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Original Research Article

A Comparative Study to Compare Efficacy of Low Dose Continuous and Low Dose Intermittent Oral Isotretinoin Therapy in Moderate and Severe Acne Vulgaris

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Abstract:

Background: Acne vulgaris is chronic inflammatory disease of pilosebaceous units characterized by comedones, papules, pustules, nodules, cysts and abscesses. Many attempts have been made to classify acne on the basis of the severity of the disease. In 1997, Doshi, Zaheer and Stiller 7 devised a Global Acne Grading System (GAGS). This system gives more accurate evaluation of the disease and has been used by many authors in research work and studies.

Methods:

The study was randomised open label, comparative study. A total of one hundred and ten consecutive patients of moderate and severe acne vulgaris, attending the Outpatient Clinic as above and satisfying the inclusion criteria were included in the study. The subjects were divided into Group A (55 patients) to be treated with low dose continuous regimen of Cap. Isotretinoin 20 mg administered orally, for a period of 16 weeks and Group B (55 patients) to be treated with low dose intermittent regimen of Cap. Isotretinoin 20 mg orally once daily, for 1 week out of every 4 weeks, for a period of 16 weeks. Patients of 18-35 years age, who presented with moderate to severe grade acne vulgaris as per Global Acne Grading System of Doshi et al and willing to take isotretinoin therapy were included in study.

Results: The study included a total of 110 patients. Total of 7 patients lost in follow-up. Final group size of study was 50 patients in each group A and B. There was no significant difference in both groups demographically. In Group A (low dose continuous Isotretinoin) statistically significant change from baseline was observed from week 4 itself and at week 16 majority of patients (96%) scored none on GAGS. In Group B (low dose intermittent Isotretinoin) change from baseline was observed from week 4 itself but statistically significant change was seen from week 8 only and at week 16, 72% patients scored none on GAGS and 28% were in mild score on GAGS. At week 4, 42 (84%) patients in Group A had moderate and remaining 8 (16%) had severe grade whereas in Group B, 30 (60%) had moderate and 20 (40%) had moderate grade. Statistically, the difference between two groups was significant ($p=0.008$, highly significant). At week 8, 20 (40%) patients in Group A had mild grade and remaining 30 (60%) had moderate grade whereas in Group B, 3 (6%) had mild, 40 (80%) had moderate and 7 (14%) had severe grade. Statistically, this difference between two groups was significant ($p<0.001$, very highly significant). At week 12, 43 (86%) patients in Group A had mild and remaining 7 (14%) had moderate grade whereas in Group B, 29 (58%) had mild and 21 (42%) had moderate grade. Statistically, this difference was significant ($p=0.002$, highly significant). At week 16, all the 48 (96%) patients in Group A were normal and 4% had mild grade whereas in Group B, 36 (72%) were normal and 14 (28%) had shifted to mild grade. ($p=0.001$, highly significant)

Discussion: Oral isotretinoin is highly effective in treatment of moderate and severe acne vulgaris. Low dose continuous isotretinoin regimen was faster, more efficacious in treatment of moderate and severe acne vulgaris and relapse rate was also significantly lower after 8 weeks of stoppage of treatment than low dose intermittent isotretinoin regimen. Low dose intermittent Isotretinoin was effective in causing remission in moderate acnevulgaris but relapse of acne vulgaris occurred in almost half of the patients within 8 weeks of stoppage of treatment.

Keywords: Isotretinoin, Acne Vulgaris, Low dose intermittent Isotretinoin, Low dose continuous Isotretinoin.

Introduction

Acne vulgaris is chronic inflammatory disease of pilosebaceous units characterized by comedones, papules, pustules, nodules, cysts and abscesses. It occurs worldwide and usually starts in adolescence and resolves by mid-twenties. [1] The overall prevalence of acne vulgaris in adolescents is reported to be 79-95% and that of moderate and severe form about 11%. [2,3]

In a study done by Smithard et al, [4] prevalence of significant acne vulgaris was 56% in boys and 45% in girls aged between 14 and 16 years, and were moderate to severe in 11%. Acne represents obstruction and inflammation of the sebaceous follicle, which is a part of the pilosebaceous unit. The primary and the pathognomonic lesion of acne is microcomedo, a microscopic lesion invisible to the eye. Some microcomedones evolve into inflammatory or noninflammatory lesions. The formation of microcomedo requires complex interplay of altered follicular keratinisation, hyperplasia of sebaceous glands and over colonization of sebaceous glands with Propionibacterium acnes. Host immune response also contributes to the clinical course. [5]

The most notable pathophysiological changes that influence the development of acne are:

1. Sebaceous gland hyperplasia and seborrhea
2. Altered follicular growth and differentiation
3. Propionibacterium acne colonization of the follicle
4. Inflammation and immune response.

Classifying Severity of Acne Vulgaris

Many attempts have been made to classify acne on the basis of the severity of the disease. Many different methods of assessment of acne severity were identified. Severity of the acne can be graded on clinical grounds as Grade I: Comedones, occasional papules (Mild), Grade II: Papules, comedones, few pustules (Moderate), Grade III: Predominant pustules, nodules, abscesses (Severe), Grade IV: Mainly cysts, abscesses, widespread scarring (Cystic). [6]

In 1997, Doshi, Zaheer and Stiller7 devised a Global Acne Grading System (GAGS). This system gives more accurate evaluation of the disease and has been used by many authors in research work and studies. GAGS divides the face, the chest and the back into six areas (forehead, each cheek, nose, chin, chest and back) and assigns a factor to each area on the basis of surface area and distribution/density of pilosebaceous units. (Forehead=2, right cheek=2, left cheek=2 nose=1, chin=1, chest and back=3). Each type of lesion is given a value depending on severity. No lesions=0, Comedones=1, Papules=2, Pustules=3 and Nodules=4.

The score for each area (Local score) is calculated using the formula: Local score = Factor x value (0-4). The global score is the sum of local scores, and acne severity was graded using the global score, A score of 0 is considered none (no acne), 1-18 is mild; 19-30 is moderate; 31-38 is severe, and >39 is very severe.

Aim

To compare the efficacy of low dose continuous and low dose intermittent oral isotretinoin therapy in moderate and severe acne vulgaris.

Material and Methods

The study was randomised open label, comparative study. It was initiated after seeking the necessary approval from the Institutional Ethics Committee. The study was conducted for a period of one and a half years, from November 2014 to May 2016, on patients attending the Outpatient Clinic in the Department of Dermatology, Era's Lucknow Medical College and Hospital, Lucknow.

A total of one hundred and ten consecutive patients of moderate and severe acne vulgaris, attending the Outpatient Clinic as above and satisfying the inclusion criteria were included in the study. The subjects were divided into Group A (55 patients) to be treated with low dose continuous regimen of Cap. Isotretinoin 20 mg administered orally, for a period of 16 weeks and Group B (55 patients) to be treated with low dose intermittent regimen of Cap. Isotretinoin 20 mg orally once daily, for 1 week out of every 4 weeks, for a period of 16 weeks.

Patients of 18-35 years age, who presented with moderate to severe grade acne vulgaris as per Global Acne Grading System of Doshi et al and willing to take isotretinoin therapy were included in study.

Those patients who are allergic to retinoids, pregnant females, subjects with abnormal lipid profile, significant hepatic dysfunction, diabetes mellitus and with underlying psychiatric disorders were excluded from study.

Sample size: Sample size was calculated on the basis of the most common adverse effect of oral isotretinoin that is "cheilitis", using the formula

$$n = \frac{(Z\alpha + Z\beta)^2}{[1n(1-e]^2}\left[\frac{1-p_1}{p_1} + \frac{1-p_2}{p_2}\right]$$

Where $p_1=0.813$, $p_2=0.696$, the proportion of chelitis (refer to the paper, study of Nadia A El Sherif et al).[8] e = 0.16, the difference considered to be medically significant.

Type I error α = 5%

Type II error β =20% for detecting results with 80% power of study.

Loss to follow-up = 10%

Hence the sample size was n = 100 (to be equally divided into two groups of 50 each.)

Methodology

Subjects between the ages of 18yrs - 35yrs and having moderate and severe acne vulgaris, according to Global Acne Grading System of Doshi et al[7] were enrolled in the study, after taking a written consent from them. The case study method was adapted for the study and the data was recorded in a specially designed case report form (CRF).

Patients with moderate and severe acne vulgaris were randomly assigned to Group A and B as follows:

Group A to be treated with low dose regimen of Cap. Isotretinoin 20 mg orally, once a day, continuously for a period of 16 weeks. Group B to be treated with low dose regimen of Cap. Isotretinoin 20 mg orally once a day for 1 week out of every 4 weeks, for a period of 16 weeks.

The patients were followed up at the interval of 4 weeks (after 4, 8, 12 and 16 weeks) during the treatment period. A follow up at 24 weeks was carried out to evaluate the relapse after completion of therapy for 16 weeks.

The outcome of the therapy was assessed by evaluating the Global Acne Grading System (GAGS) score at each visit.

Efficacy evaluation: Acne grading was evaluated and recorded at each visit during the study period, using GAGS: [7]

Global Acne Grading System

Location	Factor		Value	Lesion
Forehead	2		0	No lesions
Right cheek	2		1	≥1 Comedo
Left cheek	2		2	≥1 Papule
Nose	1		3	≥1 Pustule
Chin	1		4	≥1 Nodule
Chest and upper back	3			

The score for each area (Local score) is calculated using the formula: Local score = Factor x value (0-4). The Global score is the sum of local scores, and acne severity is graded using the global score.

Global score	Grade
0	None
1-18	Mild
19-30	Moderate
31-38	Severe
≥39	Very severe

The data was analysed using SPSS version 15.0. Chi Square Test and Student "t" test were used to test significance of two means. Paired t test was used to compare the change in a parameter at two different time intervals.

Results:

The study included a total of 110 patients. The patients were allocated in two group, with Group A (Isotretinoin continuous regimen) and Group B (Isotretinoin intermittent regimen).

7 patients were lost in follow up during study final group size was 50 patients in each group A and B.

Table 1: Demographic Profile of Patients in two Isotretinoin groups

SN	Characteristic	Group A* (n=50)		Group B** (n=50)		Statistical significance	
		No.	%	No.	%	χ^2	'p'
1.	Mean Age±SD (Range) in years	20.36±2.59 (18-28)		20.88±2.46 (18-27)		t=1.030; p=0.306	
2.	Gender						
	Male	33	66	27	54	1.500	0.221
	Female	17	34	23	46		
3.	Marital Status						
	Unmarried	50	100	50	100	-	-
	Married	-	-	-	-		

***Group A: Low dose continuous oral isotretinoin regimen, **Group B : Low dose intermittent oral isotretinoin regimen**

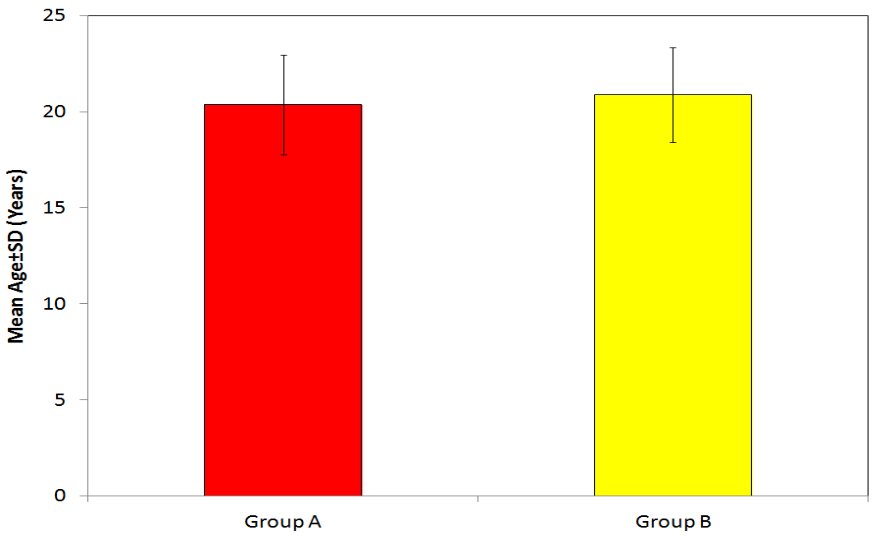

Figure 1: Age distribution of patients in two Isotretinoin groups

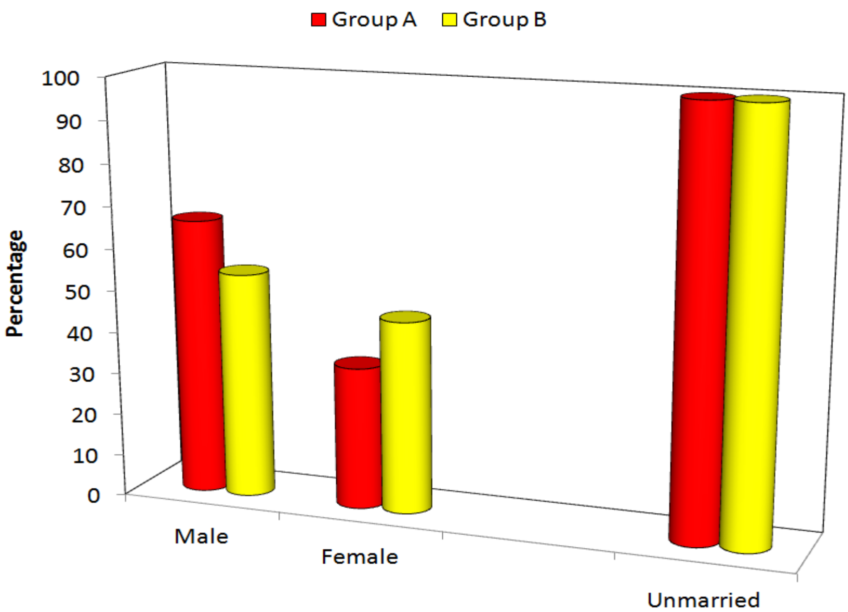

Figure 2: Gender distribution and marital status of patients in two Isotretinoin group

Age of patients enrolled in study ranged from 18 to 28 years.

Mean age of patients in Group A was 20.36±2.59 years whereas the same in Group B was 20.88±2.46 years.

Statistically, there was no significant difference between two groups with respect to age (p=0.306).

Majority of patients irrespective of group were males. Overall male to female ratio was 1.5:1. There were 66% males in Group A and 54% in Group B. Although proportion of males was higher in Group A as compared to Group B, yet statistical difference between two groups was not significant (p=0.221). Demographically the two groups were matched statistically.

Table 2: Family history of acne vulgaris in two Isotretinoin groups

SN	Family History	Group A* (n=50)		Group B** (n=50)	
		No.	%	No.	%
1.	Positive	14	28	21	42
2.	Negative	36	72	29	58

χ^2=2.154; p=0.142, *Group A : Low dose continuous oral isotretinoin regimen, **Group B : Low dose intermittent oral isotretinoin regimen

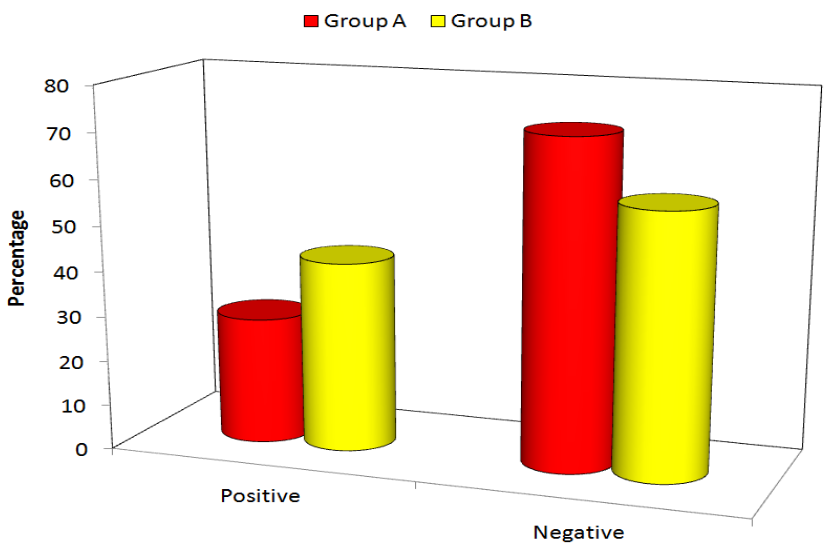

Figure 3: Family history of acne vulgaris in study groups

A total of 28% patients in Group A and 42% patients in Group B had a family history positive for Acne vulgaris. Although proportion of patients with positive family history was higher in Group B as compared to Group A yet the difference between two groups was not significant statistically (p=0.142).

Table 3 (a): Evaluation of Change in Global Acne Grading Score in low dose Continuous oral Isotretinoin (Wilcozon Signed Rank Test)

SN	FU Interval	None$	Mild	Moderate	Severe	Statistical significance	
						Z	P
1.	Baseline	0	0	23 (46%)	27 (54%)	–	–
2.	Week 4	0	0	42 (84%)	8 (16%)	3.962	<0.001*
3.	Week 8	0	20 (40%)	30 (60%)	0	6.053	<0.001*
4.	Week 12	0	43 (86%)	7 (14%)	0	6.158	<0.001*
5.	Week 16	48 (96%)	2 (4%)	0 (0%)	0	6.349	<0.001*

$ Normal/ no lesion, * Very highly significant

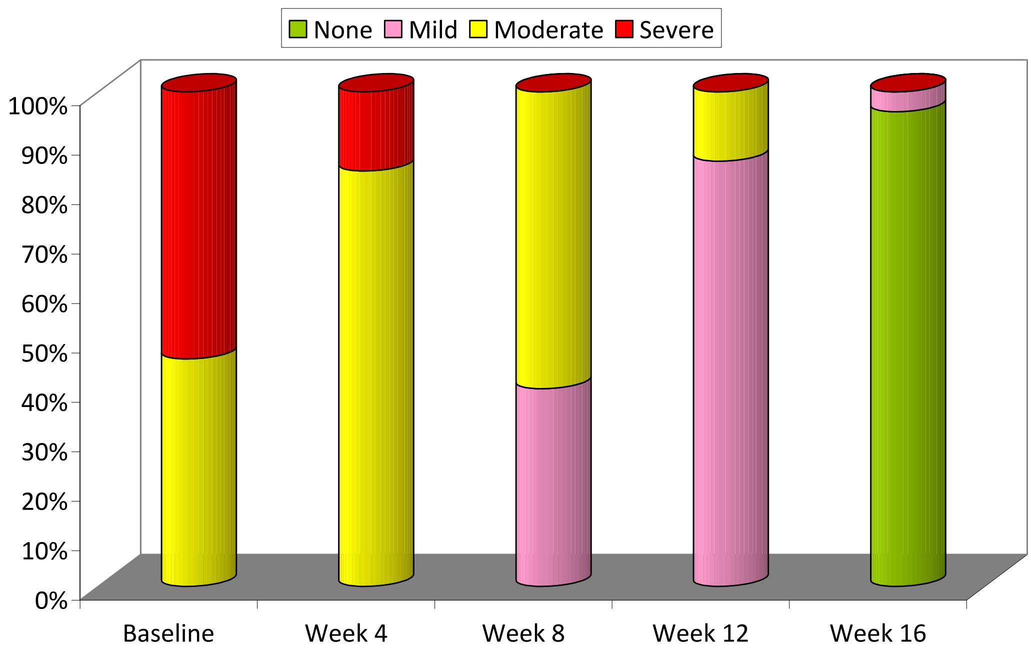

Figure 4: Response to low dose Continuous oral isotretinoin

On evaluating the change in Global Acne Grading Score in Group A as compared to baseline, statistically significant change from baseline was observed from week 4 itself and change from baseline was significant statistically at all the above follow up intervals ($p<0.001$, very highly significant)(Table 3a). At Week 24, all the patients with normal status at week 16 (n=48) were called on for follow up had been included in assessment for relapse. Table 3(b) shows the change in Global grading score at 24 weeks i.e. after 8 weeks of completion of treatment (16 weeks)

Table 3(b): Changes in Global Grading Score in low dose Continuous Isotretinoin (Wilcozon Signed Rank test)

SN	FU Interval	None[$]	Mild	Moderate	Severe	Statistical significance	
						Z	P
1.	Week 16	48 (100%)	0	0	0	–	–
2.	Week 24	47 (97.9%)	1 (2.1%)	0	0	-1.000	0.317

[$] Normal/ no lesion

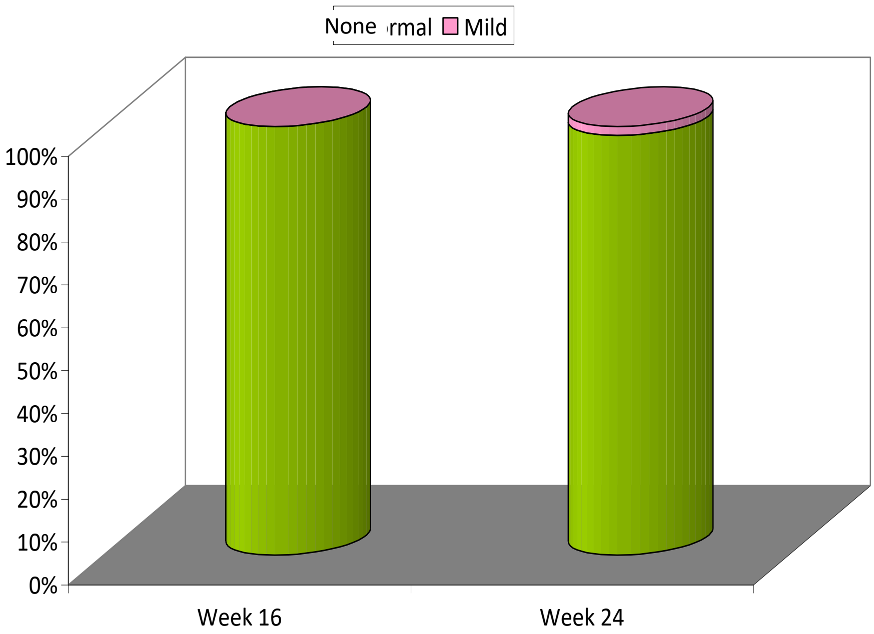

Figure 5: Relapse of acne vulgaris in low dose Continuous Isotretinoin

All the 48 patients had normal Global Acne Grading System (GAGS) score at 16 weeks while at 24 weeks GAGS score of 47 (97.9%) were found to be normal and only of 1 (2.1%) was found to be mild, change in GAGS score from that at completion of treatment was not found to be statistically significant (p=0.317).

Table 4(a): Evaluation of Change in Global Acne Grading Score in low dose Intermittent Isotretinoin (Wilcozon Signed Rank test)

SN	FU Interval	None	Mild	Moderate	Severe	Statistical significance	
						Z	P
1.	Baseline	0	0	31 (62%)	19 (38%)	–	–
2.	Week 4	0	0	30 (60%)	20 (40%)	0.577	0.564
3.	Week 8	0	3 (6%)	40 (80%)	7 (14%)	3.873	<0.001*
4.	Week 12	0	29 (58%)	21 (42%)	0	6.788	<0.001*
5.	Week 16	36 (72%)	14 (28%)	0	0	6.784	<0.001*

[$] Normal/ no lesion, * very highly significant

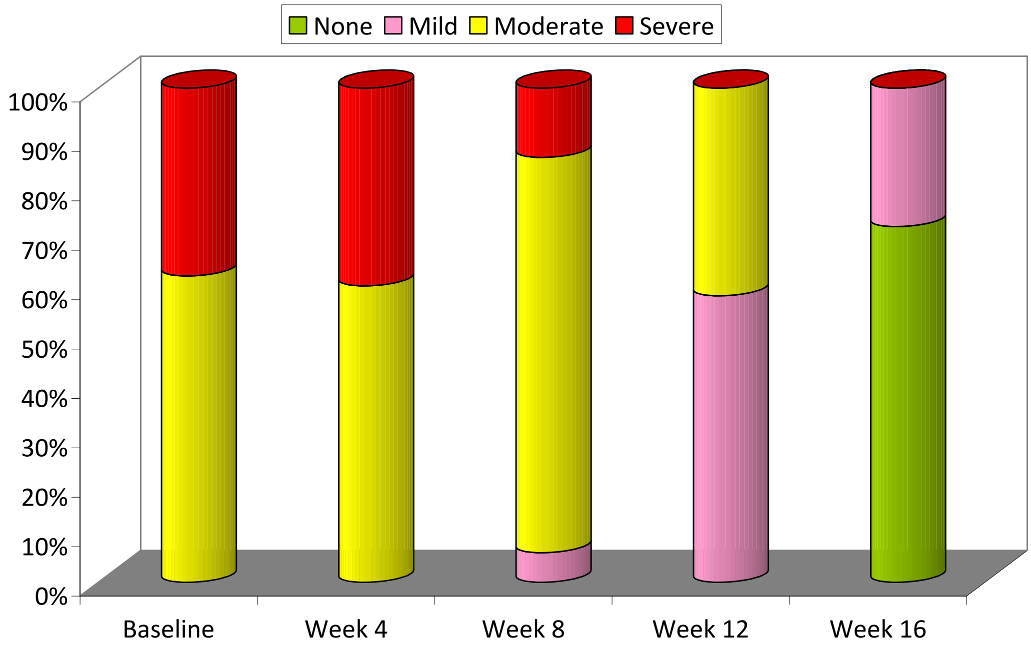

Figure 6: Response to low dose Intermittent Isotretinoin therapy

On evaluating the change in Global Acne Grading Score in Group B as compared to baseline, though change was observed at 4 weeks itself, change from baseline was found to be statistically significant from week 8 onwards (p<0.001, very highly significant)(Table 4a). At Week 24, all the patients with normal status at week 16 (n=36) were called on. Table 4(b) shows the change in GAGS from completion of treatment (16 weeks) to 8 weeks after completion of treatment (24 weeks).

Table 4(b): Change in Global Acne Grading Score in low dose Intermittent Isotretinoin (Wilcozon Signed Rank test)

SN	FU Interval	None	Mild	Moderate	Severe	Statistical significance	
						Z	P
1.	Week 16	36 (100.0)	0	0	0	–	–
2.	Week 24	19 (52.8%)	12 (33.3%)	4 (11.1%)	1 (2.8%)	5.087	<0.001*

$^{\$}$ Normal/ no lesion,*Very highly significant

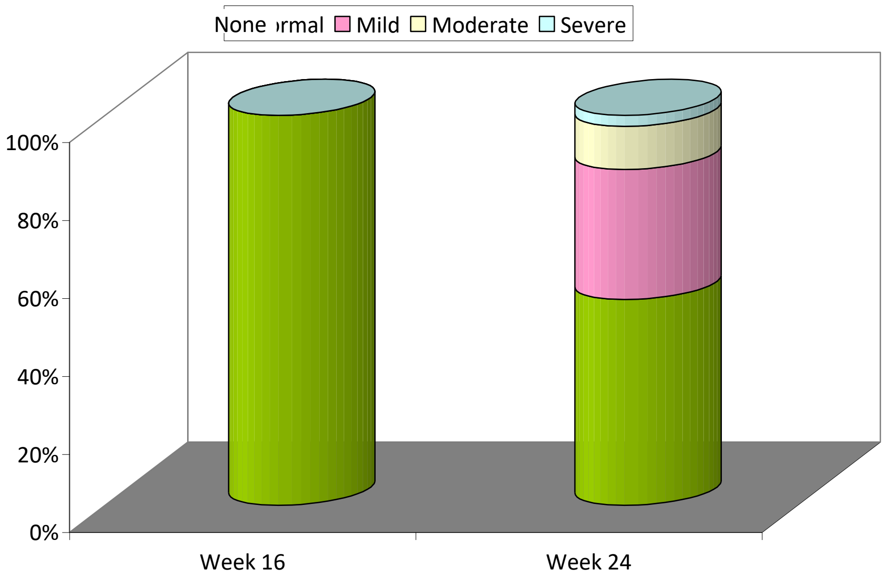

Figure 7: Relapse of acne vulgaris in low dose Intermittent Isotretinoin

At 24 weeks, all the 36 patients who had normal status at 16 weeks were called for follow up. At 24 weeks GAGS score of 19 (52.8%) were found to be normal, 12 (33.33%) was mild, 4 (11.1%) moderate and 1 (2.8%) was severe, change in GAGS score from baseline was found to be statistically significant (p<0.001, very highly significant).

Table 5: Comparison of Patients in two isotretinoin study groups (Mann Whitney U test)

SN	Time Interval	Z value	p value
1-	Baseline	1.597	0.110
2-	Week 4	2.659	0.008*
3-	Week 8	4.551	<0.001**
4-	Week 12	3.102	0.002*
5-	Week 16	3.257	0.001*
6-	Week 24	4.962	<0.001**

***Highly significant **Very highly significant**

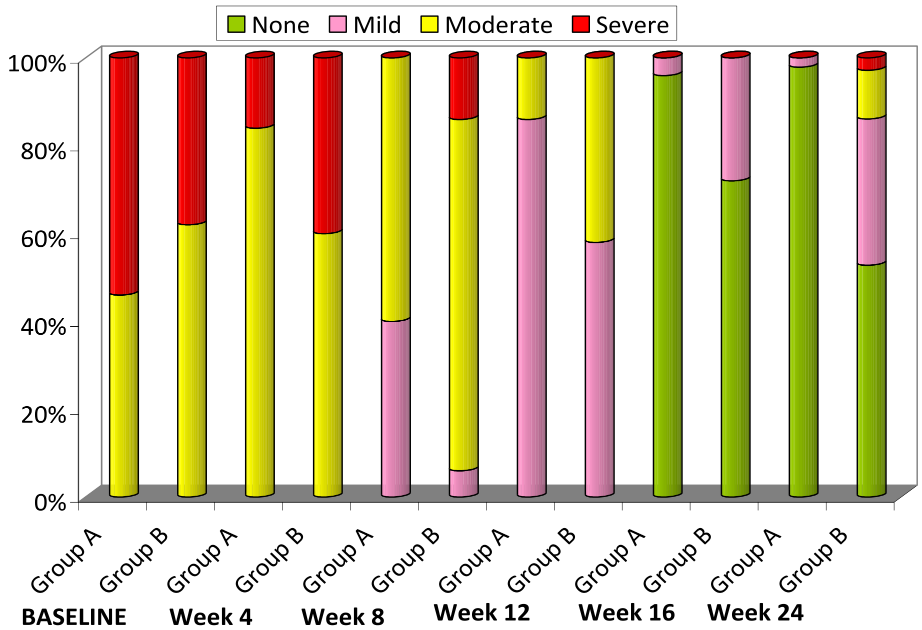

Figure 7: Comparison of Patients in two isotretinoin study groups

Above tables 3(a), 3(b), 4(a), 4(b) showed that at baseline, in Group A, 23 (46%) patients had moderate grade and 27 (54%) had severe grade whereas in Group B, 31 (62%) had moderate grade and 19 (38%) had severe grade. Statistically, the difference between two groups was not significant (p=0.110).

At week 4, 42 (84%) patients in Group A had moderate and remaining 8 (16%) had severe grade whereas in Group B, 30 (60%) had moderate and 20 (40%) had moderate grade. Statistically, the difference between two groups was significant (p=0.008, highly significant). At week 8, 20 (40%) patients in Group A had mild grade and remaining 30 (60%) had moderate grade whereas in Group B, 3 (6%) had mild, 40 (80%) had moderate and 7 (14%) had severe grade. Statistically, this difference between two groups was significant (p<0.001, very highly significant). At week 12, 43 (86%) patients in Group A had mild and remaining 7 (14%) had moderate grade whereas in Group B, 29 (58%) had mild and 21 (42%) had moderate grade. Statistically, this difference was significant (p=0.002, highly significant). At week 16, all the 48 (96%) patients in Group A were normal and 4% had mild grade whereas in Group B, 36 (72%) were normal and 14 (28%) had shifted to mild grade.(p=0.001, highly significant) At week 24, all the 84 patients (48 of Group A and 36 of Group B) who became normal at week 16 were followed up for relapse.

In Group A, only 1 (2.1%) patient had relapse and had mild grade. However, in Group B, relapse was seen in 17/36 (47.2%) patients – among these 12 (33.3%) had mild, 4 (11.1%) had moderate and 1 (2.8%) had severe grade. Statistically, the difference between two groups was significant (p<0.001).

Discussion

Oral isotretinoin is highly effective in treatment of moderate and severe acne vulgaris. This study was undertaken to evaluate the efficacy of low dose continuous and intermittent regimens of

Isotretinoin therapy.

In present study, in low dose continuous Isotretinoin group, at baseline 46% had moderate and 54% had severe grade of acne vulgaris (AV). The improvement in Global Acne Grading System (GAGS) grading was quick and by 4 weeks, 38% of patients of severe AV showed improvement by shifting from severe grade to moderate grade but none of the patients with moderate grade improved. However, by week 8 all patients with severe AV showed improvement. At week 8, 20 (40%) had shifted to mild form of the disease but still 60% were in moderate grade. This improvement in grade of severity of AV continued till week 16 by when 48 (96%) patients were relieved of active acne. The observations is in conformity with the study of Rasi et al. (2014)[9] who observed a 100% clearance of severe AV.

Intermittent low dose Isotretinoin group also showed an improvement in GAGS grade similar to low dose continuous isotretinoin group, however the response was slow and significant improvement was observed from week 8 onwards. At week 8, 26% patients shifted from severe to moderate grade while 6% improved from moderate to mild grade. At week 12, all the patients with severe grade showed improvement and 58% achieved mild grade. At the end of 16 weeks 72% patient had a complete recovery.

Low dose continuous isotretinoin showed a better response from week 4 itself and a significantly higher improvement was observed at the end of study period of 16 weeks.

However, at the end of six months no significant difference in improvement rates was observed between low dose continuous and intermittent isotretinoin regimens. In the present study the cumulative average dose of isotretinoin in low dose continuous isotretinoin group was 2240 mg as compared to 560 mg in low dose intermittent isotretinoin group.

In the present study after 8 weeks of end of the treatment, relapse was observed in 2.08% cases administered low dose Isotretinoin continuously and in 47.2% of cases administered intermittently.

The findings of present study showed that use of low-dose continuous regimen provides considerably better outcome in terms of resolution of acne during the course of treatment. This study compares the response of low dose continuous isotretinoin (0.3-0.4mg/kg daily) to low dose intermittent isotretinoin (0.3-0.4mg/kg for 1 week in 4 weeks) in treatment of moderate and severe acne vulgaris. It was questioned whether the chosen regimen are effective in treating moderate and severe acne vulgaris while avoiding the adverse effect of the drug.

Following conclusion can be drawn from the study on analyzing the results:

1. Low dose continuous Isotretinoin regimen was faster, more efficacious in treatment of moderate and severe acne vulgaris and relapse rate was also significantly lower after 8 weeks of stoppage of treatment than low dose intermittent Isotretinoin regimen.
2. Low dose intermittent Isotretinoin was effective in causing remission in moderate acne vulgaris but relapse of acne vulgaris occurred in almost half of the patients within 8 weeks of stoppage of treatment.

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