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RESEARCH ARTICLE

A randomized, open-label, comparative study of efficacy of low-dose continuous versus low-dose intermittent oral isotretinoin therapy in moderate-to-severe acne vulgaris

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ABSTRACT

Background: Acne vulgaris is a chronic inflammatory disease of pilosebaceous units. Oral isotretinoin is recommended for patients with moderate-to-severe acne vulgaris who are not responding satisfactorily to conventional therapies. Recent reports indicate that acne patients have been benefiting from the low-dose treatment protocols. **Aims and Objectives:** The aim of this study was to assess and compare the efficacy of oral isotretinoin in low-dose continuous and intermittent treatment of moderate-to-severe acne vulgaris. **Materials and Methods:** This was a prospective, randomized, open-labeled, comparative, efficacy study carried out at Outpatient Clinic in the Department of Dermatology in Mandya Institute of Medical Sciences, Mandya. Out of 120 patients screened, 100 patients were selected. Patients with moderate-to-severe acne were assigned equally (50 patients each) to one of the two treatment regimens using block randomization technique, Group A was given low-dose continuous regimen - 20 mg of oral isotretinoin once daily for 4 months and Group B was given low-dose intermittent regimen - 20 mg of oral isotretinoin once daily for 1 week out of every 4 weeks. The patients were followed up every 4th week during the treatment period. A 6-month follow-up evaluation after the end of treatment was performed. The outcome of the therapy was based on the improvement in the global acne grading system (GAGS) score and patients' satisfaction with the treatment in the 4-point scale. **Results:** This study showed statistically significant clinical improvement and difference in GAGS score between Group A and Group B ($P < 0.005$). **Conclusion:** This study suggests that, considering clinical efficacy, low-dose continuous treatment is most suitable for patients with moderate-to-severe acne vulgaris.

KEY WORDS: Acne Vulgaris; Oral Isotretinoin; Global Acne Grading System Score; Conventional Therapy

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of pilosebaceous units characterized by comedones, papules, pustules, nodules, cysts, abscesses, and later on sometimes as widespread scarring. This disease occurs worldwide and usually starts in adolescence and resolves by mid-twenties.[1] It is the most common skin disorder and the prevalence of moderate-to-severe acne vulgaris being about 11%.[2]

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The primary and pathognomonic lesion in acne is a microcomedone; a microscopic lesion invisible to the eye. The formation of microcomedone involves a complex interaction of altered follicular keratinization, hyperplasia of sebaceous follicles, and overcolonization of sebaceous

follicles with *Propionibacterium acnes*. Host immune response and inflammation also contribute to the clinical picture and course.[3]

According to the severity of acne, there are various modalities of treatment and they include both systemic and topical therapy. Moreover, new modalities of treatment have been designed due to the better understanding of the pathogenesis. The topical treatment includes benzoyl peroxide (2.5-10%), topical retinoids (tretinoin, isotretinoin, adapalene, tazarotene, etc.), topical antibiotics (erythromycin, clindamycin, etc.), and other topical agents such as salicylic acid and azelaic acid. Systemic therapy includes systemic antibiotics, hormonal therapy, and oral isotretinoin.[4] Oral isotretinoin is the most effective choice in the treatment of severe acne. Application of this drug has also been expanded to patients with less severe but scarring acne who are responding unsatisfactorily to conventional treatment. However, long-term daily use of this drug results infrequent side effects, some of which may lead to disastrous complications resulting in difficulties in complying with the treatment.[5]

Recent reports indicate that acne patients have been benefiting from the low-dose or intermittent treatment protocols. Low-dose isotretinoin, such as 0.15-0.40 mg/kg was reported to be effective with a low incidence of severe side effects. Moreover, data regarding intermittent treatment protocol are limited.[5] Hence, considerable doubt exists in deciding which protocol would give the maximum benefits, so this study has been undertaken to determine and compare the efficacy of the oral isotretinoin in low-dose continuous with low-dose intermittent in the treatment of moderate-to-severe acne vulgaris.

MATERIALS AND METHODS

After Institutional Ethical Committee approval, a randomized, open-label study was conducted from July 2012 to August 2013 in patients attending the Outpatient Clinic in the Department of Dermatology in Mandya Institute of Medical Sciences, Mandya. This study was approved by the Ethics Committee of Mandya Institute of Medical Sciences.

Trial design: Prospective, randomized (block randomization), open-label study.

Sample size calculation:[6]

Sample size (n) = Z^2 P (1-P)/d^2 = 1.96^2 × 96.03 (1-96.03)/$(19.18)^2$ = ~95

(Z is 1.96 for 95% confidence interval, P = maximum response score, and d = the difference between maximum and minimum score).

Inclusion Criteria

The patients those who volunteered to give informed consent, male and female patients in the age range of 18-45 years and diagnosed to have moderate-to-severe acne, willing to take oral isotretinoin therapy and not responded to antibiotic therapy were included in this study.

Exclusion Criteria

Patients with diabetes mellitus, allergy to isotretinoin drugs, on oral contraceptives and other drugs known to produce acne, pregnant and breastfeeding women, patients with abnormal lipid profile, significant hepatic dysfunction, and underlying psychiatric disorders were excluded from this study.

The patients were explained in the language best understood by them about the purpose of this study and its benefits to them as well as possible adverse effects. After obtaining written informed consent, patients' sociodemographic profile with family history of acne was taken. Based on the global acne grading scale, out of 120 patients screened for moderate-to-severe acne, 100 patients were selected. 50 patients in each group were randomly assigned using block randomization: Group A received low-dose continuous regimen - 20 mg oral isotretinoin once daily for 4 months and Group B received low-dose intermittent regimen - 20 mg oral isotretinoin once daily for 1 week out of every 4 weeks. The patients were followed up every 4th week during the treatment period. A 6-month follow-up evaluation after the end of treatment was performed.

The outcome of the therapy was based on the improvement in the global acne grading system (GAGS) score and patients satisfaction with the treatment in the 4-point scale.

During the treatment, acne grading was evaluated and recorded using the GAGS score at each visit. It was calculated by rating six different locations (forehead, right cheek, left cheek, nose, chin, and chest/upper back) and then multiplying each rating by a factor that is specific to that area. Factors are based on the surface area and distribution/density of pilosebaceous units.

GAGS: 0: No lesions; 1: ≥1 Comedo; 2: ≥1 Papule; 3: ≥1 Pustule; 4: ≥1 Nodule.

Multiplication Factors to Each Six Different Locations

Location	Factor
Forehead	2
Right cheek	2
Left cheek	2
Nose	1
Chin	1
Chest and upper back	3

The global score is the sum of all six location scores and global acne grade is defined according to the global score.

Global Acne Grade

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

Non-inflammatory lesions (comedones) and inflammatory lesions (papules, pustules, and nodules) were counted at 0, 12, and 24 weeks. At the end of this study, the degree of satisfaction on a 4-point scale was documented by the participants.

Degree of Satisfaction on a 4-Point Scale

Score	Grade
4	Very satisfied
3	Satisfied
2	Slightly satisfied
1	Dissatisfied

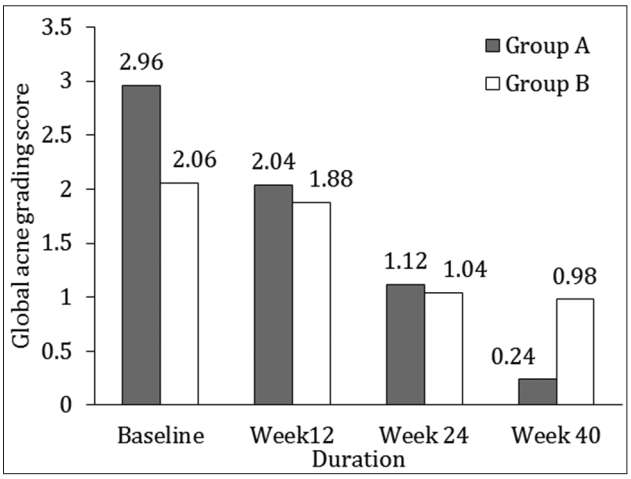
Statistical Analysis

Data were entered into Microsoft Excel and analyses were performed using the Statistical Package for the Social Sciences (SPSS). Descriptive statistics such as mean and standard deviation for continuous variables and frequency and percentage for categorical variables were determined. Chi-square test and Fisher's exact test were used to show the associations between predictor and outcome variables for categorical variables. Unpaired *t*-test was used to compare means between Group A and Group B for continuous variables. Repeated measure ANOVA was used to test the statistical difference in the mean efficacy from 0 to 40 weeks. The $P < 0.05$ was considered as statistically significant.

RESULTS

In this study, a total of 100 patients were recruited, 50 patients were received continuous oral isotretinoin regimen (Group A) and another 50 were received intermittent regimen (Group B). 72% were male and 28% were female. The prevalence age was ranged from 20 to 22 years.

Global grading score has decreased from severe to moderate to mild and then to none, as duration of the treatment advances from 0 days to 24-40 weeks (Graph 1 and Tables 1-6).



Graph 1: Effective change in global acne grading score at 0, 12, 24, and 40 weeks with Group A and Group B therapy for acne vulgaris

Table 1: Biosocial characteristics in two groups (*n*=100)

Biosocial characteristics	*n*=50 (%)	
	Group A	Group B
Age (in years)		
Mean±SD	21.74±2.07	21.02±2.29
Sex		
Male	35 (70)	37 (74)
Female	15 (30)	13 (26)
Weight (in kg)		
Mean±SD	56.1±5.12	56.3±5.26
Marital status		
Unmarried	50 (100)	50 (100)
Married	0	0
Family history		
Present	18 (36)	12 (24)
Absent	32 (64)	38 (76)
Type of acne		
Maculopapular lesions	1 (2)	44 (88)
Papulopustular	29 (58)	6 (12)
Pustulonodular	20 (40)	0
Grading of acne		
Moderate	2 (4)	47 (44)
Severe	48 (96)	3 (6)

Table 2: GG of acne at various time intervals (*n*=100)

GG	GG at day 0	GG at 12 weeks	GG at 24 weeks	GG at 40 weeks
None	0 (0.0)	0 (0.0)	0 (0.0)	43 (43.0)
Mild	0 (0.0)	7 (7.0)	92 (92.0)	53 (53.0)
Moderate	49 (49.0)	90 (90.0)	8 (8.0)	4 (4.0)
Severe	51 (51.0)	3 (3.0)	0 (0.0)	0 (0.0)

GG: Global grading

Table 3: Effective change in GG score at 0, 12, 24, and 40 weeks within Group A therapy for acne vulgaris

Factor	Mean difference	Standard error	Significant	95% confidence interval for difference[c]	
				Lower bound	Upper bound
GG-0 day					
GG-12 weeks	10.300	0.367	0.000	9.290	11.310
GG-24 weeks	21.900	0.541	0.000	20.413	23.387
GG-1 year	32.420	0.563	0.000	30.872	33.968
GG-12 weeks					
GG-0 day	−10.300	0.367	0.000	−11.310	−9.290
GG-24 weeks	11.600	0.401	0.000	10.497	12.703
GG-1 year	22.120	0.482	0.000	20.795	23.445
GG-24 weeks					
GG-0 day	−21.900	0.541	0.000	−23.387	−20.413
GG-24 weeks	−11.600	0.401	0.000	−12.703	−10.497
GG-1 year	10.520	0.465	0.000	9.241	11.799
GG-1 year					
GG-12 weeks	−32.420	0.563	0.000	−33.968	−30.872
GG-24 weeks	−22.120	0.482	0.000	−23.445	−20.795
GG-1 year	−10.520	0.465	0.000	−11.799	−9.241

Group A showed statistically significant difference in the mean efficacy between GG 0 day, week 12, week 24, and 1 year (P<0.001),
GG: Global grading

Table 4: Effective change in GG score at 0, 12, 24, and 40 weeks within Group B therapy for acne vulgaris

Factor	Mean difference	Standard error	Significant	95% confidence interval for difference[c]	
				Lower bound	Upper bound
GG-0 day					
GG-12 weeks	7.040	0.286	0.000	6.255	7.825
GG-24 weeks	14.420	0.505	0.000	13.032	15.808
GG-1 year	20.960	0.885	0.000	18.527	23.393
GG-12 weeks					
GG-0 day	−7.040	0.286	0.000	−7.825	−6.255
GG-24 weeks	7.380	0.338	0.000	6.451	8.309
GG-1 year	13.920	0.744	0.000	11.875	15.965
GG-24 weeks					
GG-0 day	−14.420	0.505	0.000	−15.808	−13.032
GG-24 weeks	−7.380	0.338	0.000	−8.309	−6.451
GG-1 year	6.540	0.589	0.000	4.920	8.160
GG-1 year					
GG-12 weeks	−20.960	0.885	0.000	−23.393	−18.527
GG-24 weeks	−13.920	0.744	0.000	−15.965	−11.875
GG-1 year	−6.540	0.589	0.000	−8.160	−4.920

Group B showed statistically significant difference in the mean efficacy between GG 0 day, week 12, week 24, and 1 year (P<0.001),
GG: Global grading

Table 5: Effective change in GG score at 0, 12, 24, and 40 weeks with Group A and Group B therapy for acne vulgaris

Global acne grading	Mean±SD		*P* value
	Group A (*n*=50)	Group B (*n*=50)	
GG score at 0 day	2.96±0.20	2.06±0.24	0.363
GG score at 12 weeks	2.04±0.28	1.88±0.32	0.061
GG score at 24 weeks	1.12±0.32	1.04±0.20	0.003
GG score at 40 weeks	0.24±0.43	0.98±0.42	0.008

GG: Global grading, SD: Standard deviation

Table 6: Degree of patient satisfaction on 4-point scale (n=100)

Groups	Very satisfied (%)	Satisfied (%)	Slightly satisfied (%)	Dissatisfied (%)
Group A	10 (20)	21 (42)	19 (38)	0
Group B	7 (14)	18 (36)	25 (50)	0

DISCUSSION

Acne vulgaris is a chronic, inflammatory disease of pilosebaceous units, characterized by comedones, papules, pustules, nodules, and often scars. Many factors including androgenic stimulation, *Propionibacterium acnes* activity, sebum production, hypercornification, as well as inflammatory mediator responses are thought to play a role in acne pathogenesis.

Isotretinoin is an FDA-approved drug for the treatment of severe cases of nodulocystic acne. Its conventional recommended dose has been 0.5-1.0 mg/kg body weight per day for 16-32 weeks, with a maximum cumulative dose of 120 mg/kg. It is used as an off-label indication for other grades of acne but erroneously in the same dose (1 mg/kg day; cumulative dose of 120 mg/kg). This regimen is known to produce good results; however, it might cause several dose-dependent side effects. In an endeavor to surmount this limitation and to make the regimen cost-effective, low-dose regimens for mild/moderate grades of acne have been advocated.[7,8]

Isotretinoin is the only drug that affects almost all factors in acne pathogenesis and is now established as a successful therapeutic option with the ability to induce long-term remission in patients with acne vulgaris. Isotretinoin was earlier prescribed for the cases of nodulocystic acne but is now increasingly used to treat patients of moderate-to-severe acne vulgaris, which are not responsive to topical therapy or oral antibiotics.[2,9]

Nadia and El-Sherif et al.[10] compared different isotretinoin regimens; daily low dose, intermittent dose, and conventional dose in treating patients with moderate acne, and concluded that a low-dose continuous treatment is most suitable for patients with moderate-to-severe acne vulgaris.

Kaymak and Ilter[11] showed the efficacy of the intermittent regimen (0.5-0.75 mg/kg daily for 1 week out of every 4 weeks for a total period of 6 months) in the treatment of 60 patients with mild-to-moderate acne. Amichai et al.[12] reported successful treatment of 638 patients with moderate acne with low-dose regimen (0.3-0.4 mg/kg daily for a total period of 6 months).

In the present comparative study, the results of the 4 months of treatment with isotretinoin showed that both low-dose continuous (Group A) and low-dose intermittent regimen (Group B) were effective in moderate-to-severe acne vulgaris yielded therapeutically desirable results in 86% and 70%, respectively. However, patients in Group A showed a more rapid effect with regard to lesion count reduction during the first few weeks (0-12 weeks) of therapy compared to Group B, but this difference was statistically insignificant.

At 24th and 40th week, there was a significant difference in GAGS score between Group A and Group B ($P < 0.03$ and < 0.008, respectively). The lesion count showed a decline in the number of inflammatory lesions and non-inflammatory lesions in both the groups. For inflammatory and non-inflammatory lesions, the low-dose intermittent regimen had less effect than low-dose continuous regimen.

It is well known that a high cumulative dose is an important factor in preventing relapse. The intermittent regimen needs a long treatment period to reach a high cumulative dose. Our study showed highest recurrence rate in Group B than Group A. These results show that low-dose continuous regimen had a better clinical outcome with lesser relapse rate than intermittent regimen. This confirms with previous studies carried out by Lee et al.[2]

The results support the existing published data showing the efficacy of low-dose continuous regimen than low-dose intermittent regimen.

To increase patient compliance, either the low-dose continuous regimen may be used or we can give the low-dose continuous regimen for initial 8 weeks and later maintain on low-dose intermittent regimen.

Comparing the treatment efficacy, we found that low-dose continuous regimen has better clinical efficacy than low-dose intermittent regimen. For severe acne, either the low-dose continuous regimen may be used or we can give the low-dose continuous regimen for initial 8 weeks and later maintain on low-dose intermittent regimen.

This study suggests that, considering tolerability, efficacy, and patient satisfaction, the low-dose continuous regimen is most suitable for patients with moderate-to-severe acne vulgaris.

Limitations to this Study

This study was open-label and unblinded. The duration of this study was short and sample size was small.

CONCLUSION

This study showed that low-dose continuous oral isotretinoin has a better clinical efficacy and patient satisfaction than low-dose intermittent therapy by producing a significant and faster

reduction of acne lesions, for the patients of moderate-to-severe acne vulgaris who have taken topical, oral antibiotics in the past but not relieved of symptoms. The quick response afforded by low-dose continuous oral isotretinoin will reduce the duration of therapy and also prevent the development of resistance. Further, large sample size randomized study was required to confirm the findings.

REFERENCES

1. Dreno B, Poli F. Epidemiology of acne. Dermatology. 2003;43:1042-8.
2. Lee JW, Yoo KH, Park KY, Han TY, Li K, Seo SJ, et al. Effectiveness of conventional, low dose and intermittent oral isotretinoin in the treatment of acne: A randomized, controlled comparative study. J Br Dermatol. 2011;164(6):1369-75.
3. Gollnick H, Cunliffe W, Berson D, Dreno B, Finlay A, Leyden JJ, et al. Management of acne: A report from a global alliance to improve outcomes in acne. J Am Acad Dermatol. 2003;49 1 Suppl: S1-37.
4. Rathi SK. Acne vulgaris treatment: The current scenario. Indian J Dermatol. 2011;56(1):7-13.
5. Akman A, Durusoy C, Senturk M, Koc CK, Soyturk D, Alpsoy E. Treatment of acne with intermittent and conventional isotretinoin: A randomized, controlled multicenter study. Arch Dermatol Res. 2007;299(10):467-73.
6. Agarwal US, Besarwal RK, Bhola K. Oral isotretinoin in different dose regimens for acne vulgaris: A randomized comparative trial. Indian J Dermatol Venerol Leprol. 2011;77(6):688-94.
7. Goulden V, Clark SM, McGeown C, Cunliffe WJ. Treatment of acne with intermittent isotretinoin. Br J Dermatol. 1997;137(1):106-8.
8. Seukeran DC, Cunliffe WJ. Acne vulgaris in the elderly: The response to low-dose isotretinoin. Br J Dermatol. 1998;139(1):99-101.
9. Melnik BC. FoxO1-the key for the pathogenesis and therapy of acne? J Dtsch Dermatol Ges. 2010;8(2):105-14.
10. El-Sherif NA, Greiw AS, Benamer AM. Efficacy of low dose versus intermittent isotretinoin regimens in patients with moderate acne vulgaris: A randomized controlled trial. Ibnosina J Med Biomed Sci. 2013;5(5):296-302.
11. Kaymak Y, Ilter N. The effectiveness of intermittent isotretinoin treatment in mild or moderate acne. J Eur Acad Dermatol Venereol. 2006;20(10):1256-60.
12. Amichai B, Shemer A, Grunwald MH. Low-dose isotretinoin in the treatment of acne vulgaris. J Am Acad Dermatol. 2006;54(4):644-6.

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