Treatment of Mild to Moderate Acne with Conventional versus Two Different Intermittent Doses and Continuous Low-dose of Isotretinoin: A Randomized, Comparative Study

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Background: Oral isotretinoin is a unique drug that affects all four basic pathogenic mechanisms and the most effective systemic drug currently available for treatment of acne vulgaris. In this study, we aimed to assess the efficacy and tolerability of two different intermittent doses and continuous low-dose and to compare them with the conventional dose of isotretinoin in the treatment of mild to moderate acne vulgaris.

Methods: Eighty patients with mild to moderate acne were enrolled and randomized to receive either isotretinoin at 0.5–0.7 mg/kg daily for six months (group A), isotretinoin at 0.5–0.7 mg/kg daily for 1 month, then daily for 1 week out of every 4 weeks for six months (group B), isotretinoin at 0.5–0.7 mg/kg daily for 1 week out of every 4 weeks for six months (group C) or isotretinoin at 0.25–0.4 mg/kg) daily for six months (group D).

Results: Patient satisfaction was highest among group D, followed by group C, then B, and then A with statistically significant differences between groups A and D (P = 0.003) and groups D and B compared to C (P = 0.019). Side effects were more frequent with conventional dose compared with

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two intermittent doses and continuous low-dose.

**Conclusions:** This study suggests that, when considering tolerability, efficacy and patient satisfaction, continuous low-dose treatment is most suitable for patients with mild to moderate acne.

**Keywords:** Acne vulgaris; isotretinoin; conventional; intermittent; low-dose treatment.

1. INTRODUCTION

Acne vulgaris is a chronic, inflammatory disease with a multifactorial etiology influencing the pilosebaceous units of the skin which commonly affecting adolescents and young adults. An estimated 75–95% of all teenagers suffer from acne to some degree [1].

Skin with the highest density of hormonally responsive sebaceous follicles is most commonly affected. It is clinically seen most often on the face, neck, upper trunk, back and upper arms. Where the, patients present with open and closed comedones, inflammatory papules, pustules, cysts and nodules, and in some cases, permanent scarring [2]. Both genetic and environmental factors play a role in acne pathogenesis [3]. The disease has a significant impact on quality of life, and treatment has been shown to significantly improve self-esteem [4].

The pathogenesis of acne is multifactorial, caused by a combination of follicular hyperkeratinization, sebum production, propionibacterium acnes (P. acnes) colonization, and inflammation [5].

The treatment for acne vulgaris available includes systemic and topical retinoids, systemic and topical antimicrobials, hormonal treatment for females, azelaic acid, as well as laser and light-based treatment. These treatments are usually utilized in combination to overcome the pathogenic factors as possible [6].

Oral isotretinoin is a unique drug that affects all four basic pathogenic mechanisms and the most effective systemic drug currently available for treatment of acne vulgaris. The present conventional recommended dose is 0.5-1.0 mg/kg daily for 16–32 weeks, reaching a cumulative dose of 120 mg/kg. This regimen is well known to produce good results, but causes several dose-dependent side effects, such as mild cheilitis, mild xerosis, epistaxis, as well as elevation of aspartate aminotransferase (AST), alanine aminotransferase (ALT), cholesterol and triglycerides. Because of these side effects, some patients have difficulty complying with conventional treatment. In an effort to overcome this concern, intermittent and continuous low-dose regimens have been introduced. Expert opinion supported by clinical data hold up the use of isotretinoin for patients with mild to moderate acne who are failing to respond to conventional therapy, for whatever reason. Acne may produce scars in 30% of patients with moderate disease, and significant psychological morbidity in 12–13% [7].

There have been no previous studies, to our knowledge, comparing all isotretinoin therapeutic regimens simultaneously. The aim of this study was to evaluate the efficacy and tolerability of the two different intermittent doses of isotretinoin and continuous low-dose of isotretinoin and to compare them with the conventional dose of isotretinoin in the treatment of mild to moderate acne vulgaris.

2. PATIENTS AND METHODS

2.1 Study Design

This study was a comparative and randomized study. The patients were selected from the outpatient dermatology clinic, College of Medicine, Qassim University, Saudi Arabia between January 2013 and June 2014.

2.2 Patients

Eighty patients (56 female and 24 male) with mild or moderate acne localized on the face were enrolled in the study. Only acne patients with a chronic clinical course either unresponsive to conventional treatments (other than systemic isotretinoin) or psychosocial effect caused by the disease and patients who had not responded to antibiotic therapy or who had rapidly relapsed after antibiotic therapy were included. All systemic or topical treatment was stopped at least four weeks prior to the study.

The exclusion criteria were patients with severe acne types, such as conglobata or fulminans, history of oral isotretinoin in the preceding 3 months, other systemic diseases, patients on regular medication for some other diseases,
pregnant female or had a plan to be pregnant during the study or one month after, and lactation.

2.2.1 Liver function tests

Aspartate transaminase (AST), alanine transaminase (ALT), and lipid profiles (total cholesterol and triglyceride) were evaluated for all patients before treatment initiation and at monthly follow-ups. Female patients underwent pregnancy test.

2.3 Isotretinoin Doses

Patients were randomly assigned to one of four treatment regimens. They were randomized to receive either isotretinoin at 0.5–0.7 mg/kg/day (group A) as conventional treatment group, isotretinoin at 0.5–0.7 mg/kg/day for the first month followed by 0.5-0.7 mg/kg/day for the first 7 days of each additional month (group B) as intermittent I treatment group, isotretinoin at 0.5-0.7 mg/kg/day for the first 7 days of each month (group C) as intermittent II treatment group and isotretinoin at 0.25–0.4 mg/kg/day (group D) as continuous low dose group. There were 20 patients per group. The total periods of drug administration were 6 months in all groups.

The patients visited our clinic every month during the treatment period for clinical evaluation and biochemical tests. At six months follow-up evaluation after the end of treatment was also performed. Other treatments except for standard washing procedures and moisturizing were restricted for each patient.

2.4 Patient’s Evaluation

Before treatment was initiated, age, weight, duration of acne, previous treatment of patients and laboratory investigation were recorded. During the treatment, acne was evaluated and the severity was recorded using the global acne grading system (GAGS) score at each visit at the beginning and every 3-months. The GAGS score was used to assess acne severity. The GAGS global score (Table 1) is calculated by rating six different locations (i.e. forehead, right cheek, left cheek, nose, chin and chest /upper back) as 0 (no lesions), 1 (≥1 comedo), 2 (≥1 papule), 3 (≥1 pustule) or 4 (≥1 nodule), and then multiplying each rating by a factor that is specific to that area. Factors are based on the surface area and distribution /density of the pilosebaceous units. The global score is the sum of all six location scores, and the global grade is defined according to the global score (0, none; 1–18, mild; 19–30, moderate; 31–38, severe; ≥39, very severe [8]. The patients had an acne grade less than 30 and the inflammatory lesions on the forehead, cheeks, chin and neck were counted.

Table 1. The global acne grading system

<table>
<thead>
<tr>
<th>Location</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forehead</td>
<td>2</td>
</tr>
<tr>
<td>Right cheek</td>
<td>2</td>
</tr>
<tr>
<td>Left cheek</td>
<td>2</td>
</tr>
<tr>
<td>Nose</td>
<td>1</td>
</tr>
<tr>
<td>Chin</td>
<td>1</td>
</tr>
<tr>
<td>Chest and upper back</td>
<td>3</td>
</tr>
</tbody>
</table>

Note: Each type of lesion is given a value depending on severity: no lesions = 0, comedones = 1, papules = 2, pustules = 3 and nodules = 4. The score for each area (Local score) is calculated using the formula: Local score = Factor Grade (0-4). The global score is the sum of local scores, and acne severity was graded using the global score. A score of 1-18 is considered mild; 19-30, moderate; 31-38, severe; and >39, very severe

Data was entered into the Statistical Package for the Social Sciences (SPSS) software version 21. Frequencies, means and standard deviation were inferred, and categorical data were compared using a Fisher Exact test. One-way ANOVA was used to compare means of continuous variables and the post hoc for comparison between groups. P value of <0.05 was considered significant.

2.5 Ethical Consideration

Before the initiation of the study, informed consent was obtained from all individuals chosen for the study. The aim and the value of the work were explained to them in a simplified manner. There was no harm being inflicted on them. On the contrary, all would have the benefits of follow-up and the results of the study. The study was approved by the ethics committee of the Faculty of Medicine, Qassim University.

3. RESULTS

Eighty patients with mild or moderate acne localized on the face were included in the study (56 female and 24 male) with an age range of 18-29 years. There were no statistically significant differences between the studied groups with regard to age, gender, marital status, height and weights (Table 2) and the severity of acne (Fig. 1) among different groups.
The mean global acne grading system scores (Table 3) were not significantly different among patients receiving the different doses at the beginning ($p=0.451$) and at 12 months of therapy ($p=0.126$). However, they were significantly different at 3, 6 and mostly at 9 months, $p=0.010$, $p=0.008$ and $p<0.001$ respectively. Post hoc comparisons using the Fisher LSD test revealed that patients showed a significantly less reduction of GAGS in group C (intermittent II treatment group) compared to those in group A (conventional treatment group) or D (continuous low dose group) but similar to group B (intermittent I treatment group) at 3 and 9 months of starting treatment. Moreover, patient in group B continued to have high GAGS at 9 months ($p<0.001$).

### Table 2. Comparisons of demographic and anthropometric data between groups treated on different regime using one way ANOVA or Chi square test

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=20)</th>
<th>Group B (n=20)</th>
<th>Group C (n=20)</th>
<th>Group D (n=20)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD, range in years)</td>
<td>21.00±2.55, 18–26</td>
<td>21.85±2.76, 18–27</td>
<td>22.05±3.17, 18–29</td>
<td>21.80±2.50, 18–27</td>
<td>0.990</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (n) (%)</td>
<td>15 (75%)</td>
<td>14 (70%)</td>
<td>14 (70%)</td>
<td>13 (65%)</td>
<td>0.924</td>
</tr>
<tr>
<td>Male (n) (%)</td>
<td>5 (25%)</td>
<td>6 (30%)</td>
<td>6 (30%)</td>
<td>7 (35%)</td>
<td></td>
</tr>
<tr>
<td>Marital state</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.792</td>
</tr>
<tr>
<td>Single (n) (%)</td>
<td>19 (95%)</td>
<td>19 (95%)</td>
<td>20 (100%)</td>
<td>19 (95%)</td>
<td></td>
</tr>
<tr>
<td>Married (n) (%)</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Height(cm)</td>
<td>169.15±2.60</td>
<td>169.30±2.76</td>
<td>169.05±2.04</td>
<td>168.10±1.89</td>
<td>0.367</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>73.35±5.45</td>
<td>63.50±9.74</td>
<td>67.25±9.96</td>
<td>65.50±12.19</td>
<td>0.057</td>
</tr>
</tbody>
</table>

### Table 3. The global acne grading system result in the studied groups

<table>
<thead>
<tr>
<th>GAGS</th>
<th>Group A (n=20)</th>
<th>Group B (n=20)</th>
<th>Group C (n=20)</th>
<th>Group D (n=20)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>At the beginning</td>
<td>19</td>
<td>19</td>
<td>21</td>
<td>21</td>
<td>0.451</td>
</tr>
<tr>
<td>Three months</td>
<td>9</td>
<td>10</td>
<td>12</td>
<td>11</td>
<td>0.010</td>
</tr>
<tr>
<td>Six months</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>0.008</td>
</tr>
<tr>
<td>Nine months</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Twelve months</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>0.126</td>
</tr>
</tbody>
</table>

![Fig. 1. Distribution of patient in different groups according to acne severity (n=80, $P=0.067$)](image-url)
The side effects observed during the study are presented in Table 4. All side effects were found to be mild and did not require discontinuation of the treatment. The most common side effects were chilitis and dry skin.

Colitis was significantly higher among the conventional treatment group (group A) compared with the both intermittent treatment groups (group B&C) and continuous low-dose groups (group D) ($P < 0.001$). Likewise, the frequency of dry skin was also significantly higher among group A compared with group B, C and D groups ($P < 0.001$). There were no statistically significant differences between the studied groups with regard to epistaxis, fatigue and facial redness.

4. DISCUSSION

To the best of our knowledge, this is the first study comparing all therapeutic regimens (conventional, continuous low-dose and two intermittent regimens doses) of isotretinoin in patients with mild to moderate acne in a single study.

In this report, there was no clinical difference with regards to severity of acne on the GAGS at the beginning of therapy. Patients on the intermittent II dose (group C) demonstrated more severity on GAGS than all other modalities of treatment. Chelitis as the more encountered and severe side effect of isotretinoin was more common among patient receiving conventional therapy (group A).

New isotretinoin formulations and continuous low-dose or intermittent application protocols have been previously tried. Continuous low-dose protocols with doses such as 0.1 mg/kg/day and intermittent application protocols, especially for adult patients, those with oily skin, or with chronic moderate or mild acne have been reported [8,9].

Several studies indicate that acne patients have been benefiting from the continuous low-dose or intermittent treatment protocols, and more preferable to reducing adverse effects and higher patient compliance [10-17]. However, these studies did not compare all regimens as in this result. The response to treatment in this cohort in contrast to these reports was similar.

Kaymak and Iter [11] showed the efficacy of the intermittent regimen (0.5–0.75 mg/kg) daily for 1 week out of every 4 weeks for a total period of 6 months) in the treatment of 60 patients with mild to moderate acne. The response to the treatment was similar, they used Leeds grading scale while in this study GAGS is used and they used one regimen in their study.

Amichai et al. [10] reported successful treatment of 638 patients with moderate acne with a continuous low-dose regimen (0.3–0.4 mg/kg) daily for a total period of 6 months). The response to the treatment was similar, they also used Leeds grading scale while in the current study GAGS is used and they used one regimen in their study.

Boyraz and Mustak [6] compared the efficacies of intermittent and continuous low-dose isotretinoin regimens in moderate acne (20 mg daily for continuous low-dose, 0.5–0.75 mg/kg per day for one week every month for intermittent dose). The result of the study was similar to this study, but they don’t use any grading score.

### Table 4. The frequency of side effects caused by isotretinoin

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Group A (n=20)</th>
<th>Group B (n=20)</th>
<th>Group C (n=20)</th>
<th>Group D (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chilitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>10 (50%)</td>
<td>7 (35%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 (10%)</td>
<td>11 (55%)</td>
<td>7 (35%)</td>
<td>7 (35%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>18 (90%)</td>
<td>9 (45%)</td>
<td>3 (15%)</td>
<td>6 (30%)</td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td>9 (45%)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.104</td>
</tr>
<tr>
<td>Facial redness</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td>0.283</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.283</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.283</td>
</tr>
<tr>
<td>High ALT level</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.818</td>
</tr>
<tr>
<td>High AST level</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.801</td>
</tr>
<tr>
<td>High triglyceride level</td>
<td>3 (15%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td>0.709</td>
</tr>
<tr>
<td>High cholesterol level</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.894</td>
</tr>
</tbody>
</table>
Agarwal et al. [18] compared oral isotretinoin in different dose regimens. Group A was prescribed isotretinoin 1 mg/kg/day, Group B 1 mg/kg alternate day, Group C 1 mg/kg/day for one week/four weeks and Group D 20 mg every alternate day for 16 weeks. Total acne load scores were used to assess the patients. Patients with mild acne had almost similar results in all the groups while patients with moderate acne did better in Group A, B and D. Frequency and severity of treatment-related side-effects were significantly higher in treatment Group A as compared to Group B, C and D. Our results were similar, but the score assessment and the duration of the treatment were different.

Lee et al. [19] compared the effectiveness of conventional, low-dose and intermittent dose (0.5–0.7 mg/kg daily (group A), 0.25–0.4 mg/kg daily (group B), 0.5–0.7 mg/kg daily for 1 week out of every 4 weeks (group C). GAGS scores were statistically significant between groups A and C and groups B and C. Side-effects were more frequent with conventional treatment compared with low-dose and intermittent treatments. Their results suggested that intermittent treatment had less effect than either conventional or low-dose treatments. But in patient satisfaction, low-dose regimen was superior to other regimens (conventional or intermittent). Results in this report were similar to their findings, but there was a difference in the methodology where they used only one intermittent dose regimen in their study while two intermittent doses were studied in this report.

The majority of the side effects of isotretinoin therapy is known to be dose related; therefore, it is clear that intermittent dose and continuous low-dose treatments can reduce the risk of side effects [20]. Continuous low-dose isotretinoin, such as 0.15–0.40 mg/kg was reported to be effective with a low incidence of severe side effects [10,21]. Patients, in this study, except for quite tolerable mucocutaneous dryness and other significant side effects experienced fewer side effects in comparison with the conventional group, a finding similar to this result.

The intermittent regimen needs a longer treatment period to reach a high cumulative dose; therefore it is less suitable for use due to potential disadvantages such as widening the window of opportunity for particular side effects to appear [19].

Topical adapalene was prescribed to 5 patients as maintenance therapy after cessation of the systemic retinoid. Extension of treatment in these patients was similar to Boyraz and Mustak [6] study in which they extended the treatment for all group study.

There are some limitations to this study. The study did not include patients with severe acne and the sample size was relatively small and the post-treatment follow-up duration was short. A larger study is needed to fully investigate this new concept of intermittent dose of isotretinoin regimen with greater follow-up duration e.g (2 years). The patients’ report of their side effects was subjective and variable depending on the tolerance of each hence result cannot be safely generalized.

5. CONCLUSION

Intermittent and continuous low-dose isotretinoin treatments are successful and safe in the treatment of mild to moderate acne vulgaris. A continuous low-dose regimen seems to be superior to an intermittent regimen both in terms of patient adherence to the treatment and relapse rates. Patients on isotretinoin at 0.5–0.7 mg/kg/day for the first 7 days of each month demonstrated more severity on GAGS than all other modalities of treatment. Chelitis as the more encountered and severe side effect of isotretinoin was more common among patient receiving conventional therapy.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES


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