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Original Research Article

A randomized open label comparative study to determine the various side effects and patient satisfaction 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 chronic inflammatory disease of pilosebaceous units. Oral isotretinoin is recommended for 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. However, long term daily use of this drug results in frequent side effects such mucocutaneous and systemic side effects. Our aim was to assess and compare the various side effects and patient satisfaction of oral isotretinoin in low dose continuous and intermittent treatment of moderate to severe acne vulgaris.
Methods: This was a prospective randomized open labeled comparative study carried out at outpatient department in the Department of Dermatology in Mandya Institute of Medical sciences, Mandya. Patients with moderate to severe acne were assigned equally (50 subjects each) to one of the two treatment regimens by using block randomization technique, Group A was given low dose continuous regimen-20 mg oral isotretinoin once daily for 4 months and Group B was given 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. The patients were examined and side effects were noted in each visit. A six month follow-up evaluation was done to analyze patient satisfaction.
Results: Muco-cutaneous dryness was most common adverse effect noted in both the groups A and B. Itching (42%), Alopecia (44%), Myalgia (36%) were seen most commonly in group A and Acne flaring (47%) was most common with group B. With regard to patient satisfaction, in group A 42% were satisfied and 20% were very satisfied, in group B 36% were satisfied and 14% were very satisfied.
Conclusions: Study suggests that, Muco-cutaneous dryness was most common side effect in both treatment regimens. Side effects were more frequent with low dose continuous than low dose intermittent isotretinoin regimen. Patient satisfaction was better in continuous regimen.

Keywords: Acne vulgaris, Conventional therapy, Oral isotretinoin, Muco-cutaneous side effects

INTRODUCTION

Acne Vulgaris is 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,

prevalence of moderate to severe acne vulgaris being about 11%.[2]

According to the severity of acne there are various modalities of treatment and they include both systemic and topical therapy. Systemic therapy includes systemic antibiotics, hormonal therapy and oral isotretinoin. 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 like (salicylic acid, azelaic acid etc.).[3]

Oral isotretinoin is recommended for 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. However, long term daily use of this drug results in frequent side effects, some of which may lead to disastrous complications resulting in difficulties in complying with the treatment.[4] Oral retinoids have multiple mucocutaneous and systemic side effects. Mucocutaneous toxicity is the most commonly observed side effect of isotretinoin use. This study to determine and compare the various side effects with oral isotretinoin in low dose continuous and intermittent treatment of moderate to severe acne vulgaris.

Objectives

- *Primary objective:* To determine the various side effects and patient satisfaction with oral isotretinoin in low dose continuous and intermittent treatment of moderate to severe acne vulgaris.
- *Secondary objectives:* To compare the various side effects and patient satisfaction with oral isotretinoin in low dose continuous and intermittent treatment of moderate to severe acne vulgaris

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. The study was approved by the ethics committee of Mandya Institute of Medical Sciences.

Prospective randomized (Block randomization) open label study.

Sample size calculation[5]

$$\text{Sample size (n)} = Z^2\ P\ (1\text{-}P) / d^2 = 1.96^2 \text{ X } 96.03\ (1\text{-}96.03) / (19.18)^2 = \sim 95$$

(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.

Exclusion criteria

Patients with Diabetes mellitus, Allergy to isotretinoin drugs, on oral contraceptives and other drugs known to produce acne, Pregnant and breast-feeding women, subjects with abnormal lipid profile, significant hepatic dysfunction and underlying psychiatric disorders.

The subjects were explained in the language best understood by them about the purpose of 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 were taken. Based on the Global Acne Grading scale (Table 1) out of 126 patients screened 100 subjects were diagnosed to have moderate to severe acne. 50 subjects in each group were randomly assigned by using block randomization technique: Group A received low dose continuous regimen - 20mg oral isotretinoin once daily for 4 months and Group B received low dose intermittent regimen - 20mg 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 six month follow-up evaluation after the end of treatment was performed to analyze patient satisfaction.

The patients were examined, and side effects were noted in each visit.

Table 1: Global acne grading scale (for patient selection).

Age group	Parameter
0	None
1-18	Mild
19-30	Moderate
31-38	Severe
≥39	Very severe

At the end of the study, the degree of satisfaction on a four-point scale (Table 2) was documented by the participants.

Table 2: Degree of satisfaction on a four point scale.

Four point scale	Parameter
4	Very satisfied
3	Satisfied
2	Slightly satisfied
1	Dissatisfied

Data was entered into Microsoft excel and analyses were done using the Statistical Package for Social Sciences (SPSS). Descriptive statistics such as mean and standard deviation (SD) for continuous variables, and frequency and percentage for categorical variables were determined. Unpaired 't' test was used to compare means between group A and group B for continuous variables. P <0.05 was considered as significant.

RESULTS

In the study, a total of 100 patients were recruited, 50 patients were received continuous low dose oral isotretinoin regimen (group A) and another 50 were received intermittent low dose oral isotretinoin regimen (group B).

There were 72% males and 28% were females. The prevalence age was ranged from 20-22 years. 58% of the patients had Papulo-pustular and 40% had pustule- nodular lesions in group A and 88% of patients in group B had maculopapular lesion. 96% of study subjects in group A showed severe form of acne and 94% in group B showed moderate form of acne (Table 3).

Table 3: Bio-social characteristics in two groups (N = 100).

Bio-Social characteristics	Group A (n=50)	Group B (n=50)
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		
Maculo-papular lesions	1 (2%)	44 (88%)
Papulo-pustular	29 (58%)	6 (12%)
Pustule-nodular	20 (40%)	0
Grading of acne		
Moderate	2 (4%)	47 (94%)
Severe	48 (96%)	3 (6%)

In the study subjects commonly seen adverse effects were mucocutaneous dryness (99%), itching (60%), acne flare (54%), alopecia (54%) and myalgia (42%) (Figure 1).

Muco-cutaneous dryness (Figure 2) was most common adverse effect noted in both the groups A and group B. Itching (42%), Alopecia (44%), Myalgia (36%) were seen most commonly in group A and Acne flaring (47%) was most common with group B and there was statistical difference (P<0.001) between the groups. Acne flaring (14%) was least common side effect in group A (Table 4 and Figure 3).

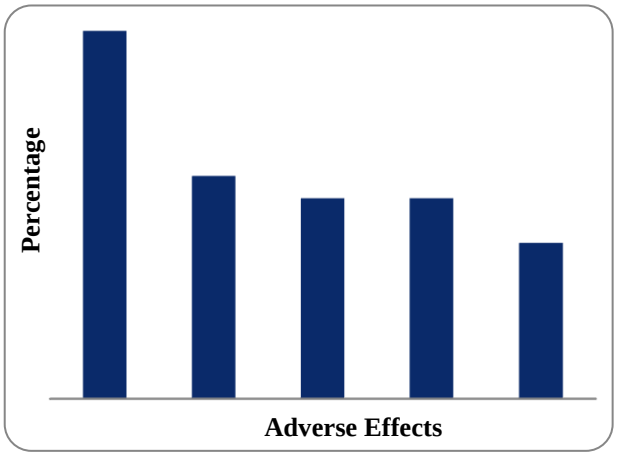

Figure 1: Distribution of patients according to their adverse effects during therapy for acne vulgaris (N = 100).

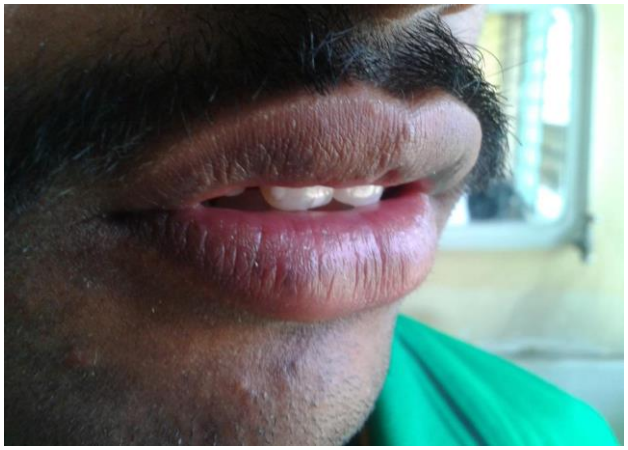

Figure 2: Mucocutaneous side effects.

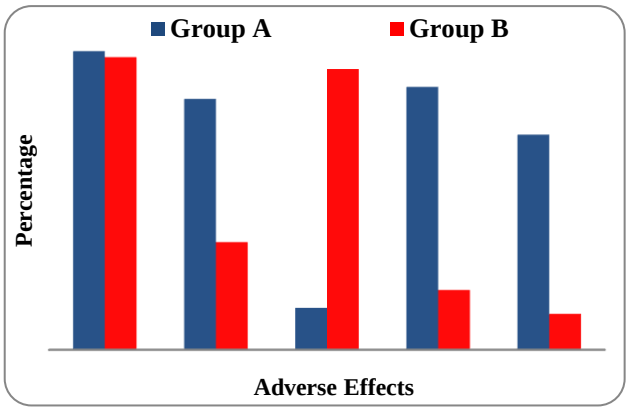

Figure 3: Association of adverse effects seen in Group A and Group B in the low dose oral isotretinoin treatment of acne vulgaris patients.

Table 4: Association of mode of therapy for acne vulgaris patients with their adverse effects during their therapy (N = 100) bio-social characteristics.

	Group A (n=50)	Group B (n=50)	P Value
Muco-cutaneous dryness			
Yes	50 (100.0)	49 (98.0)	0.315
No	0 (0.0)	1 (2.0)	
Itching			
Yes	42 (84.0)	18 (36.0)	<0.001
No	8 (16.0)	32 (64.0)	
Acne flare			
Yes	7 (14.0)	47 (94.0)	<0.001
No	43 (86.0)	3 (6.0)	
Alopecia			
Yes	44 (88.0)	10 (20.0)	<0.001
No	6 (12.0)	40 (80.0)	
Myalgia			
Yes	36 (72.0)	6 (12.0)	<0.001
No	14 (28.0)	44 (88.0)	

Statistical significant difference seen in the side effects of itching, acne flaring, alopecia and myalgia between Group A and Group B ($p<0.001$)

With regard to patient satisfaction, in group A 42% were satisfied and 20% were very satisfied, in group B 36% were satisfied and 14% were very satisfied (Figure 4).

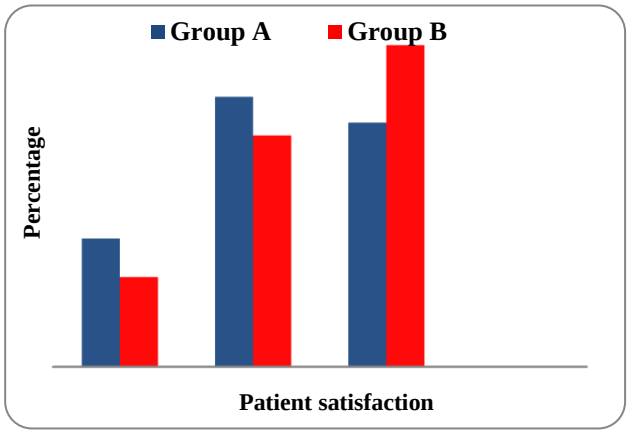

Figure 4: Patient satisfaction with low dose oral isotretinoin therapy in continuous (Group A) and intermittent (Group B) regimen.

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 the only drug that affects almost all factors in acne pathogenesis and is now established as a successful therapeutic option with ability to induce long term remission in patients with acne vulgaris. Isotretinoin was earlier prescribed for 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.[2,6]

In the study muco-cutaneous dryness was most common adverse effect noted in both the groups, similar result was observed in Lee JW et al.[2] study but Rao PK et al, study showed cheilitis was the most common among the side effects observed and was seen in 98% of the participants.[7]

Nadia A El-Sherif et al, study showed no statistically significant differences among both groups regarding the frequency and severity of the side effects.[8] In this study the frequency and severity of treatment related side effects like dry skin, alopecia, itching was significantly higher in low dose continuous regimen as compared to low dose intermittent regimen. Acne flaring was more common in low dose intermittent than low dose continuous.

The patient satisfaction score was highest in low dose continuous regimen as compared with intermittent regimen. This result suggests that the low dose continuous regimen is slightly superior to low dose intermittent regimen in terms of patient satisfaction. Boyraz, N et al, and Lee JW et al, studies had shown similar results.[2,9]

The result of our study suggests that, low dose continuous regimen has shown higher adverse effect and better patient satisfaction than low dose intermittent regimen for patients with moderate to severe acne.

Limitations

The sample size was small. Not many investigations done to detect side effects.

CONCLUSION

The result of our study suggests that, low dose continuous regimen has shown higher adverse effect and better patient satisfaction than low dose intermittent regimen for patients with moderate to severe acne. Muco-cutaneous dryness was most common side effect in both treatment regimens. Itching, alopecia and myalgia were common with low dose continuous and acne flaring was most commonly seen in intermittent regimen.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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;164:1369-75.
3. Rathi SK. Acne vulgaris treatment: The Current Scenario. Indian J Dermatol Venereol. 2011;56:7-13.
4. 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;299:467-73.
5. 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;77:688-94.
6. Melnik BC. FoxO1- the key for the pathogenesis and therapy of acne? J Dtsch Dermatol Ges. 2010;8:105-14.
7. Rao PK, Bhat RM, Nandakishore B, Dandakeri S, Martis J, Kamath GH. Safety and Efficacy of Low-Dose Isotretinoin in the Treatment of Moderate to Severe Acne Vulgaris. Ind J of Dermatol. 2014;59(3):316.
8. Nadia A El-Sherif, Azza SH Greiw, Benamer AM. Efficacy of low dose versus intermittent isotretinoin regimens in patients with moderate acne vulgaris: A randomized controlled trial. Ibnosina J Med B S. 2013;5(5):296-302.
9. Boyraz N, Mustak PK. Comparison of the efficacies of intermittent and continuous low-dose isotretinoin regimens in the treatment of moderate acne vulgaris. Int J of Dermatol. 2013 Oct 1;52(10):1265-7.

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