COMPARISON OF THE INTERMITTENT AND STANDARD ISOTRETINOIN TREATMENT IN MODERATE AND SEVERE ACNE VULGARIS CASES

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Abstract

Background: Isotretinoin is the most effective drug in severe acne vulgaris. Recently, its use has been extended for the treatment of chronic mild or moderate acne unresponsive to conventional antibiotic therapy. It has been reported that isotretionin treatment may lead to social phobia, depression, anxiety, tendency to suicide. In some patients, isotretinoin is not well tolerated due to its side effects. The objective of our trial was to asses the efficacy and safety of intermittent isotretinoin treatment and compare them with standart isotretinoin therapy in moderate and severe acne cases.
Methods: In our trial, 84 patients with moderate to severe acne were randomized to receive isotretinoin 0.75 mg/kg/day for six months (group 1, 45 patients) or 0.75 mg/kg, in the first 10 days of each month, for six months (group 2, 39 patients), according to the acne grades and number of inflammatory lesions. Patients were examined for clinical improvement, acne grades and side-effects at baseline, six months treatment period and during the monthly and yearly follow-up period in a three-month interval.
Results: All cases completed the six-month therapy. Acne severity scores were significantly decreased in both groups at the end of the treatment and follow-up period ($p<0.001$). Side effects were mild and discontinuation of the treatment was not necessary. There were no statistically significant differences between the two groups regarding treatment efficacy ($p=0.524$). The frequency and severity of isotretinoin related adverse effects were higher in group 1 compared to group 2.
Discussion: Intermittent isotretinoin treatment might be an alternative choice for moderate and severe acne vulgaris cases due to its low incidence and severity of adverse effects. It could be indicated in patients who cannot tolerate conventional treatment.

Keywords:

acne vulgaris,
isotretinoin,
intermittent treatment

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Introduction

Acne vulgaris is a chronic inflammatory disorders of pilosebaceous unit, common in adolescents, characterized by comedones, papules, pustules, cysts, nodules and scars (1). Acne occurs in both sexes and in all age groups. Its pathogenesis is multifactorial and polymorphic. The four main factors involved in the pathogenesis of acne are follicular hyperkeratinization, sebaceous hypersecretion due to androgen stimulation, follicular colonization of *Propionibacteriun acnes*, immune and inflammatory response (1). Many different theraphies exist for acne vulgaris. These include topical treatments such as antibiotics, azelaic acid, salicylic acid, benzoyl peroxide, retinoic acids and their combinations. Systemic treatments include antibiotics, hormonal agents and retinoids (2). Systemic isotretinoin treatment is the most effective intervention in severe acne vulgaris (2-4). Isotretinoin counteracts the etiopathogenic mechanisms of acne vulgaris (3-5). Although combined treatment modalities are found to be effective in acne vulgaris, as indicated in clinical trials, scar formation is observed in patients unresponsive to conventional antibiotic and combined treatments (6). It has been reported that isotretinoin treatment may lead to social phobia, depression, anxiety, tendency to suicide (7, 8).

Isotretinoin is administered at a dose of 0.5-1 mg/kg/day in moderate and severe acne vulgaris cases (9). In some patients, isotretinoin is not well tolerated due to its side effects.

This study aims to compare the intermittent and standart treatment modalities in terms of efficacy and adverse effects.

Materials and methods

A total of 84 patients unresponsive to conventional treatments such as topical antibiotics, azelaic acid, salicylic acid, benzoyl peroxide, retinoic acids, systemic antibiotics and their combinations or patients who exhibited a rebound phenomenon after these treatments were included in this study. The age, weight, duration of treatment, previous treatments and acne severity scores were recorded prior to treatment. Leeds adjusted acne rating scale was used for acne severity score determination (10). The grading of acne lesions on the face, the chest and the back of the patients was rated *via* inspection and palpation by the investigator, based on reference clinical photos within the range of 0–10 (none very severe). The range of 0-2 is further subdivided (0.25, 0.5, 0.75, 1.0, 1.25, 1.5 and 1.75); the range of 0.25–1.0 indicates minor acne, while that of 1.5–10 indicates major acne. The number of inflammatory lesions on the face, chest and back were recorded. The acne severity score of patients participating to the study was above 1.5.

The patients in the first group received isotretinoin 0.75 mg/kg/day for six months. The patients in the second group received isotretinoin 0.75 mg/kg in the first 10 days of each month for six months. Patients were examined for clinical improvement, acne grades and side effects during the six-month treatment period and during the monthly and yearly follow-up period at three-month interval. Total follow-up period was 12 months.

Liver function tests (ALT, AST, GGT, ALP) and lipid profile (total cholesterol and triglyceride) were realized prior to treatment and at monthly follow-ups. Pregnancy test was taken by female patients and patiens were advised to use birth control methods during therapy and for three months after therapy. We obtained informed consent from the patients. This study was approved by the institutional ethics committee.

Mann Whitney U test was used to compare the differences between study groups. Ki-square and Fisher's exact ki-square tests were used to compare the treatment responses.

Results

Forty five patients (27 females, 18 males; mean age 21.31±1.96 years) in the first group and 39 patients (24 females, 15 males; mean age 19.59±7.47 years) in the second group completed the study. Clinical findings are showed in Table 1. In our trial, we reported that there was no statistically significant difference between the two groups in terms of age (p 0.46) and sex (p 0.52).

There was a significant decrease in acne scores before and after treatment in both groups ($p<0.001$). Acne severity score was also found to be significantly decreased in both groups at the end of the 12-month follow-up period compared to the pre-treatment period ($p<0.001$). In our study, there was no statistically significant difference between the two groups (p 0.524).

Severe acne was detected in 24 patients out of 45 in the first group and in 21 out of 39 in the

Table 1. Clinical data

	Group 1	Group 2
Age	15-39	13-33
Number of patients	45	39
Female/male ratio	1.5	1.6
Mean age	21.31±1.96	19.59±7.47
Mean weight (kg)	55.7	54.5
Mean cumulative dose (mg/kg)	122.4	42.6

second group, while moderate acne was present in 21 and 18 patients, respectively. There was no statistically significant difference in terms of efficacy between moderate and severe acne cases in both groups (p 0.553).

While there were no recurrences in the first group, six patients (15.38%) receiving the intermittent therapy in the second group exhibited recurrence.

Side effects detected in both groups are showed in Table 2. Cheilitis and dry skin were the most common side effects. Nose bleeding, myalgia, headache were only seen in patients from the first group. Cheilitis and dry skin appeared in the first month of treatment, while other side effects were observable by the second month in both groups. Also one patient in the first group exhibited an increase in blood GGT level (63, ranged from 10-45 mg/dL) by the fourth month of treatment, while an increase in blood triglyceride level (361, ranged from 0-150 mg/dL) was detected in one patient by the third month of the treatment. The patient with high level of triglyceride was advised to assume a poor-lipid diet and triglyceride level decreased in the follow-up period. Treatment was continued in the patient with a high level of GGT since serum transaminase level was normal; the patient was advised not to consume alcohol and drugs with a liver toxic effect. During the follow-up period, the GGT level of this patient did not increase to cause the isotretinoin treatment discontinuation.

Table 2. Type and frequency of side effects observed in both groups

Side effects	Group 1	Group 2
Cheilitis	45 (100%)	32 (82%)
Dry skin	35 (77.8%)	25 (64.1%)
Nose bleeding	6 (13.3%)	-
Myalgia	3 (6.7%)	-
Headache	2 (4.4%)	-
Increase in liver function tests	1 (2.2%)	-
Increase in triglyceride level	1 (2.2%)	-

The frequency and severity of adverse effects were higher in the standard treatment group compared to the intermittent treatment group. Cheilitis was seen more often at a statistically significant level in the first group compared to the second group (p 0.034). Dry skin was significantly higher in the first group compared to the second group (p 0.001).

Discussion

In our study, we observed that the intermittent isotretinoin treatment was as effective as the standard treatment modality and the frequency of side effects was lower and milder in the moderate and severe acne vulgaris cases. Acne severity scores significantly decreased in both groups after treatment compared to pre-treatment level. Post-treatment acne grades were not statistically different between groups. There was no recurrence in the standart treatment group after the 12-month follow-up period, but recurrence was detected in six patients (15.38%) in the group receiving intermittent treatment.

The intermittent isotretinoin therapy was indicated in mild and moderate acne vulgaris cases. Goulden *et al.* administered intermittent isotretinoin, 0.5 mg/kg/day, in 80 patients with moderate acne vulgaris unresponsive to conventional treatments for one week every four weeks over a six-month period (11). They reported that total acne score and the number of lesion were significantly decreased, the treatment was well tolerated and no side effect besides mild cheilitis were observed in 68 patients (88%) out of 75, who completed the treatment and they detected recurrence in 26 patients (39%) (11). In our study, recurrence was observed in six patients (15.38%) in the intermittent treatment group during the 12-month follow-up period. The recurrence rate in our study was lower compared to that of Goulden *et al.*'s study. We suggest that the lower rate of reccurence in our study was due to the higher cumulative dose of isotretinoin in our application.

Kaymak and Ilter administered intermittent isotretinoin, 0.5-0.75 mg/kg/day, for one week every four weeks over a six-month duration and reported that complete remission was attained in 34 patients (82.9) out of 41, who completed the treatment and that no adverse effects leading to treatment discontinuation occurred (12).

In a multicenter, controlled trial conducted by Akman *et al.*, intermittent and standard isotretinoin treatments were compared in terms of efficacy and side effects in moderate and severe acne vulgaris cases and it was reported that the intermittent isotretinoin treatment caused less side effects and it was as effective as the standard treatment (13).

In our study, it was shown that the intermittent treatment modality was as effective as the standard treatment and less and milder side effects were observed. The intermittent treatment could be used in patients who cannot tolerate the standard treatment.

In conclusion, standard and intermittent isotretinoin are very effective medications in the treat-

ment af acne. Intermittent treatment can be used in patients who cannot tolerate standard therapy.

Conflicts of interest: none declared.
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