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Comparative Efficacy and Safety of Low Dose versus High Dose Isotretinoin in Severe Acne Vulgaris Patients

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ABSTRACT

Background: Oral isotretinoin is the recommended treatment for acne vulgaris, a skin disease especially common in teenagers and adolescents. This study was designed to compare the efficacy and safety of low dose with high dose isotretinoin in severe acne vulgaris patients.

Material and Methods: This randomized controlled trial included 110 patients with a clinical diagnosis of acne vulgaris. They were divided into two groups. Both groups were matched for age (mean 18.2±3.7 vs 17.6±3.2 years), weight (mean 58±10.2 vs 60.7±9.3 Kg), gender and disease duration (3±1.1 vs 3±1.0 years). Group A received low dose oral isotretinoin (20 mg/day) while group B received standard high dose regimen (1mg/kg/day). All patients were followed up for 16 weeks to assess efficacy (assessment of complete remission) and safety (mucocutaneous side effects). All calculations were performed using SPSS v. 16 with p value <0.05 considered as statistically significant.

Results: There was no statistically significant difference in efficacy. However, significantly fewer mucocutaneous side effects were reported in group A (80%) as compared to group B (100%). This safety profile spectrum was observed across all pre-defined subsets i.e chielitis (78.1% vs 98.2%), dry skin (69.1% vs 92.7%), dry mouth (47.2% vs 72.7%) and facial rash (12.7% vs 30.9%).

Conclusion: In patients with severe acne vulgaris, efficacy (complete remission) of low dose oral isotretinoin is almost equal to conventional high dose regimen but it is statistically superior in terms of safety (mucocutaneous side effects).

Key words: Acne vulgaris, Isotretinoin, Mucocutaneous, Nodulocystic

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Introduction

Acne vulgaris (AV) is the most common skin disease worldwide characterized by chronic inflammation of pilosebaceous units which, if left untreated, may lead to detrimental physical and psychological effects.[1] The disease is more common in younger age groups, ranging from 70%[2] in teenagers to as high as 90% in adolescents.[3] Currently, oral and topical antibiotics and retinoids represent the most widely accepted conventional therapies for acne. Isotretinoin (13-cis retinoic acid) represents the single most important pharmacological advancement in acne therapeutics. Its conventional dose is 0.5-1 mg/kg/day in single or divided doses. The current practices follow a cumulative oral isotretinoin dose of 120-150 mg/kg of body weight in severe acne, over a period of 16-24 weeks. However, the common dose-dependent side-effects have compelled the researchers to look for substitute protocols.[4] Some recent studies have proposed a safer and almost as efficacious regimen with lower doses of oral isotretinoin, while others have failed to show any significant alternative.[4-6] Sardana et al and Agarwal et al reported comparative efficacy of 69% vs. 96% (low dose isotretinoin vs. high dose isotretinoin) in terms of

complete remission of acne vulgaris over a period of sixteen weeks.[5,6]

Similarly, low dose to high dose mucocutaneous side effects at 89% vs. 100% have been documented.[6] However, such protocols have not been advocated in the guidelines so far due to the paucity of published data for an optimal dosage regimen. Some of the physicians are thus opting for institution-based practices of high dose, low dose, pulsed and alternate day isotretinoin, while others have failed to show any dosage regimens. The pursuit of a robust regimen becomes all the more important in our setting considering the unique acne dynamics of South Asian population[7] as well as the financially constrained healthcare system. This study aims to find the efficacy and safety of high and low doses of oral isotretinoin in severe acne vulgaris patients presenting in our tertiary care hospital set-up.

Material and Methods

This randomized controlled trial was conducted at Dermatology out-patient department of Pakistan Institute of Medical Sciences (PIMS), Islamabad from 10th March, 2013 to 9th January, 2014. Sample size was computed using WHO calculator taking 5% level of significance with 95% power of the test.[6] Calculated sample size was 55 in each group. Both male and female patients with severe acne vulgaris, more than 12 years of age, presenting at the out-patient of Dermatology unit were included. Pregnant and breast-feeding, married females desiring to have pregnancy within 6 months after initiation of therapy were excluded.

Patients having Hypersensitivity to retinoids, patients with baseline triglyceride levels > 400 mg/dL and/or total cholesterol > 300 mg/dL, ALT > 60/uL and/or AST > 80/Ul were also excluded from the study. Drug induced acne i.e. acne in patients on isoniazid, phenytoin, lithium, azathioprine, cyclosporine and those already on anti-acne treatment were not included in the study. Permission was taken from the hospital's ethical committee. Informed written consent was taken from the enrolled patients and confidentiality was maintained throughout the study. Detailed history and clinical examination of all severe acne vulgaris patients was done at first hospital visit to assess for the suitability for enrollment in the study. FDA global acne scale was applied to assess the baseline severity of disease. Liver function tests (LFTs) and lipid profile were obtained.

All enrolled patients were equally divided into Group A (low dose isotretinoin) and Group B (high dose isotretinoin) by lottery method. Single blinded protocol was followed by concealing any information about their allotment group from the patients. Group A was prescribed oral isotretinoin at a dose of 20 mg once a day while Group B was given 1 mg/kg/day in divided doses. All patients were asked to swallow the capsule with meal to avoid gastrointestinal side effects. Furthermore, all patients were advised to apply topical 1% clindamycin gel twice daily as per the standard acne guidelines. Strict compliance with the treatment protocol was advocated throughout the study period. Patients were followed for sixteen weeks at monthly intervals. LFTs and lipid profile were checked on each follow up visit.

Therapy was discontinued if blood tests showed AST > 80/ul or ALT > 60/ul or Cholesterol > 300mg/dl or Triglycerides > 400mg/dl. Treatment protocol was termed efficacious if there was complete resolution of acne vulgaris features on clinical examination at 16 weeks of therapy. Patients were asked to report in clinic if they experienced any mucocutaneous side effects as already described. Patients not presenting for follow up were contacted on telephone and early clinic visit was emphasized. Subjects withdrawing consent and those who discontinued therapy by themselves for more than a week were addressed as "drop out" and excluded in the outcome analysis, same as for patients lost to follow up.

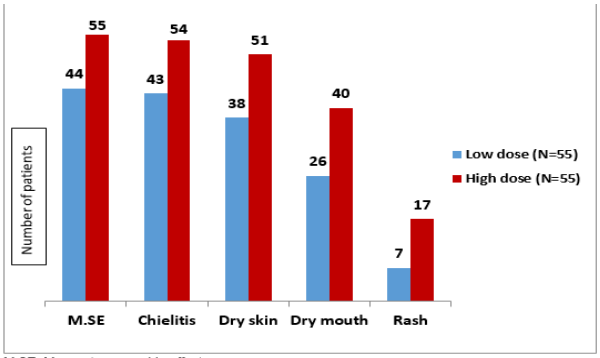
All statistical calculations were performed using SPSS version 16 (Statistical Package for the Social Sciences, SPSS Inc. USA). Mean and standard deviation were calculated for age, weight and duration of the disease. Frequency and percentages were calculated for categorical variables such as gender, efficacy and safety. Effect modifiers like site and duration of disease, age, gender was controlled by stratification. Independent sample t test was applied to test baseline characteristics. Chi square test was used to compare efficacy and safety outcomes. *P* value of less than 0.05 was considered statistically significant.

Results

A total of 110 patients were included in the analysis (55 in each group). Table I shows the baseline characteristics of the study sample. In group A, females were more while in group B, there was male dominancy. In group A, median age was 17 years with an age range 12-27 years. In group B, median age was 17 years with a range of 12-25 years. Subjects of group A had median weight of 57 kg (range 36-85 Kg) while in group B, median weight was 60 Kg (range was 37-82 Kg). No statistically significant difference was noted in both groups as far as age (p=0.38), weight (p=0.15), gender (p=0.18) and duration of disease (p=1.0) were considered. Table II shows efficacy and safety outcomes of both groups after 16 weeks follow-up. Although complete remission of acne was observed in 52 patients (94.5%) of group A and all patients of group B (100%), the difference was not statistically significant (p= 0.07). However, significantly fewer mucocutaneous side effects were reported in low dose isotretinoin group (80%) as compared to conventional high dose isotretinoin group (100%) (Table II) (RRR 20%, p 0.0004) (Figure 1).

Table I: Baseline characteristics of patients (n= 110)

Variables	Group A (low dose) (n=55)	Group B (high dose) (n=55)
Age (years); mean + SD	18.2 ± 3.7	17.6 ± 3.2
Male; n (%)	27 (49)	34 (61)
Female; n (%)	28 (51)	21 (39)
Weight (Kg); mean + SD	58.0 ± 10.2	60.7 ± 9.3
Duration of disease (Years); mean + SD	3.0 ± 1.1	3.0 ± 1.0



M.SE: Mucucutaneous side effects

Figure 1: Safety outcome at 16 weeks

This safety profile spectrum was observed across all pre-defined subsets (Table II) i.e. cheilitis (RRR 20%, p 0.001), dry skin (RRR 25%, p 0.002), dry mouth (RRR 34%, p 0.006) and rash (RRR 60%, p 0.02) (Figure 1). An excellent (100%) follow up in both groups was achieved at 16 weeks and no major side effect leading to discontinuation of study drug was reported.

Discussion

Acne vulgaris (AV) is an extremely prevalent skin condition[1,2] affecting majority of teenagers to a certain degree at some point. The onset of AV is usually shortly before or during early adolescence; however, some cases start in latter childhood with the subset of preadolescent acne defined within the ages of 7 and 11 years.[8] The impact on the quality of life of young people is highly significant. It has a greater negative effect on the emotions and social functioning of teenagers than diseases like asthma and epilepsy.[3] It is often associated with anxiety, depression and unemployment[3]. The impact of the condition is often difficult to determine clinically, but

Table II: Efficacy and Safety Outcomes of Isotretinoin at 16 weeks (n=110)

Efficacy outcome	Group A (n=55) n (%)	Group B (n=55) n (%)	Odds ratio (OR)	Relative Risk Reduction (RRR %)	95% Confidence interval (CI)	p value
Complete remission	52 (94.5)	55 (100)	0.48		0.40-0.59	0.07
Safety outcome						
Mucocutaneous side effects	44 (80)	55 (100)	0.44	20	0.35-0.55	<0.001
Cheilitis	43 (78.1)	54 (98.2)	0.06	20	0.008-0.53	0.001
Dry skin	38 (69.1)	51 (92.7)	0.17	25	0.05-0.56	0.002
Dry mouth	26 (47.2)	40 (72.7)	0.33	34	0.15-0.74	0.006
Rash	7 (12.7)	17 (30.9)	0.32	60	0.12-0.86	0.02

one can assume that almost all acne patients will experience this impact to some degree. Medical treatment can make a very big difference, often clearing the condition completely, or bringing about significant improvement in those who do not experience complete clearance. Isotretinoin is regarded as a useful therapeutic advance in the management of acne. It has been recommended for the treatment of severe nodulocystic acne in the doses of 1-2 mg/day.[5,6]

While using this treatment protocol, the incidence of side-effects is quite high and requires regular monitoring including a watch on the serum lipid profile.[9] In this study, we have tested the notion that compared to conventional high dose, lower dose of oral isotretinoin is superior in terms of complete remission as well as carries a much better safety profile in patients of severe AV. Although no statistically significant superiority in efficacy is established in this regard, it cannot be ascertained at present whether lower doses are actually inferior to conventional (high) dosing in terms of complete remission of acne. However, in our study, lower doses have shown significant superiority by limiting mucocutaneous side effects. This superiority is dictated throughout the spectrum of pre-defined side effects i.e. cheilitis, dry skin, dry mouth and rash. Another interesting finding is the possible association of efficacy to the duration of disease.

All three cases of treatment failure had acne for more than four years. However, this study was not designed or powered to assess such parameter. To decrease the incidence of side-effects and to make the therapy protocol simpler, the lower dose regimen has been tried by various authors before.[5,6,10] However, unlike our study, most of these studies targeted mild to moderate acne population. Sardana et al[5] studied lower doses of oral isotretinoin in mild to moderate acne and reported efficacy of up to 90% with statistically significant non-inferiority to conventional high dose regimen. Long-term relapse rate was also same across both groups. Similarly, Agerwal et al [6] reported better efficacy (69% vs 96%) and safety outcomes (89% vs 100%) in favor of lower doses of oral isotretinoin across different stages of acne. Each of these studies had one or more major limitations, including retrospective nature of the data collection, statistically insignificant number of patients and selection of low acne load patients with mild to moderate class. This study may be influenced by several limitations as well. Only patients with severe acne load were addressed. It was left up to the discretion of patients which Isotretinoin preparations to buy from available brands. Furthermore, relevance on patient interview or clinician impression may be insufficient to detect poor adherence to medications. Despite these limitations, this study provides new insights into the possibility of finding a more robust, efficacious, much safer regimen of oral isotretinoin than the one in practice for severe acne vulgaris.

Conclusion

Low dose oral isotretinoin, over a period of 16 weeks, is not superior to conventional high dose regimen in terms of complete remission of severe acne vulgaris. However, it has a statistically significant safety profile accounting for fewer mucocutaneous side effects as compared to latter. Future studies should be designed to prospectively test such unorthodox regimens for the overall cost effectiveness, and to assess for both superiority as well as non-inferiority compared to high dose regimen.

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