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ARTICLE

Efficacy of Daily Low Dose versus Intermittent Isotretinoin Regimens in Patients with Moderate Acne Vulgaris: A Randomized-Controlled Trial

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Abstract

Background: Oral isotretinoin, a vitamin A acid derivative, is the most effective treatment of severe acne. As its use is associated with many side effects, low-dose and intermittent application protocols for patients with mild or moderate acne have been reported. ***Aim:*** Our purpose was to compare the outcome of two different regimens of low dose isotretinoin; daily versus monthly doses in patients with moderate acne vulgaris. ***Patients and methods:*** A randomized controlled trial was conducted on 75 patients with moderate acne vulgaris attending outpatient clinic in the dermatology department at El-Jumhuriya hospital in Benghazi city during the period of June 2009 to June 2011. The patients were randomly assigned to two groups. Group 1 consisted of 45 patients, treated with a daily fixed dose of 20 mg of isotretinoin and group 2 consisted of 30 patients, treated with 20 mg of isotretinoin twice daily for seven days every month. Both groups were treated for a total period of four months. No topical treatments were permitted for both groups. Clinical assessment was done at 0, 4, 8, 12, and 16 weeks, which included acne lesion counts, total acne load, the assessment of severity score of acne and the side effects of the treatment. Patients were followed for six months after stopping treatment. ***Results:*** Fifty five patients with moderate acne vulgaris completed the study. Group 1 consisted of 32 patients with equal proportion of females and males; their mean age and standard deviation (SD) was 20.2±4.1 years. Group 2 consisted of 23 patients; 52.2% were females and 47.8% were males, their mean age and SD was 20±3.4 years. No statistically significant difference was observed according to the age and gender among both groups. Acne scores in each group were significantly lower at the end of treatment period. The mean decrease in the inflammatory and non-inflammatory lesion counts was more and earlier in group 1 compared to group 2, this difference was statistically insignificant. Both treatment regimens were well tolerated; cheilitis was the most frequent side-effect seen in 81.3% and 69.6% of patients

in group 1 and group 2 respectively. However, there was no statistically significant differences among both groups regarding the frequency and severity of the side effects. The total cumulative dose was significantly higher in group 1 as compared to group 2 (P=0.000). During the follow-up period there was no statistically significant difference between both groups in relapse rate which has been seen in 7 (21.9%) patients in group1 and 9 (39.1%) patients in group 2. ***Conclusion:*** Both isotretinoin regimens were safe and effective treatment for moderate acne vulgaris, however, intermittent sotretinoin regimen may be a cost-effective alternative.

Key words: Acne vulgaris, Isotretinoin, Intermittent, Low dose.

Introduction

Acne vulgaris is a common dermatological disorder of the pilosebaceous unit presenting usually at puberty (1). It is characterized by the formation of open and closed comedones (non-inflammatory lesions), papules, pustules, and nodules (inflammatory lesions) generally affecting the face, arms, and back (2). The pathogenesis of acne is complex and multifactorial, which includes abnormal sebum production, follicular hyperkeratinization, bacterial proliferation and inflammation (3). Many treatment modalities for acne vulgaris have been used including topical comedolytics, antibiotics and retinoids, and systemic antibiotics, retinoids and hormones (3). Isotretinoin is a synthetic oral retinoid that has great efficacy against severe, recalcitrant acne vulgaris and acne conglobate (4). Isotretinoin is the only currently available drug that affects all four pathogenic factors of acne. It reduces sebum production and has keratolytic and anti-inflammatory actions (5). With increasing clinical experience, the use of isotretinoin has been expanded to include patients with mild and moderate acne unresponsive to antibiotic therapy, and those with a tendency to scarring (6-9). Moreover, isotretinoin has been used with different low doses and regimens in an attempt to reduce the side effects reported with its uses in standard regimen (10-12). These basic facts prompted us to perform a randomized controlled study to compare the outcome of two different regimens of low dose isotretinoin; daily versus monthly doses in patients with moderate acne vulgaris.

Patients and Methods

A randomized controlled trial was conducted on 75 patients with moderate acne vulgaris attending the outpatient clinic in the dermatology department at El-Jumhuriya hospital in Benghazi city during the period extended from June 2009 to June 2011. Patients were excluded if they had a history of hyperlipidemia or diabetes and those having drug-induced acne. Married females or those who were to be married within a few months were also excluded. Detailed demographic data were recorded and the patients' skin were examined and the grading of acne was defined according to the Global Acne Grading System (GAGS) score (13). Only facial lesions were studied. The patients were randomly assigned to two groups. Group 1 consisted of 45 patients treated with a daily single dose of 20 mg of isotretinoin, and group 2 consisted of 30 patients treated with 20 mg of isotretinoin twice daily for seven days every month. Both groups were treated for a total period of four months. No topical treatment was permitted for both groups. Clinical assessment was done at baseline, 4, 8, 12, and 16 weeks and included inflammatory and non-inflammatory lesions counts, total acne count (TAC), and the acne severity index (ASI). The acne severity index (ASI) was calculated as described by Michaelsson et al (14). Any side effects due to drug administration were recorded. A complete blood picture, liver function tests, total serum cholesterol, and serum triglyceride were evaluated for all patients before treatment initiation and at monthly follow up. Data were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows version 11.5 (Manufacturer, City). Data are presented as mean ± standard deviation (SD). For comparing the efficacy of those treatment regimens, statistical t-test and χ^2 tests were used and a P value of <0.05 was considered to be statistically significant.

Results

Patients' characteristics

Seventy five patients with moderate acne vulgaris were enrolled in the study. The patients were randomly assigned to two groups. Twenty patients (13 from group1 and 7 from group2) were withdrawn from the study either due to poor compliance or lost to follow up and were not included in further analyses. Fifty-five patients completed the study. Table 1 shows the demographic data of the patients under study, no statistically significant difference was observed regarding the age, gender and disease characteristics among both groups.

Evaluation of Efficacy

Both treatment regimens resulted in a reduction in the number of both non- inflammatory, and inflammatory lesions, although the mean decrease in both lesion counts was more and sooner in group 1 as compare to group 2, this

Table 1. The demographic data of the patients' groups

Patients Number (T)	Group 1 (32)	Group 2 (23)	P value
Age mean±SD (years)	21.1±4.5	20±3.4	0.940
Gender	F (16) M(16)	F (12) M (11)	0.734
Disease duration (years ±SD)	3.5±2	2.9±1.5	0.227
GAGS	22.6±3.2	21.3±2.3	0.480

GAGS: Global Acne Grading System

Table 2. Total acne count of both groups.

	Group 1	Group 2	P value
TAC (at baseline)	60±22	59±21.9	0.653
TAC (at 16 weeks)	4±3.6	6±7.7	0.068
P value	0.000	0.000	

TAC: Total acne count

difference not being statistically significant. Within group analysis of both treatment regimens, a progressive decline in the total acne count and ASI were observed from the baseline and at 16 weeks and showed a highly significant difference in both groups (P=0.000) (Table 2). Between group analysis of TAC and ASI at the baseline the end of study (16 week) did not show any statistically significant difference (Figure 1). Both regimens yielded therapeutically desirable results with a reduction of more than 50% in the number of their acne lesions from baseline in 27 (84.4%) patients and 18 (78.3%) patients in group 1 and group 2 respectively (Figures 2-4). There was no statistically significant difference between patient's age, gender or acne duration and the clinical response to treatment in either group.

Tolerability

Both treatment regimens were generally well tolerated; mucocutaneous side effects were the most common seen in both groups; cheilitis was the most frequent side effect seen in 81.3% and 69.6% of patients in group1 and group 2 respectively (Figure .5). Although, there were no statistically significant differences among both groups regarding the frequency and severity of the side effects, they appeared earlier in group1 at four weeks of treatment, while they appeared at the eighth week in group 2. Both treatment regimens were continued for 16 weeks. There was a statistically significant difference regarding the daily and the total cumulative doses of isotretinoin among both groups (Table 3). During the follow-up period there was no statistically significant differences between both groups in relapse rates which had been seen in 7 (21.9%) patients in group1 and 9 (39.1%) patients in group 2. Moreover, female predominate in relapse rates in both groups showed no statistically significant differences (Figure 6).

Discussion

In the present comparative study, the results of the four months of treatment with isotretinoin showed that both regimens of isotretinoin were effective in moderate acne,

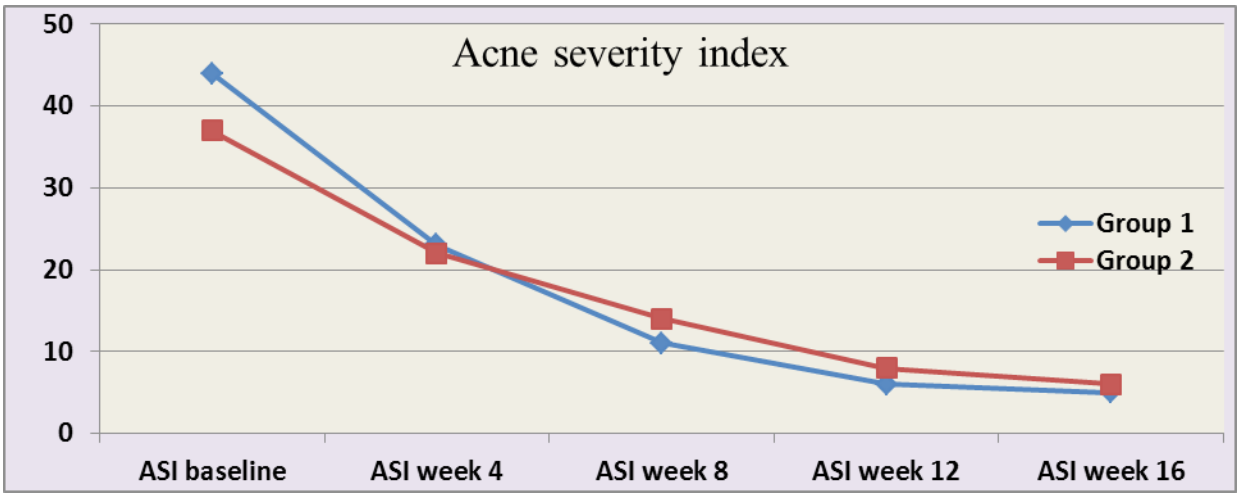

Figure 1. Reduction of the acne severity index in both groups

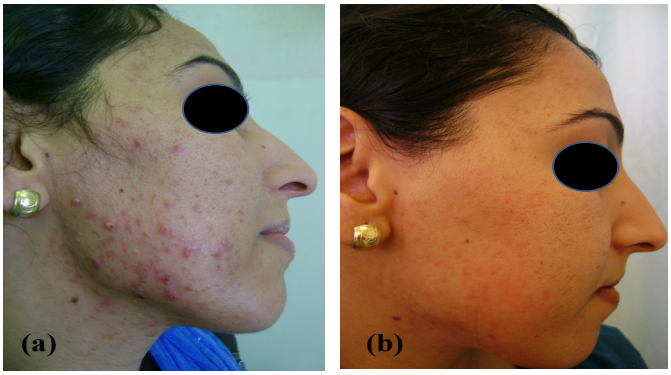

Figure 2. (a) Facial acne at base line. (b) Very good response after treatment

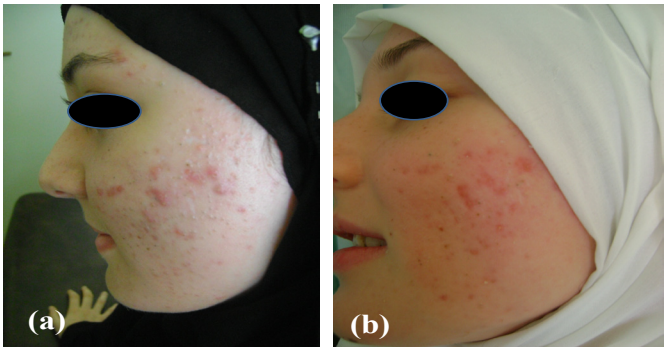

Figure 4. Facial acne at baseline (a). Poor response after 16 week treatment with isotretinoin (b).

and yielded therapeutically desirable results in 84.3% and 78.2% of the patients in group 1 and group 2 respectively. However, patients in group 1 showed a small, more rapid effect with regard to lesion count reduction during the first

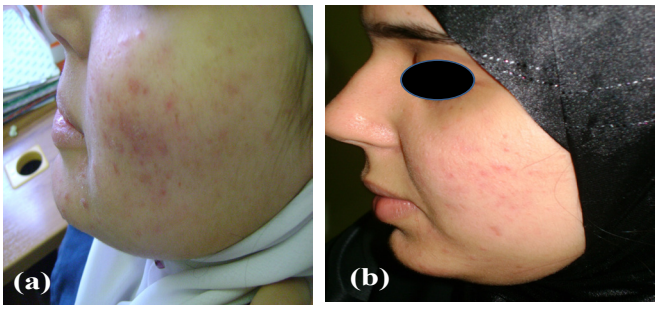

Figure 3. Facial acne at baseline (a). Good response at the end of treatment (b).

month as compared to group 2, but this difference was statistically insignificant. Sardana et al. and Amichai et al. found that alternate-day isotretinoin 20 mg plus topical 1% clindamycin gel, and daily low-dose isotretinoin 20 mg/day respectively to be effective in the treatment of moderate acne in adult patients, with a low incidence of side-effects (11,5). Moreover, Lee et al. compared different isotretinoin regimens; daily low dose, intermittent dose and conventional dose in treating patients with moderate acne, and concluded that a low-dose treatment is the most suitable for patients with moderate acne (15). The low dose of isotretinoin used in the present study for both groups was in the same range of doses used in previous studies (6-10), however the degree of improvement was reported to be higher than in our patients, this could be due to either the use of adjuvant topical treatment (9,11) or because of a longer treatment period among previous studied patients (6,7,16,17). The mean of the total cumulative doses of isotretinoin in our study were in the range of the reported cumulative doses in the previous studies which vary from

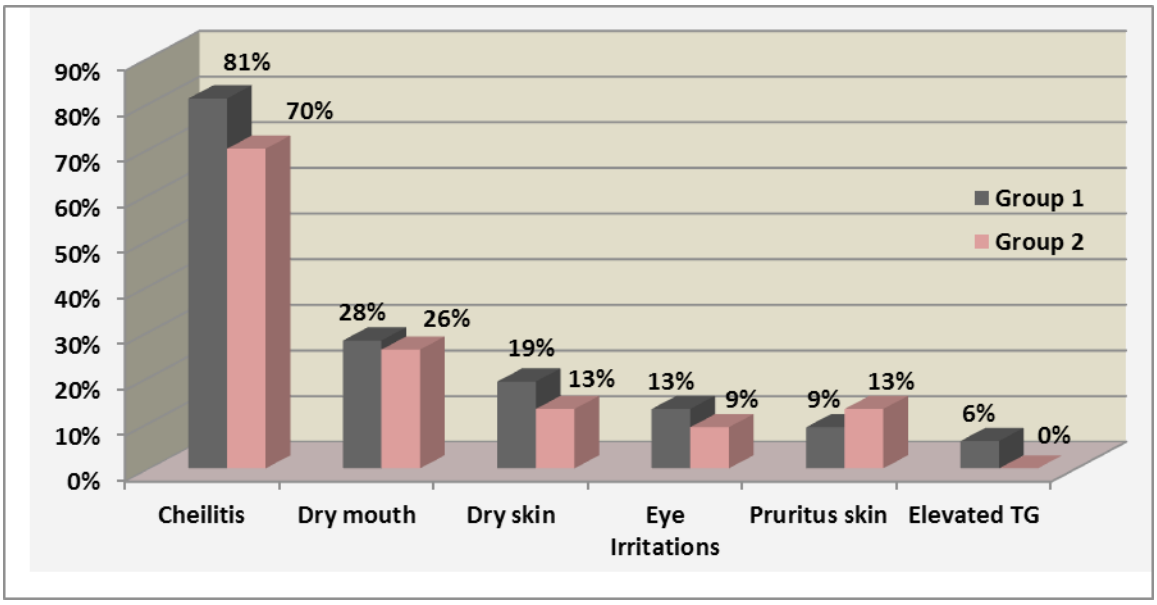

Figure 5. Frequency of therapy side effects in patients under study.

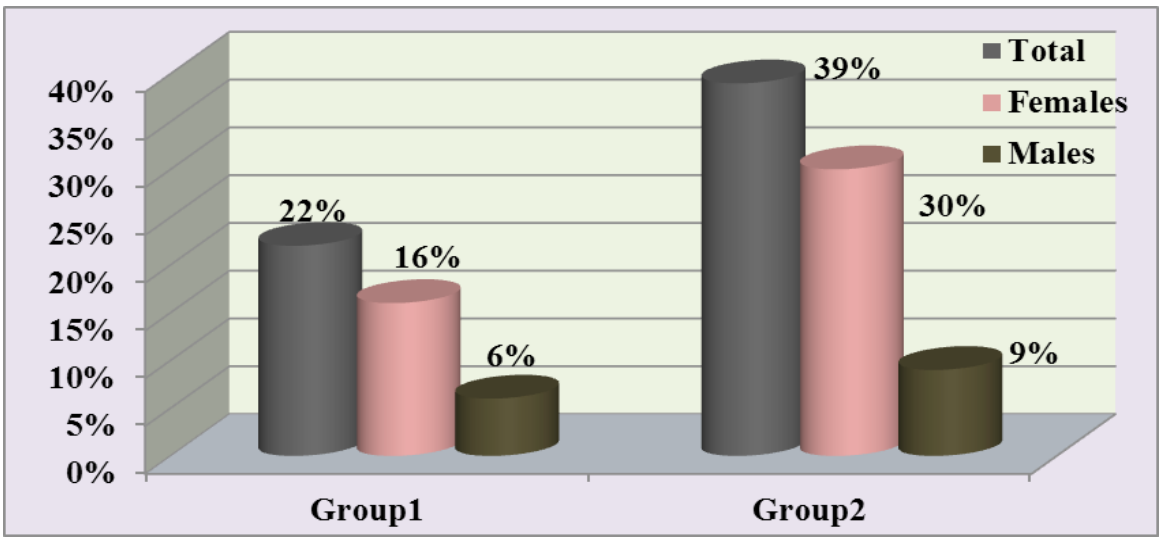

Figure 6. Relapse rates among the study patients.

21 mg/kg (6) to as high as 180 mg/kg (17) with a mean dose of 49.71 mg/kg (5,8,9,11,16). Although the low cumulative dosage in some studies has been explained by the administered concomitant topical therapy (11). In the present study the low cumulative dose can be explained as we administered isotretinoin for a short period (only four months) whereas other studies continued its usage for 6 to 8 months (5,8). Moreover, other studies reported a higher cumulative dose of isotretinoin when administered as monotherapy (5,17). These differences between studies can be explained by the type of dosage (6), sites treated (18) and grade of acne studied (6,17).

Most of the side effects reported with the use of isotretinoin were dose dependent (18). Moreover, previous studies had also shown that low-dose isotretinoin has lesser side-effects as compared to conventional high-dose regimens (15). In the present study both treatment regimens were generally well tolerated and mucocutaneous side effect were most common in both groups. It is well known that mucocutaneous side effects are the most common with the use of isotretinoin (7-9,11). None of our patients in either group developed initial activation of their acne lesions. Recent studies reported that doses of isotretinoin less than 0.2 mg/kg reduce the risk of acne flare upon initiation of

therapy (19).

The relapse rates in the present study were in agreement with earlier studies of low-dose isotretinoin where the relapse rates were found to vary from 33% to 39% (6.17,6). Lower relapse rates of 3.9% and 5.9% have been reported by others (5). The difference could be due to a longer treatment period which was for six months (5). Furthermore, the lower cumulative dose may act as a factor that predisposes to an increase in the relapse rate. A comparison of the relapse rates of standard isotretinoin therapy [1 mg/kg/day] (20-22), versus the studies on low-dose isotretinoin therapy (5-11) revealed that low dose therapy has a relapse rate comparable with that of the standard therapy.

In conclusion, low dose isotretinoin (less than 0.5 mg/ kg/ day) can be effectively and safely used in patients with moderate acne. Moreover, it can be given in any regimen (daily or intermittent). Isotretinoin is an expensive drug and may be a financial burden on many families, so a low dose regimen makes it more cost-effective. The problem to be resolved is to arrive at a cumulative dose of low dose isotretinoin to prevent relapses, as a threshold total dose to prevent a relapse has not been estimated yet. Long-term follow-up studies after clinical resolution in patients on low dose isotretinoin might shed some light on this issue.

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