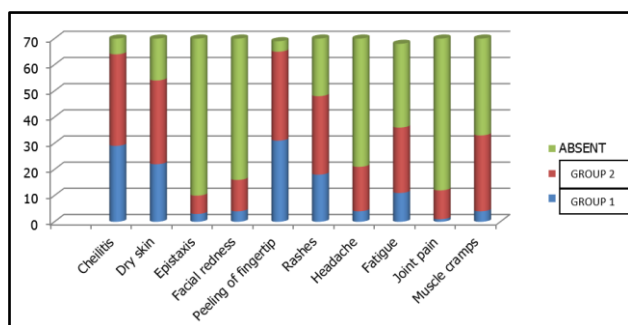
Pretreatment acne load more than 250- There were 15 and 14 patients in group 1 and 2 respectively with acne load more than 250. The mean acne load in group 1 patients was 312.80 ± 31.09 , which decreased to 296.87 ± 29.62 at 2 weeks. It further decreased to 240.50 ± 32.46 , 174.23 ± 28.44 , 123.80 ± 33.71 and 39.53 ± 24.06 at 4 weeks, 8 weeks, 12 weeks and 16 weeks, respectively. The decrease in mean acne load in percentage of pretreatment acne load was 5.05 ± 3.41 at 2 weeks, 22.89 ± 8.52 at 4 weeks, 44.14 ± 8.81 at 8 weeks, 60.49 ± 10.18 at 12 weeks and 87.35 ± 8.09 at 16 weeks.

In group 2, pretreatment mean acne load was 298.39 ± 36.44 , which decreased to 250.36 ± 35.23 at 2 weeks. It further decreased to 190.26 ± 41.44 , 112.04 ± 33.63 , 56.32 ± 20.47 and 17.36 ± 14.11 at 4 weeks, 8 weeks, 12 weeks and 16 weeks, respectively. The decrease in mean acne load in percentage of pretreatment acne load was 15.85 ± 8.69 at 2 weeks, 36.49 ± 10.09 at 4 weeks, 62.14 ± 10.96 at 8 weeks, 80.91 ± 7.36 at 12 weeks and 94.06 ± 4.73 at 16 weeks.

Side Effect Profile- There was wide variation in adverse effects of therapy between group 1 and group 2 patients. Overall, in both the groups, the adverse effects increased in both frequency and severity with duration of the therapy. But, the adverse effects were more frequent and severe in group 2 patients in comparison to group 1 patients.

Adverse Effects	Group 1	Group 2	Absent
Cheilitis	29	35	6
Dry skin	22	32	16
Epistaxis	3	7	60
Facial redness	4	12	54
Peeling of fingertip	31	34	4
Rashes	18	30	22
Headache	4	17	49
Fatigue	11	25	32
Joint pain	1	11	58
Muscle cramps	4	29	37

Table 6. Representing Different Side Effect Profile



Graph 5. Proportion of Different Side Effects

SUMMARY AND DISCUSSION

Treatment results of group 1 vs. group 2 - The pretreatment mean acne load in group 1 patients was 232.36 ± 85.97 with range of 77.00-373.50, which decreased to 221.10 ± 81.40 with range of 77.50-353.00 at 2 weeks. It decreased to mean acne load of 179.41 ± 66.38 with range of 63.50-331.50 at 4 weeks. It decreased to 131.19 ± 49.91 with range of 48.50-207.50, 86.41 ± 43.27 with range of 28.00-186.00 and 29.41 ± 20.39 with range of 3.50-74.00 at 8 weeks, 12 weeks and 16 weeks, respectively.

The decrease in mean acne load in comparison with pretreatment level in percentage was $4.71 \pm 3.54\%$ (range 0.00-12.18), $22.16 \pm 6.78\%$ (range 8.04-42.03), $42.96 \pm 8.07\%$ (range 27.06-62.01), $63.16 \pm 9.80\%$ (range 42.06-80.13) and $87.31 \pm 7.13\%$ (range 72.73-98.04) at 2, 4, 8, 12 and 16 weeks respectively of therapy.

The pretreatment mean acne load in group 2 patients was 225.34 ± 78.13 with range of 84.00-367.50, which decreased to 191.37 ± 66.70 with range of 71.50-318.00 at 2 weeks. It decreased to mean acne load of 142.07 ± 56.47 with range of 54.50-254.00 at 4 weeks. It decreased to 83.80 ± 38.38 with range of 28.00-166.00, 40.49 ± 21.95 with range of 8.50-87.50 and 12.86 ± 10.69 with range of 0.50-50.00 at 8 weeks, 12 weeks and 16 weeks, respectively.

The decrease in mean acne load in comparison with pretreatment level in percentage was $14.85 \pm 7.34\%$ (range 1.11-29.06), $36.97 \pm 10.09\%$ (range 18.45-61.13), $63.02 \pm 9.79\%$ (range 41.67-80.00), $83.14 \pm 7.17\%$ (range 67.04-93.15) and $94.45 \pm 3.60\%$ (range 84.10-99.83) at 2, 4, 8, 12 and 16 weeks respectively of therapy.

On comparison of group 1 with group 2 with Student's t-test, p value was 0.10 at 2 weeks of therapy indicating there was no difference between the efficacies of these two treatment groups at 2 weeks. However, the p value

calculated for 4 weeks, 8 weeks, 12 weeks and 16 weeks were 0.01, 0.00, 0.00 and 0.00. This indicated that therapy with standard dose was more effective.

Group 1 males vs. group 2 males- In group 1, the decrease in mean acne load in percentage of pretreatment acne load was 5.62 ± 3.62 at 2 weeks, 24.10 ± 7.47 at 4 weeks, 43.21 ± 8.16 at 8 weeks, 61.98 ± 10.05 at 12 weeks and 84.76 ± 6.93 at 16 weeks.

In group 2, the decrease in mean acne load in percentage of pretreatment acne load was 14.39 ± 7.76 at 2 weeks, 37.10 ± 9.96 at 4 weeks, 61.23 ± 9.73 at 8 weeks, 80.87 ± 6.50 at 12 weeks and 94.34 ± 3.86 at 16 weeks.

There was no significant difference in decrease in total acne load in both the groups initially, but at 12 and 16 weeks, there was significant difference in decrease in total acne load.

Group 1 females vs. group 2 females- In group 1, the decrease in mean acne load in percentage of pretreatment acne load was 3.33 ± 3.03 at 2 weeks, 19.26 ± 4.41 at 4 weeks, 42.59 ± 8.23 at 8 weeks, 64.94 ± 9.49 at 12 weeks and 91.14 ± 5.76 at 16 weeks.

In group 2, the decrease in mean acne load in percentage of pretreatment acne load was 16.01 ± 6.39 at 2 weeks, 36.65 ± 10.97 at 4 weeks, 67.50 ± 8.87 at 8 weeks, 85.31 ± 8.14 at 12 weeks and 94.71 ± 3.55 at 16 weeks.

Only significant difference in both groups was noted at 12 weeks, but there was no significant difference at 16 weeks between both the groups.

Results as per acne load- Depending upon the pretreatment acne load, patients of group 1 and 2 were further divided into 3 groups.

Pretreatment acne load less than 150- There were 8 patients in group 1 and 2 each with acne load less than 150. In group 1, the decrease in mean acne load in percentage of pretreatment acne load was 4.35 ± 4.44 at 2 weeks, 20.00 ± 5.02 at 4 weeks, 42.15 ± 6.60 at 8 weeks, 63.46 ± 9.76 at 12 weeks and 86.76 ± 8.05 at 16 weeks.

In group 2, the decrease in mean acne load in percentage of pretreatment acne load was 15.45 ± 6.02 at 2 weeks, 34.78 ± 11.35 at 4 weeks, 64.03 ± 11.02 at 8 weeks, 81.54 ± 8.37 at 12 weeks and 95.63 ± 3.13 at 16 weeks.

Pretreatment acne load 150-250- There were 12 and 13 patients in group 1 and 2 respectively with acne load between 150 and 250. The decrease in mean acne load in group 1 in percentage of pretreatment acne load was 4.51 ± 3.32 at 2 weeks, 22.69 ± 5.42 at 4 weeks, 42.02 ± 8.46 at 8 weeks, 66.31 ± 9.15 at 12 weeks and 87.64 ± 5.70 at 16 weeks.

In group 2, the decrease in mean acne load in percentage of pretreatment acne load was 13.41 ± 6.78 at 2 weeks, 38.84 ± 9.80 at 4 weeks, 63.34 ± 8.30 at 8 weeks, 83.83 ± 6.42 at 12 weeks and 94.14 ± 2.36 at 16 weeks.

Pretreatment acne load more than 250- There were 15 and 14 patients in group 1 and 2 respectively with acne load more than 250. The decrease in mean acne load in

percentage of pretreatment acne load was 5.05 ± 3.41 at 2 weeks, 22.89 ± 8.52 at 4 weeks, 44.14 ± 8.81 at 8 weeks, 60.49 ± 10.18 at 12 weeks and 87.35 ± 8.09 at 16 weeks.

In group 2, the decrease in mean acne load in percentage of pretreatment acne load was 15.85 ± 8.69 at 2 weeks, 36.49 ± 10.09 at 4 weeks, 62.14 ± 10.96 at 8 weeks, 80.91 ± 17.36 at 12 weeks and 94.06 ± 4.73 at 16 weeks.

Thus, low-dose therapy is equally effective to standard dose therapy, irrespective of pretreatment mean acne load.

CONCLUSION

1. The results from this study indicate that on comparing total acne load at end of 16 weeks therapy, low-dose isotretinoin therapy is slightly less in efficacy (87.31%) than standard dose isotretinoin therapy (94.45%), but they are comparable.
2. Taking into account the side effect profile, they are significantly less in incidence and severity in low-dose therapy than the standard dose therapy.
3. The burden of cost of treatment is much higher (3 to 6 times) for the standard dose therapy as compared to low-dose therapy.
4. Thus, though the standard dose isotretinoin therapy (1 mg/kg/day) is gold standard for moderate-to-severe acne, low-dose isotretinoin therapy (20 mg alternate day) has efficacy comparable to it with advantage of much less side effects and more cost-effectiveness.

The limitation of the present study are-

1. The sample size was small.
2. Study period was of 16 weeks, so relapse rate was not taken into consideration.

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