ORIGINAL ARTICLE

Effectiveness Of Oral Intermittent Vs Oral Continuous Isotretinoin Therapy in Patients with Moderate to Severe Acne Vulgaris; A Randomized Controlled Trial

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ABSTRACT

Objective: To compare the effectiveness of oral intermittent Isotretinoin treatment vs daily Isotretinoin therapy in patients with moderate to severe acne vulgaris.

Study Design: Randomized controlled trial.

Place and Duration of Study: The study was conducted for 06 months (1st March to 30th August 2021) at department of Dermatology, Pakistan railway hospital, Rawalpindi.

Materials and Methods: A total of 100 patients with moderate to severe acne selected through random sampling were divided into two groups A & B, each having 50 patients. In Group A, a daily dose of 0.5-0.75mg/kg of oral Isotretinoin was given only for 01 week, every 4th week for 04 months. Group B patients were given the same dose of oral Isotretinoin once daily regularly for 04 months. The clinical improvement was measured as difference in GAGS score calculated before and after the treatment using Global Acne Grading System (GAGS). The results were compared & analysed by using paired t-test.

Results: The age, weight, and GAGS scores of the patients in both groups were comparable at the baseline. The GAGS score at baseline was 29.94 $\pm$ 4.42 in group A, while in group B, the score was 29.84 $\pm$ 4.69. After 04 months of treatment, the difference in GAGS from baseline in group A was 17.44 $\pm$ 4.07 in group A compared to 19.09 $\pm$ 5.02 in group B. The P value of 0.006 was significant to prove the association of results.

Conclusion: The oral intermittent Isotretinoin therapy is more effective than daily continuous Isotretinoin therapy in patients with moderate to severe acne vulgaris.

Key Words: *Acne Vulgaris, Global Acne Grading System, Isotretinoin.*

Introduction

One of the most frequently occurring skin disorders, mainly affecting adolescents is acne vulgaris, with the prevalence of 87% worldwide.[1] It varies among countries and different ethnic groups.[2] The pathophysiology of this disease is multifactorial, an intense inflammatory process involving the pilosebaceous units with altered androgen activity at puberty, enhanced sebum production, follicular hyperkeratinisation and later invasion of the follicle by the Propionibacterium acnes are the key underlying factors.[3] Acne vulgaris has serious impact on affected individuals with negative effects on self-esteem, social isolation and cosmetic disfigurement by causing permanent facial scarring.[4]

There are multiple treatment options available which can be used alone or in various combinations. These include topical agents like salicylic acid, benzoyl peroxide, antibiotics, and retinoids. Among the systemic therapy, there are tetracycline, macrolides, clindamycin, and Isotretinoin.[5] The sensitivity of various antibiotics has decreased over the last two decades, and oral Isotretinoin has emerged as a treatment of choice. [6] It is FDA approved and its efficacy is well established in a conventional dose of 0·5–1·0 mg/kg per day for a period of 4 to 8 months, reaching to a cumulative dose of 120 mg/kg.[7] However, at this dose it is frequently associated with many side effects like dryness of skin, cracked lips chapped lips, hyperlipidaemia, and elevated liver enzymes.[8]

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The efficacy of low dose isotretinoin is well established through a number of clinical trials with better clinical outcome, good safety profile, and cost-effectiveness in moderately severe Acne vulgaris.[9,10] An intermittent regimen with low dose oral Isotretinoin has gained popularity over last decade but there is lack of literature on comparative studies with different regimens of intermittent oral isotretinoin in south Asia.[11] The objective of this study was to assess the effectiveness of intermittent Isotretinoin therapy in comparison to continuous daily Isotretinoin therapy in our population.

Materials and Methods

This randomized controlled trial was carried at department of Dermatology, Pakistan Railway hospital, affiliated with Islamic International medical college. The duration of study was 06 months. A sample of 100 patients (50 in each group A & B) was calculated with 95% confidence interval and 80% power using the open-source calculator, Open epi version 3, after approval from the ethical review committee (Ref No. Riphah/IIMC/IRC/21/51).

A strict inclusion criterion was applied, all the patients selected in the study had GAGS > 19 (below 19 = mild acne) and the age limit of >12 years was followed. The married females, patients who had any topical or oral anti-acne medication 04 weeks prior to study were not enrolled in the study. The patients using medication for any other systemic illness were also excluded. After informed verbal consent, the patients in Group A were given oral intermittent Isotretinoin, once daily for 01 week, every 4th week for 04 months. Patients in Group B were given continuous Isotretinoin once daily for 04 months regularly. The clinical improvement was measured as difference in GAGS score calculated before (at baseline) and after the treatment (at the end of 04 months) using Global Acne Grading System (GAGS).

A standard proforma was used to record the personal profile, weight (to calculate dose of the drug), dose of Isotretinoin, GAGS scores, liver enzymes & fasting triglyceride level. The treatment side effects like dry chapped lips, dry skin, elevated triglycerides, and liver enzyme were also recorded at baseline, 01, 02 and 04 months of treatment.

The data was entered and analysed in SPSS version 21. Mean reduction in GAGS score was compared in both groups by using Paired t-test as the data was parametric.

Results

Out of 100 total patients, with 50 patients in each group, only one patient in group A was dropped due to raised triglycerides and transaminases.

The mean age of participants in group A was 19.8 ± 3.09 years and in group B was 19.86 ±3.23 years with mean weight of 59.14 ± 12.35 Kg in group A and 57.54 ± 9.12 Kg in group B. The gender distribution in both groups is shown in figure 1.

The mean GAGS score at the baseline was 29.94 ± 4.42 in group A and 29.84 ± 4.69 in group B. The GAGS score at 01, 02, and 04 months after the treatment with P-values comparison is given in table 1. The overall decrease in the GAGS scores were 17.44 ± 4.07 in group A and 19.09 ± 5.02 in group B with the P value of 0.006, table 1.

Most frequent side effects were dry skin and dry lips, reported by more patients in group B compared to group A, table II.

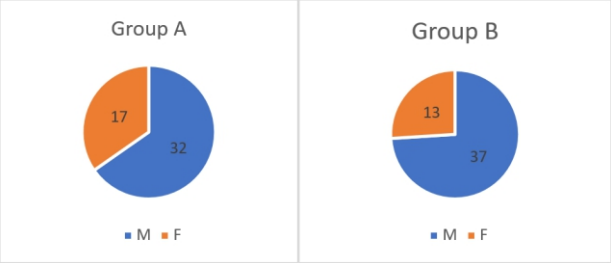

Fig:1 Gender Distribution in Both Groups

Table I: Global Acne Grading System Score (GAGS score)

Mean GAGS Score (Mean ± SD)	Group A (Intermittent Regime) (n=49)	Group B (Daily Regime) (n=50)	P Value
Baseline	29.94 ± 4.42	29.84 ± 4.69	0.328
01 month	24.37 ± 4.95	24.92 ± 4.91	0.578
02 months	19.37±4.38	18.96 ± 4.79	0.660
04 months	12.5 ± 3.07	10.84 ± 3.70	0.032
Overall reduction in GAGS Score (GAGS scores at base line – GAGS scores after 04 months)	**17.44 ± 4.07**	**19.09 ± 5.02**	**0.006**

Table II: Side Effects of Treatment

Side Effects		Group A (Intermittent Regime)		Group B (Daily Regime)	
		N	%	n	%
Dry Lips		3	6.12	20	20.0
Dry Skin		13	26.53	18	36.0
Triglycerides		1	2.04	0	0.0
Liver Enzymes		1	2.04	0	0.0
Others	Body aches	0	0.0	1	2.0
	Itching on face	0	0.0	2	4.0
	Scaling on face	0	0.0	1	2.0

Discussion

In this study, intermittent Isotretinoin regimen was found more effective with few & less severe side effects. At 04-month, acne severity was decreased, as measured by GAGS score, from 29.94 $\pm$ 4.42 to 17.44 $\pm$ 4.07 in intermittent Isotretinoin regimen group compared to daily Isotretinoin regimen group where GAGS score decreased from 29.84 $\pm$ 4.69 to 19.09 $\pm$ 5.02. This difference was significant with P-value of 0.006.

The concept of oral intermittent isotretinoin treatment is not new.[12] The comparative trials are lacking, except for few comparative studies there are mostly single group trials. Goulden et al. used the intermittent regimen in patients with moderately severe acne in 1997.[13] The efficacy of oral intermittent Isotretinoin therapy was later confirmed by Kaymak et al. in 2006. The study included all three categories of mild, moderate & severe acne patients. The results were promising in all the patients but a comparative group was missing.[14]

In another randomized controlled trial, conducted by Lee et al., in 2011, the conventional therapy of isotretinoin was compared with low doses continuous & intermittent therapy. A total of 60 patients were divided into 3 groups; in group A, the isotretinoin daily dose was 0.5–0.7 mg/kg/day, in group B the daily dose was 0.25–0.4 mg/kg/day, and the group C took the intermittent regimen at the dose of 0.5–0.7 mg/kg/day for 7 days followed by a 3-weeks break in every month. The treatment continued for a period of 6 months. The GAGS score was calculated in all the groups before and 6 months after the completion of treatment. The results suggested the better efficacy of low dose Isotretinoin in both continuous & intermittent regimens over the high dose therapy.[15] The sample size was less as compared to our study, but the outcome was comparable to our results regarding better efficacy of intermittent low dose therapy over conventional treatment regimen.

In a study conducted by Faghihi G et al., low-dose isotretinoin was compared with standard dose in 60 patients with moderately severe acne. There were two treatment groups, one received the regular dose of isotretinoin (0.5 mg/kg/day) and the other received low-dose isotretinoin (0.25 mg/kg/day), for a period of 06 months. The results were noted at 6 months and at 12 months after the completion of treatment. The improvement in acne score was more in low dose group and the most frequent side effects like xerosis cutis & loss of hair were 17% in the low-dose group vs 33.2% in the conventional dose group. The results are similar to our study in terms of outcome & lower incidence of side effects in the low-dose isotretinoin group.[16] The difference was of continuous vs intermittent dosing schedules, but the common thing was effectiveness of low dose either given as a continuous dose or as intermittent dosing schedule. The opposite findings were noted in a study conducted in India.[17] It was a comparative trial on a sample of 100 patients, with 50 in each group A & B. Group A was given isotretinoin at a low dose of 20 mg once daily for 4 months while group B was given the same dose but in intermittent regimen, once daily for 1 week out of every 4 weeks. The outcome was improvement in the global acne grading system (GAGS) score at 6 months in both groups. The study suggested that low-dose continuous treatment is most suitable for patients with moderate to severe acne vulgaris. The difference in the findings may be due to the reason that we calculated the dose according to the weight of patients in both groups which seems more appropriate & logical, while Sethi et al. used a fixed dose of 20 mg /day irrespective of the weights of the patients in both groups.

Mandekou-Lefaki et al., in 2003, conducted a comparative study on patients with different severity

of acne, using conventional therapy @ 0.5–1.0 mg/kg/day in one group & a low dose regimen @ 0.15–0.40 mg/kg/day in the other group, up to cumulative dosage of 120 mg/kg. There were total of 64 patients divided into 2 groups. The low doses were effective in terms of clinical improvement, safety profile & better effect on scars. The conventional therapy was having added advantage of less recurrences.[18] Although it was given in continuous regimen but here again the low dose was equally effective as compared to the conventional dose.

In another multicentre study by Akman et al, 66 patients with moderate to severe acne were enrolled into 03 treatment groups, two groups with intermittent unconventional dose in different regimen and one group with conventional dose for 06 months.[19]The group 1 received Isotretinoin for the first 10 days of each month, group 2 received each day in the first month, afterwards the first 10 days of each month for 5 months and for group 3 it was daily dose for 6 months. The dosage was 0.5 mg/kg/day in all groups. The follow-up was done for 12 months. There were statistically no significant differences in the outcome among all the treatment groups in patients with moderate acne, except for the significant difference in patients with severe acne, between group 1 and group 3. The conclusion was same as our study, intermittent isotretinoin treatment is an effective alternative in the management of moderate acne with a lower incidence of side effects.

In another study with patients of moderately severe acne vulgaris, a fixed daily dose of 20 mg of isotretinoin was given to half of the patients while the remaining half were treated with the alternate dose regimen for 24 weeks. Both the regimens were well tolerated by the patients but the alternate day regimen was more effective in treatment of moderate acne.[20]

There are many studies in favor of low dose intermittent Isotretinoin as an effective treatment for moderate acne vulgaris, and the results of our study are also consistent with efficacy of intermittent, low dose regimen with few & less severe side effects.

Conclusion

The oral intermittent Isotretinoin therapy is more effective as compared to continuous daily Isotretinoin therapy in patients with moderate to severe acne vulgaris.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.