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**Original Article**

# Comparison of safety and efficacy of low dose isotretinoin versus the conventional dosing regime in the treatment of acne vulgaris

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## Abstract

***Background*** Isotretinoin is a derivative of retinol used in the treatment of acne vulgaris. Treatment with isotretinoin may cause many adverse effects.

***Objective*** To compare the efficacy and safety of low dose isotretinoin with the conventional dosing regimen in the treatment of acne vulgaris.

***Methods*** This randomized controlled trial study was conducted in the Department of Dermatology Nishtar Hospital Multan form 1st June 2018 to 30th November 2018. A total of 140 patients of both gender with acne vulgaris were included in the study and divided into two groups of 70 sample size by randomization. In group A patients oral isotretinoin 20mg/day and in group B 80mg/day was given for 12 weeks. Final evaluation of efficacy was done after 12 weeks of treatment in both groups. Efficacy and safety was noted.

***Results*** Age range in this study was from 15 to 40 years with mean age of 25.114±4.14 years in Group A while 26.171±3.71 years in Group B. Mean duration of complain was 11.557±4.43 months in Group A and 11.242±4.38 months in Group B. Mean weight was 62.942±6.42 kg in group A and 62.285±6.01 kg in group B. Mean height was 1.584±0.06 meters in group A and 1.588±0.07 meters in group B. Mean BMI was 25.210±3.33 $Kg/m^2$ in Group A and 24.851±3.44 $Kg/m^2$ in Group B and mean baseline GAGS score was 25.914±2.04 in Group A and 26.014±2.88 in Group B. In both groups majority of patients belonged to 15-30 years age group. In both groups majority of patients were female. Efficacy was seen in 50% patients in Group A as compare to 71.4% in Group B (p=0.009). Dry eyes was seen in 31.4% patients in Group A as compare to 42.9% in Group B (p=0.161). Headache was seen in 14.3% patients in Group A as compare to 17.1% in Group B (p=0.642).

***Conclusion*** Conventional dosing regimen has more efficacy but less safety than low dose isotretinoin in the treatment of acne vulgaris.

***Key words***
Acne vulgaris, low dose isotretinoin, efficacy, safety.

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## Introduction

Isotretinoin is a derivative of retinol (vitamin A).[1] Isotretinoin is indicated mainly for keloidal acne, phlegmonous and fulminans acne, as well as for severe papulopustular acne resistant to antibiotics.[2]

The recommended daily dosage ranges from 0.5 to 1 mg/kg/day. The therapy should be continued for many months to reach the cumulative doses in total of 120–150 mg/kg.[2] The effective therapy is associated with subsidence of symptoms, prevention of scar development, strengthening of treatment results and minimizing the risk of recurrence.[3]

Isotretinoin may cause many adverse effects, its teratogenic activity is the most serious.[4] Effective contraception one month before, during and one month after the therapy is indicated. The most common side effects include dry eyes, cheilitis, blepharoconjunctivitis, rhinitis, erythema and dry facial skin, headaches, muscle and joint pains, and biochemical abnormalities such as increase in bilirubin, transaminase, triglycerides, decreased levels of high-density lipoprotein (HDL) and increased low-density lipoprotein (LDL) cholesterol and uric acid.[5]

Low-dose isotretinoin has been used to treat acne in various regimens, like daily dose, intermittent therapy, alternate day therapy or gradually increasing the daily dose.[6] As there is marked heterogeneity in these regimens, a more logical way is to compare them on the basis of dose per day (mg/kg/day), which ranges from 0.14 mg/kg/day to 0.75 mg/kg/day. Except for one study, low-dose isotretinoin was uniformly of a dose less than 0.5 mg/kg/day.[7]

## Material and Methods

This Randomized Controlled Trial was conducted in the Department of Dermatology Nishtar Hospital Multan from 1st June 2018 to 30th November 2018.The patients were selected via Non-Probability Consecutive Sampling. A total of 140 patients were enrolled meeting the inclusion criteria. Patient diagnosed clinically with acne vulgaris between ages 15-40 years of both genders were included in the study. Patients requiring repeated and prolonged courses of systemic antibiotics, drug induced acne, using estrogens/birth control pill, pregnant on laboratory test and patients who lost to follow up were excluded. Total sample size was divided into two groups. 70 sample size for low dose isotretinoin Group or Group A while 70 sample size for conventional dosing regimen group or Group B. In group A patients, oral isotretinoin 20mg/day for 12 weeks was given. In group B patients, oral isotretinoin 80mg/day for 12 weeks was given. No other medication or cosmetics were allowed to use during the study period. All treatments were administered from baseline through 12 weeks. Patients were called for follow up after every 15 days for assessment of safety. Final evaluation of efficacy was done after 12 weeks of treatment in both groups.

## Results

Age range in this study was from 15 to 40 years with mean age of 25.114± 4.14 years in Group A while 26.171±3.71 years in Group B. Mean duration of complain was 11.557±4.43 months in Group A and 11.242±4.38 months in Group B. Mean weight was 62.942±6.42 kg in group A and 62.285±6.01 kg in group B. Mean height was 1.584±0.06 meters in group A and 1.588±0.07 meters in group B. Mean BMI was 25.210±3.33 $Kg/m^2$ in Group A and 24.851±3.44 $Kg/m^2$ in Group B and mean baseline GAGS score was 25.914±2.04 in Group A and 26.014±2.88 in Group B**.**

In both groups majority of patients belonged to 15-30 years age group. In both groups majority of patients belonged to female gender. Efficacy was seen in 50% patients in Group A as compare to 71.4% in Group B (p=0.009)

Dry eyes was seen in 31.4% patients in Group A as compared to 42.9% in Group B (p=0.161).

Headache was observed in 14.3% patients in Group A as compared to 17.1% in Group B (p=0.642) Stratification of Efficacy, dry eyes and headache in both groups with regard to age, gender, duration of complain, GAGS score and BMI are shown in **Tables 1-3** respectively.

**Table 1** Stratification of Efficacy

| | | *Group A* | | *Group B* | | *P* |
|---|---|---|---|---|---|---|
| | | *Yes* | *No* | *Yes* | *No* | *Value* |
| With respect to age | For Age 15-30 years | 32(51.6%) | 30(48.4%) | 44(71%) | 18(29%) | 0.026 |
| | For Age 31-40 years | 3(37.5%) | 5(62.5%) | 6(75%) | 2(25%) | 0.130 |
| With respect to gender | For Male | 12(57.1%) | 9(42.9%) | 12(66.7%) | 6(33.3%) | 0.542 |
| | For Female | 23(46.9%) | 26(53.1%) | 38(73.1%) | 14(26.9%) | 0.007 |
| With respect to duration of complain | For duration ≤ 12 months | 23(57.5%) | 17(42.5%) | 24(64.9%) | 13(35.1%) | 0.507 |
| | For duration > 12 months | 12(40%) | 18(60%) | 26(78.8%) | 7(21.2%) | 0.001 |
| With respect to GAGS score | For GAGS score 19-24 | 15(88.2%) | 2(11.8%) | 12(63.2%) | 7(36.8%) | 0.082 |
| | For GAGS score 25-30 | 20(37.7%) | 33(62.3%) | 38(74.5%) | 13(25.5%) | 0.000 |
| With respect to BMI | For BMI ≤ 25 Kg/m2 | 13(39.4%) | 20(60.6%) | 27(75%) | 9(25%) | 0.002 |
| | For BMI > 25 Kg/m2 | 22(59.5%) | 15(40.5%) | 23(67.6%) | 11(32.4%) | 0.474 |

**Table 2** Stratification of dry eyes

| | | *Group A* | | *Group B* | | *P* |
|---|---|---|---|---|---|---|
| | | *Yes* | *No* | *Yes* | *No* | *Value* |
| With respect to age | For Age 15-30 years | 19(30.6%) | 43(69.4%) | 26(41.9%) | 36(58.1%) | 0.191 |
| | For Age 31-40 years | 3(37.5%) | 5(62.5%) | 4(50%) | 4(50%) | 0.614 |
| With respect to gender | For Male | 7(33.3%) | 14(66.7%) | 5(27.8%) | 13(72.2%) | 0.707 |
| | For Female | 15(30.6%) | 34(69.4%) | 25(48.1%) | 27(51.9%) | 0.672 |
| With respect to duration of complain | For duration ≤ 12 months | 11(27.5%) | 29(72.5%) | 17(45.9%) | 20(54.1%) | 0.092 |
| | For duration > 12 months | 11(36.7%) | 19(63.3%) | 13(39.4%) | 20(60.6%) | 0.823 |
| With respect to GAGS score | For GAGS score 19-24 | 5(29.4%) | 12(70.6%) | 11(57.9%) | 8(42.1%) | 0.086 |
| | For GAGS score 25-30 | 17(32.1%) | 36(67.9%) | 19(37.3%) | 32(62.7%) | 0.578 |
| With respect to BMI | For BMI ≤ 25 Kg/m2 | 10(30.3%) | 23(69.7%) | 15(41.7%) | 21(58.3%) | 0.326 |
| | For BMI > 25 Kg/m2 | 12(32.4%) | 25(67.6%) | 15(44.1%) | 19(55.9%) | 0.311 |

**Table 3** Stratification of Headache

| | | *Group A* | | Group B | | P |
|---|---|---|---|---|---|---|
| | | *Yes* | *No* | *Yes* | *No* | Value |
| With respect to age | For Age 15-30 years | 9(14.5%) | 53(85.5%) | 11(17.7%) | 51(82.3%) | 0.625 |
| | For Age 31-40 years | 1(12.5%) | 7(87.5%) | 1(12.5%) | 7(87.5%) | 1.000 |
| With respect to gender | For Male | 1(4.8%) | 20(95.2%) | 5(27.8%) | 13(72.2%) | 0.047 |
| | For Female | 9(18.4%) | 40(81.6%) | 7(13.5%) | 45(86.5%) | 0.499 |
| With respect to duration of complain | For duration ≤ 12 months | 6(15%) | 34(85%) | 8(21.6%) | 29(78.4%) | 0.451 |
| | For duration > 12 months | 4(13.3%) | 26(86.7%) | 4(12.1%) | 29(87.9%) | 0.885 |
| With respect to GAGS score | For GAGS score 19-24 | 5(29.4%) | 12(70.6%) | 3(15.8%) | 16(84.2%) | 0.326 |
| | For GAGS score 25-30 | 5(9.4%) | 48(90.6%) | 9(17.6%) | 42(82.4%) | 0.219 |
| With respect to BMI | For BMI ≤ 25 Kg/m2 | 7(21.2%) | 26(78.8%) | 6(16.7%) | 30(83.3%) | 0.629 |
| | For BMI > 25 Kg/m2 | 3(8.1%) | 34(91.9%) | 6(17.6%) | 28(82.4%) | 0.227 |

## Discussion

Acne is a chronic inflammatory disease of the pilosebaceous units, characterized by the formation of comedones, erythematous papules and pustules, less frequently by nodules or pseudocysts. In some cases it is accompanied by scarring. Isotretinoin is unique in a way that it influences all the basic pathogenic factors for acne: suppresses sebum production, demonstrates comedolytic activity, has direct and indirect anti-inflammatory activity, despite having no antibacterial properties, significantly reduces *Propionibacterium acnes* population. Isotretinoin effect on metalloproteinases (MMP) and tissue inhibitors of MMP (TIMP) contribute to matrix degradation, preventing scarring.[8]

Treatment with isotretinoin although very effective but it is associated with various adverse effects so the quest to determine a better treatment regime continues.

In our study, Conventional dosing regimen showed more efficacy (71.4%) whereas low dose regime was less efficacious (50%). Low dose therapy was safer with 31.4% patients complaining of dry eyes and 14.3% complained of headaches as compared with 42.9% complaining of dry eyes and 17.1% patient had headache receiving conventional therapy.

Over the last 15 years, apart from papers on intermittent isotretinoin therapy, there have been papers on giving low doses of isotretinoin.

Blasiak RC, *et al.* has shown in a study that efficacy of low dose isotretinoin was 57.7% versus 71.9% with the conventional dosing regimen, while dry eyes was 31.6% versus 43.6% and headache was 13.2% versus 17.9% in the treatment of acne vulgaris.[9]

Dhaked DR, *et al.* has showed in a study that dry eyes was 7.6% and headache was 1.7% with low dose isotretinoin in the treatment of acne vulgaris.[10]

In 2003, Mandekou-Lefaki *et al.*[11] published the results of the study on comparison between the use of conventional therapy and that with low doses in patients with different acne severity. Efficacy of the therapy was 69% in patients receiving low dose isotretinoin(0.15-0.40mg/kg/day) and 91% in conventional dosing group(0.5-1.0mg/kg/day). The authors concluded that the therapy with low doses is effective, causes fewer adverse effects, has a beneficial effect on scars while the conventional therapy is more effective, protects from recurrences and scarring.

In a study by Sardana *et al.*[12] isotretinoin at the dose of 20 mg/day combined with local application of 1% clindamycin gel was administered every second day, for 6 months. This regime was found to be effective in the treatment of moderate acne in adult patients with low incidence of side effects.

In 2011, Lee *et al.*[13] published the results of randomized controlled study aimed at the comparison of conventional therapy with isotretinoin (0.5–0.7 mg/kg/day for 24 weeks), vs. therapy with low doses (0.25–0.4 mg/kg/day also for 24 weeks) vs. intermittent therapy(dosed 0.5–0.7 mg/kg/day for 7 days followed by a 3-week interval, for 6 months). The authors found that when considering tolerability, efficacy and patient satisfaction, low dose treatment was most suitable for patients with moderate acne.

In 2014, Rasi *et al.*[14] treated his patients with isotretinoin dosed 20 mg/day until a cumulative dose of 120 mg/kg was reached. Authors concluded that the low dose isotretinoin was an effective treatment option in patients with moderate to severe acne with low incidence of side-effects.

Kotori[15] treated his patients with 20 mg/kg isotretinoin for 3 months. The author concluded that a 3-month therapy with isotretinoin dosed 20 mg/day in patients with moderate acne is safe, carries a low risk of developing adverse effects, and the cost of the therapy is lower compared to the conventional therapy.

In conclusion, isotretinoin in conventional dosing regime is more effective in the treatment of acne vulgaris as compared with the low dose regime, but in terms of side effects low dose therapy is better.

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