Original Article

Comparing the Efficacy of Low Dose and Conventional Dose of Oral Isotretinoin in Treatment of Moderate and Severe Acne Vulgaris

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ABSTRACT

Objective: This study was conducted to compare the effect of low-dose isotretinoin with its conventional dose in patients with moderate and severe acne. **Methods:** This was a clinical trial conducted on 60 male and female patients with moderate and severe acne vulgaris. The patients were divided into two treatment groups: 0.5 mg/kg/day isotretinoin capsule and low-dose isotretinoin capsule (0.25 mg/kg/day). Patients in both groups received 6-month treatment. At the end of the 6th month and 12th month (6 months after the end of the treatment), they were examined again, and their improvement was determined and compared. **Findings:** The average severity of acne in the two treatment groups did not differ significantly within any of the study periods. The most common side effects were nose dryness in the low-dose group (17%) and hair thinning and loss in the conventional-dose group (33.2%), although all the patients had dry lips. **Conclusion:** According to the same severity of the acne in two groups in different study periods, as well as fewer side effects and more patients' satisfaction, the low-dose isotretinoin can be considered in the treatment of acne.

Keywords: *Acne vulgaris, efficacy, Isotretinoin*

Introduction

Acne vulgaris is a common disease during adolescence. It is the most common inflammatory diseases of the sebaceous unit and a chronic inflammatory disease of the sebaceous glands.[1]

There are different common treatments for acne vulgaris based on the severity of lesions.[2] In that, topical solutions (e.g., clindamycin or erythromycin), topical ointment (e.g., tretinoin, benzoyl peroxide, and adapalene), and other keratolytic drugs (e.g., alpha-hydroxy acid), salicylic acid-containing medicine, and/or sulfur or azelaic acid-containing drugs are used to treat mild cases. In more severe cases, systemic treatments, such as tetracycline, doxycycline, azithromycin, minocycline, azithromycin, and cotrimoxazole are used. In cases with the risk of scar, oral isotretinoin is administered. In cases with associated hormonal abnormalities, androgen, estrogen, spironolactone, and dexamethasone are used.[3,4]

Despite all traditional and modern treatments, retinoid compounds are key components in the treatment of acne.[5] In early 1980, the administration of oral isotretinoin was limited in patients with nodulocystic acne. Nevertheless, the use of oral isotretinoin was made wider with broadening relevant experience. It was also prescribed for patients with milder acne, who did not respond satisfactorily to common treatments, such as topical retinoids plus oral antibiotics. Patients with moderate acne, who exhibit the scar symptoms, are also a candidate for treatment with oral isotretinoin. Acne is mainly associated with physical and cosmetic morbidity. The psychological consequences of acne vary from depression and anxiety to work and interpersonal relationship disorders. Studies, used quality of life instruments, have shown that the treatment with isotretinoin results in a significant improvement of socialization and self-confidence.[6] There may be a delay of 1–3 months before the initiation of treatment

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effects. In many cases, improvement continues even after discontinuation of the treatment. Therefore, the continuation of the treatment until the complete healing of lesions is not necessary.[7]

Although isotretinoin is a very effective medication for the treatment of acne, its association with several complications necessitates the precise selection of patients.[6] The recommended dose is 0.5–1 mg/kg/day for 4–6 months.[8] A study conducted in India (2014) on 50 patients with moderate to severe acne showed the effectiveness of low-dose isotretinoin with lesser complications and greater cost-effectiveness. In this study, patients received 0.3–0.4 mg/kg/day isotretinoin.[9] In addition, a study (2012) showed the effective treatment of severe acne with low-dose isotretinoin (0.1–0.3 mg/kg/day).[8] Since, side effects of this medication are dose-dependent, the administration of low-dose isotretinoin (0.25 mg/kg/day) for 6 months seems logical; however, there is no relevant, comprehensive study with follow-up period in Iran, and although the patient's compliance is dependent on side effect and cost of drug and its cost and economic status of patients has turned it into a significant problem.[10] Thus, the present study has been conducted to compare the low- and common-dose oral isotretinoin in patients with moderate and severe acne vulgaris.

Methods

This study was a prospective randomized clinical trial conducted during 2014–2015. The population comprised patients (both male and female) with moderate to severe acne vulgaris referred for treatment to Alzahra Medical and Training Center, several clinics affiliated to Isfahan University of Medical Sciences and a privately-owned doctor's office. The inclusion criteria are as following: patient consent to participate in the study, no sensitivity to retinoids, no pregnancy, not willing to become pregnant, and absence of hormonal disorders in patients. Patients with the following criteria excluded from the study: Failure of the patient to attend follow-up sessions for any reason, and adoption of other supplementary therapies during the study.

The required sample size was estimated to be 30 patients using the sample size formula, serving to compare the ratios given the confidence level of 95% ($Z1-\alpha/2 = 1.96$) and test power of 80% ($Z1-\beta = 0.84$). The minimum significant difference between the two groups was considered to be 0.25.

After obtaining a permit from the Ethics Committee of Isfahan University of Medical Sciences that Ethical code is 393894 and IRCT code is 2015061722780N1, the simple sampling was applied to patients (male and female) with moderate acne vulgaris and referred for treatment to one of the largest referral centers in isfahan (Iran`s third largest city, located in the center of Iran). The patients were randomly treated by 0.5 and 0.25 mg/kg/day of oral isotretinoin (Roaccutane, F. HOFFMAN-LA ROCHE Switzerland) for 6 months. The effort was made every day to arrange equal numbers of patients in Groups 1 and 2 so as to fulfill the random sampling. The patients were advised to take the medication with meals, avoid fat-free diet, and yet refrain from the excessive fat intake. This process continued until the number of patients per group amounted to 30. The method of follow-up in two groups was an intention to treat.

At the baseline and 6 months later, the patients were examined for the severity of acne by a dermatologist that was blinded to intervention group. The severity of acne was determined through the Global Acne Grading System.[11] This system was used in studies conducted by the British Association of Dermatologists and the American Society for Dermatologic Surgery (2013 and 2014).[12] In this system, the numbers of lesions including comedones, papules, pustules, and nodules were counted on the forehead, right cheek, left cheek, nose, chin, chest, and upper back torso. Each type of lesion is given a grade based on its severity as follows: 1 - comedones; 2 - papules; 3 - pustules; and 4 - nodules. Moreover, each zone is given a factor as follows: 1 - nose, chin; 2 - forehead, right cheek, left cheek; and 3 - chest, back and upper back torso. The severity of lesion for each zone (local score) is calculated as follows: local score = Factor × grade (0–4). Global score is obtained from the sum of local scores in different zones. The severity of acne is considered based on the global score as follows: mild: 1–18; moderate: 19–30; severe: 31–38; and very severe: Over 38.

To prevent the complications of treatment, the female subjects in reproductive age were initially tested for pregnancy. They were included in the study if the results were negative. Then, the test was repeated every month. At baseline and at the end of 1st, 2nd, 4th, and 6th months, the levels of liver enzymes, blood cholesterol, and triglyceride were checked in all patients. The treatment discontinued in case the triglyceride level elevated over 400 mg/dl, cholesterol over 300 mg/dl, alkaline phosphatase over 246, alanine aminotransferase over 62, and aspartate aminotransferase over 80.[13]

All patients were simultaneously treated with daily 250 mg of oral azithromycin in the first 2 weeks.[13] Moreover, 0.25 mg of prednisolone was prescribed to treat patients with isotretinoin over the first week. To prevent complications such as dry lips and skin, identical topical emollient was administered on all patients.

Furthermore, they were advised to apply sunscreen regularly and avoid sunlight as much as possible. After the end of treatment with isotretinoin, the patients went through local treatment with 2% clindamycin during the follow-up phase.

The patients were visited on a monthly basis. The cases with no new lesions were recorded in a data collection form. At the end, it was found out which group recovered from the lesions sooner than the other. The side effects of isotretinoin were examined and recorded at each visit by a dermatologist that was blinded to intervention group. The patient satisfaction level was assessed and recorded at the end of treatment by visual analogue scale (VAS) for satisfaction.[14] VAS was a horizontal line. The patient rated his satisfaction by making a vertical mark on the line. There were two descriptors representing extremes of satisfaction (i.e., no satisfaction [0 point] and extreme satisfaction [5 points]). We analyzed complications by the questionnaire, physical examination, and laboratory tests that were conducted by a dermatologist that was blinded to intervention group.

The collected data were described through several tables, graphs and measures of central tendency and dispersion. Then, they were analyzed by Chi-square test, independent *t*-test, and we used two-way repeated measure ANCOVA to determine the significance difference between these two sets of observations within the same group and then to compare the significant difference between the low dose versus high-dose therapy. The SPSS 22 (released 2013, SPSS Inc, Chicago, IL) was also used as statistical software.

Results

Results of the frequency distribution of demographic variables (qualitative and quantitative) in each treatment group indicated that the average age of participants in the first treatment group (low dose) and second group (conventional dose) was 22.94 ± 6.25 and 23.1 ± 4.66 years, respectively. Therefore, there was no statistically significant difference between age results ($P = 0.911$). Similarly, the average age and duration of acne did not differ significantly in the two groups ($P > 0.05$). Frequency distributions of qualitative research variables including gender differed significantly in the two groups, because 5 participants in the first group (13.9%) and 8 participants in the second group (26.7%), which added up to 13 (19.7%), were male, whereas 31 participants in the first group (86.1%) and 22 (73.3%) in the second group (which added up to 53 or 80.3%) were female ($P = 0.011$). However, there was no significant difference between the two groups in terms of family history of acne and frequency of previous acne treatments ($P > 0.05$).

Results of determining and comparing the average severity of acne vulgaris in the first group prior to treatment (mean = 54.6, standard deviation [SD] = 2.9), 6 months into treatment (mean = 2.5, SD = 0.8), and 6 months following the treatment (mean = 8.7, SD = 0.8), showed that there was a significant difference in the average severity of acne in the first group before treatment and 6 months into the treatment as well as before treatment and 6 months following the treatment in the 12th month ($P < 0.001$). According to the classification of severity of acne based on the global score, it was found that average severity of acne was extremely high in the first group before treatment (with average acne severity of 58.6), while 6 months into treatment and 6 months following the treatment severity of acne was mild (with respective average acne severity of 2.5 and 8.7). Figure 1 depicts the linear diagram of changes of average acne severity over the three periods under study. Frequency distributions of acne severity in the first and second groups before treatment, 6 months into treatment, and 6 months after treatment based on the gender and age variables revealed that there was no significant difference between the two groups in terms of severity of acne based on gender and age ($P > 0.05$).

Results of determining and comparing the average severity of acne vulgaris in the second group (which received 0.5 mg isotretinoin capsules) before treatment (mean = 58.8, SD = 3.1), 6 months into treatment (mean = 1.8, SD = 0.7), and 6 months following the treatment (mean = 9.7, SD = 1.1) showed there was a significant difference in the average severity of acne in the second group before treatment and 6 months into the treatment as well as before the treatment and 6 months following the treatment in the 12th month ($P < 0.001$). According to the classification of severity of acne based on the global score, it was found that average severity of acne was extremely high in the second group before treatment (with average acne severity of 58.87), while

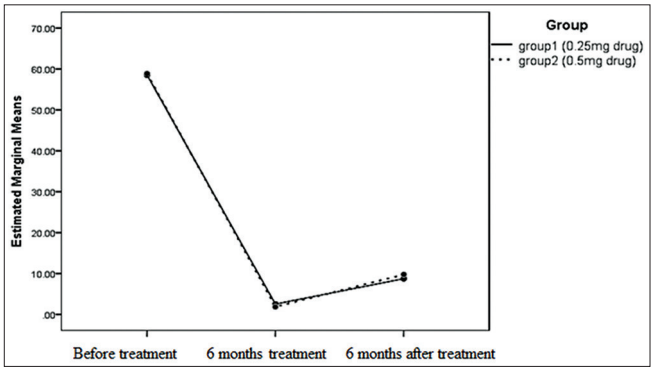

Figure 1: Diagram of changes of acne average severity in the two treatment groups over three study periods

6 months into treatment and 6 months following the treatment severity of acne was mild (with respective average acne severity of 1.87 and 9.73).

Results of comparing the average severity of acne in the two study groups showed that the average severity of acne in the two treatment groups did not differ significantly within any of the study periods ($P > 0.05$). Figure 1 shows the linear diagram of changes of average acne severity in the two groups over different periods.

Results of comparing the average severity of acne in the two treatment groups before treatment, 6 months into treatment, and 6 months after treatment based on the gender and age variables showed that there was no significance difference between the severity of acne in the two groups based on gender and age ($P > 0.05$).

The frequency distribution of the severity of acne in the first and the second groups before treatment, 6 months after treatment, and finally 6 months after completion of treatment in terms of duration of acne showed that no significant difference existed between the severity and duration of acne vulgaris in the first and second groups separately in any of the studied times ($P > 0.05$). In addition, comparison of the mean severity of acne in both treatment groups before treatment, 6 months after treatment, and 6 months after completion of treatment in terms of duration of acne showed no significant difference between the mean severities of acne in terms of the duration of acne in both groups ($P > 0.05$).

The frequency distribution of the severity of acne in the first and second groups separately, before treatment, 6 months after treatment, and finally 6 months after completion of treatment in terms of family history of acne showed that no significant difference existed between the severity of acne and family history of acne in none of the groups in any of the studied times ($P > 0.05$). In addition, comparison of the mean severity of acne in both treatment groups at different times in terms of family history of acne showed no significant difference between the mean severities of acne in terms of family history of acne ($P > 0.05$).

Considering the significance level of 5%, a significant difference can be observed between patients' satisfaction in the two treatment groups ($P < 0.05$), so the average of patients' satisfaction score in the first group (mean = 4.78, SD = 0.4) was significantly higher than the second group (mean = 4.43, SD = 0.6) ($P = 0.02$), which shows that the satisfaction of patients treated with lower doses of medication (Group I) was higher than patients treated with higher doses of the drug (Group II).

Table 1: The frequency of adverse reactions in patients with acne in the study groups

Adverse reactions	Groups		*P**
	Low-dose group	Conventional group	
Itching	4 (40)	6 (60)	0.316
Dry mouth	1 (34)	6 (56)	0.240
Dry nose	6 (33)	12 (67)	0.340
Repeated rhinorrhea	0	6 (100)	0.005
Dry eyes	4 (33)	6 (67)	0.103
Spontaneous skin damage	1 (100)	0	0.358
Skin redness	1 (20)	4 (80)	0.107
Palm and sole skin scaling	1 (50)	1 (50)	0.896
Skin photosensitivity	2 (25)	6 (75)	0.073
Palm and sole burning	0	1 (100)	0.270
Nail damage	2 (50)	2 (50)	0.851
Hair thinning and loss	2 (22)	7 (78)	0.036
Poor night vision	0	3 (100)	0.052
Eye photosensitivity	1 (33)	2 (67)	0.450
Muscular pain	0	1 (100)	0.270
Joint pain	2 (67)	1 (33)	0.666
Gastrointestinal effects	4 (44)	5 (56)	0.513
Headache	1 (33)	2 (67)	0.450
Fatigue	0	2 (100)	0.116
Depression	2 (50)	2 (50)	0.896

Data are presented as *n* (%). *Fisher's exact test

As shown in Table 1, considering the significance level of 5%, a significant difference can be seen in the frequency of side effects dry mouth, dry nose, repeated rhinorrhea, and hair thinning and loss in both groups ($P < 0.05$), so that the frequency of side effects in the group receiving a higher dose of the drug (the second group) was more than the group receiving the low dose of the drug (the first group). Table 1 shows the most common side effects were nose dryness in the first group (17%) and hair thinning and loss in the second group (33.2%) also all the patients had dry lips.

Discussion

There are different studies about this study that we mentioned some of them here. Amichai *et al*. and Lee *et al*. believed that doses of isotretinoin lower than 0.5 mg/kg/day may be effective for the treatment of some patients with acne.[15,16] In another study, Rasi *et al*. investigated the efficacy of low daily dose isotretinoin in moderate to severe acne patients. They found that low-dose isotretinoin was found to be a safe and effective choice for patients with moderate to severe scar prone acne vulgaris[17] so their results are consistent with our results.

Ghalamkarpour and Nasiri studied about isotretinoin in the treatment of acne and this study was performed on patients with acne to examine the therapeutic effects,

recurrence rate, and adverse effects of this drug. They concluded that oral isotretinoin appears to have favorable results and the least adverse effects in the treatment of carefully-selected patients with acne.[18]

In addition, no significant difference was observed between the severity of acne and patients' sex and age at any time point in our results.

Furthermore, in the study of Duman *et al*. there were no statistically significant differences between control and acne groups with respect to age, sex, and Hospital Anxiety and Depression Scale (HAD) score.[19]

A significant difference was observed between the two groups in terms of the frequency of the side effects such as dry mouth, nasal dryness, frequent nosebleeds, thinning hair, and hair loss. The above-mentioned side effects were more frequent in the high-dose group (second group) than in the low-dose group (first group). Therefore, prescribing lower doses of this drug is more appropriate and effective in such patients.

Our results are supported by the findings of a study from India, a low-dose isotretinoin treatment (0.15–0.28 mg/kg/day) lead to clinically significant results in 87.54% of the participants, including 68.20% very good and 19.34% of good results.[20]

Another study that is about safety and efficacy of low-dose isotretinoin in the treatment of moderate to severe acne vulgaris and conducted by Rao *et al*. In this study, they evaluated 50 participants diagnosed as having moderate to severe acne vulgaris and the participants were recruited over a period of 2 years and were followed up for 3 months to know the safety and efficacy of low-dose isotretinoin in the treatment of moderate to severe acne vulgaris. Hence, they recommended that judicious use of low-dose isotretinoin in patients with moderate to severe acne because acne not only scars the face, but also the mind and the heart.[9]

Lee *et al*. evaluated the clinical efficacy and tolerability of low-dose and intermittent isotretinoin regimens and to compare them directly with conventional isotretinoin treatment. They suggested that when considering tolerability, efficacy and patient satisfaction, low-dose treatment is most suitable for patients with moderate acne[15] which is consistent with this study results. The results of this study are consistent with the results of the previous study. This study shows the results of determining and comparing the average severity of acne vulgaris in the group receiving isotretinoin (0.5 mg capsules). The results show that in this group, there was a significant difference between the average acne intensity before and 6 months after treatment. Moreover, there was a significant difference between the average severity of disease before and 6 months after treatment.

The satisfaction level of the low-dose patients was higher than the high-dose patients. In addition, the frequency of complications was greater in the high-dose patients (the second group) than in the low-dose patients (the first group). On average, there was no significant between-groups different in terms of the severity of the acne in the aforementioned times. According to the same recurrence of patients with acne after follow-up at 6 months, more satisfied patients and fewer side effects can be considered low-dose isotretinoin in the treatment of acne.

Authors' Contribution

Gita Faghihi and Fatemeh Mokhtari contribute to Concept and design of study. Nasrin Motamedi Fard contribute to intervention and data gathering. Narges Motamedi contribute to Drafting the article and revising it. Sayed Mohsen Hosseini contribute to analysis and interpretation of data.

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Conflicts of interest

There are no conflicts of interest.

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