

A Study of Conventional Dosage Versus Interrupted Dosage of Oral Isotretinoin Therapy in Moderate to Severe Acne Vulgaris

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ABSTRACT

Introduction: Oral isotretinoin is used for the treatment of moderate to severe acne vulgaris in refractory cases. Prospective observational clinical study to assess and compare two different regimens of isotretinoin with respect to efficacy of treatment and side effects.

Material and Methods: Hundred patients of either sex having moderate to severe acne vulgaris, according to Global Acne Grading System in age group of 18-35 years were enrolled. The patients were divided into two treatment groups. Group A patients received conventional dosage isotretinoin i.e. 20mg oral once daily for 4 months and Group B patients received interrupted dosage Isotretinoin – 20mg once daily for one week out of every 4 weeks. Acne grading was evaluated and recorded using the global acne grading system (GAGS) score for treatment and its efficacy.

Results: Sixty five percent patients were less than 20 years age. Disease was more common in males (77%) than females (23%). Muco-cutaneous dryness was the most common adverse effect noted in both the groups. Low dose of continuous oral isotretinoin proved better in terms of clinical efficacy than low dose interrupted therapy, considering improvement in lesions and patients satisfaction level.

Conclusion: Low dose continuous isotretinoin is safe, effective and well tolerated with lesser side effects in the treatment of acne vulgaris.

Keyword: Acne vulgaris, oral isotretinoin therapy, conventional, interrupted

cases of acne, the discovery of isotretinoin as acne treatment was welcomed by many dermatologists despite its teratogenic properties.³

Oral isotretinoin (ISO) is recommended as treatment of acne especially severe variety in recent guidelines. Drug acts by decreasing sebum production and ultimately reduces the severity of scarring in acne. The outstanding effects of isotretinoin on acne were first reported in a small open study of 14 patients with treatment-resistant cystic acne.⁴ Use of the drug for a long time leads to many side effects as receptors which are blocked by the drug are ubiquitous in the body. There by compliance is the problem.

Up till now it is clear that acne patients are benefited with the low dose or interrupted dosage schedules. Low dose of course causes lesser degree of side effects. There exists doubt in deciding which protocol would be the best. Therefore the study was conducted to evaluate and compare the efficacy of conventional dosage versus interrupted dosage of oral isotretinoin in acne.

MATERIAL AND METHODS

A prospective observational clinical study was conducted at the department of Dermatology with the approval of ethics committee and in accordance with ethical standards. 100 patients of either sex in age group of 18-35 years, suffering from moderate to severe acne were enrolled. Global acne grading system (GAGS) score was used to assess the severity of acne and prognosis after treatment. GAGS score includes:- 0 score – no lesions, score 1- ≥ 1 comedone, score 2- ≥ 1 papule, score 3 - ≥ 1 pustule and score 4 - ≥ 1 nodule. It is calculated by rating six different locations like forehead, right cheek, left cheek, nose, chin, chest and upper back. Multiplication factor of each six different locations includes forehead 2, right cheek 2, left cheek 2, nose 1, chin 1, chest and upper back 3. Global score was the sum of six location scores and acne was graded like none for 0, mild for 1-18, for 19-30 score moderate 31-38 severe and ≥ 39 very severe. We have excluded the patients suffering from diabetes mellitus, pregnancy, lactating women, allergy to drugs like isotretinoin, unwilling to take isotretinoin therapy, on oral contraceptives, on drugs which are known to cause acne, with abnormal lipid profile, hepatic dysfunction and psychiatric disorders.

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INTRODUCTION

A pilo sebaceous gland unit disease characterized by areas of blackheads, whiteheads, papules pimples, pustules papulo pustules cysts at times abscesses, with greasy skin, and possibly scarring, which may be disfiguring the face and effects upper part of back and chest.

Acne vulgaris is the single most common skin disease affecting almost 80% of adolescents and young adults aged 11-30 years.¹ The pathophysiology of acne is complex and multifactorial and is associated with multiple potential inflammatory processes. The four major pathophysiological effects that have been correlated with acne formation are: 1) sebaceous gland hyperplasia and excess sebum production 2) abnormal follicular epithelial desquamation, 3) Propionibacterium acnes proliferation with a variety of direct or indirect pro-inflammatory effects, and 4) pre-clinical(subclinical) and visible inflammation.²

There are various ways of treating acne as per severity of the disease like local applications of drugs and systemic therapies but none is satisfactory. In words of Jenny Bryan.³ ‘Like it or loathe it, the acne treatment with isotretinoin has changed the lives of thousands of teenagers since it was licensed in the UK in 1983’. At that time dermatologists were desperate to use anti leprosy drugs and systemic steroids for the most severe

Patients were divided into two groups in accordance to treatment regimens. Group A patients were treated with low dose continuous regimen with 20mg oral isotretinoin daily for 4 months. Group B patients were treated with low dose interrupted regimen of isotretinoin 20mg daily for one week out of every four weeks, total duration of drug administration was 16 weeks in group A and 4 weeks in group B. The patients were followed up every 4th week during the course of study and six month evaluation after the end of treatment was performed. Non-inflammatory lesions (comedone) and inflammatory lesions like papules, pustules and nodules were counted at 0, 12 and 24 weeks. Side effects of drug were recorded at each visit.

Degree of satisfaction was 1 for dissatisfied, 2 slightly satisfied, 3 satisfied and 4 very satisfied.

STATISTICAL ANALYSIS

Statistically data was analyzed by using unpaired 't' test using SPSS software.

RESULTS

The mean age in group A was 20.96 years (range -18-35) and in group B it was 20.34 years (range -18-35). There were 77 males and 23 females, out of hundred patients. Family history of acne was reported in 40% of patients, where as 60% did not have any family history.

Morphological distribution of acne vulgaris was papular 47%, papulo-pustular 31%, pustulo-nodular (1%), nodulo-cystic 21%.

Treatment in group A and group B were effective in moderate to severe acne vulgaris and subsided the lesions in patients of both the groups. However, patients in group A showed a more rapid effect with regard to lesion count reduction during the first few weeks (0 weeks to 12 weeks) of therapy as compared to group B. Statistically the difference was insignificant.

Both regimens showed efficacy based on investigators evaluation using GAG score. At 24 weeks there was significant difference in GAG score between the two groups ($p < 0.021$). The lesion count showed a decline in the number of inflammatory lesions and non-inflammatory lesions in both the groups. For inflammatory and non-inflammatory lesions, the low dose interrupted regimen had less effect than low dose continuous regimen.

Degree of satisfaction in group A was, very satisfied 11 (22%), satisfied 20 (40%) and rest were slightly satisfied, where as in group B, very satisfied 6 (12%), satisfied 16 (32%), slightly satisfied 28 (56%) and none was dissatisfied in both the groups. On comparison it was statistically significant.

During the course of treatment there were few side effects in group A like mucocutaneous dryness 50 (100%), itching 38 (76%), acne flare 11 (22%), alopecia 18 (36%), myalgia 6 (12%) and group B, mucocutaneous dryness 50 (100%), itching 9 (18%), acne flare 46 (92%), alopecia 6 (12%) and myalgia 2 (4%). When group A was compared to group B it was statistically significant ($p < 0.001$).

DISCUSSION

Acne vulgaris is treated by various regimes like low interrupted and conventional doses of isotretinoin. Isotretinoin affects all the pathological process involved in acne vulgaris and produces excellent symptom reduction. It was earlier used in the treatment of nodulocystic acne, however, moderate to severe acne vulgaris

which are resistant to topical or oral antibiotics can be treated with adequate doses of isotretinoin. El-Sherif, Greiw and Amal M⁵ described the different regimes of isotretinoin like daily low, interrupted and conventional doses in patients with moderate acne. They concluded that low dose continuous treatment is most effective in moderate to severe acne vulgaris. Another study by Tan J, Boyal S. et al⁶ shows low dose regimen are better tolerated and effective in inducing acne clearance.

A randomized comparative trial of two low-dose oral isotretinoin regimens in moderate to severe acne vulgaris by Dhaked Dr., Meena RS et. Al.⁷ shows both regimens were well tolerated and found to be effective. However, in moderate acne 20mg alternate day regimen may be preferred. A 20 mg daily regimen is a better choice for severe acne in terms of response.

Recently in 2015 in an editorial from Pakistan by Javed Akhtar and Izaz Hussain⁸ summarise as follows: - in acne treatment it's not the daily dose of isotretinoin but achievement of cumulative dose of 120-150mg/kg. which defines long term success.

In the present study the mean age in both groups was 20 years (range 18-35) and males are affected more than females. Collier et al⁹ reported that 20 years is the age of growth and development which affects every tissue of the body. Smithard et al¹⁰ described more prevalence of moderate to severe acne in males as compared to females which is consistent with our study. Modern diet rich in glycogenic food may possibly be behind the problem. Link between high glycemic index and influence of hyperinsulinemia at the beginning of acne has been discussed by Berra B and Rizzo AM¹¹

Morphological distribution of common lesions in both groups was papulo-pustular 31 (31%), papular 47 (47%), pustulo-nodular 1(1%) and nodulo-cystic 21 (21%).

In both regimens result of 4 months treatment was more effective in low dose continuous regimen as compared to low dose interrupted regimen. However, patients in group A showed a more rapid reduction in count of acne lesions during first few weeks (0-12 weeks) as compared to group B which was insignificant statistically.

Efficacy in both regimens based on investigators evaluation using GAG score, at 24 weeks was significantly different. The lesion count showed a decline in the number of inflammatory lesions and non-inflammatory lesions in both the groups, however, the low dose interrupted regimen had less effect than low dose continuous regimen.

Side effects reported with the use of isotretinoin were dose dependent, however, earlier studies had also shown that low dose isotretinoin has lesser side effects as compared to conventional high dose regimen.⁶ In the present study both treatment regimens were generally well tolerated and mucocutaneous side effects were the most common in both groups which is consistent with earlier studies.⁵ Mucocutaneous dryness is the most common side effect with use of isotretinoin. The frequency and severity of treatment related side effects like cheilitis, dry skin, dry mouth, alopecia, itching were significantly higher in group A as compared to group B. Acne flaring was more common in low dose interrupted (group B) than (group A). Sweetman described mucocutaneous side effects of isotretinoin in his series.¹² The patient satisfaction score was higher in group A (very satisfied, satisfied) as compared to group B. This result suggests that the low dose continuous regimen is superior to low dose interrupted

regimen in terms of patient satisfaction. Earlier studies had also showed that low dose continuous isotretinoin regimen has more patient satisfaction than low dose interrupted regimen.⁶

High cumulative dose is a known factor for preventing relapse. The interrupted regimen required a long term treatment period to reach a high cumulative dose. Our study showed higher recurrence rate in group B than group A. These results showed that low dose continuous regimen had better clinical outcome with lesser relapse rate than interrupted regimen. Post inflammatory hyperpigmentation is a common complication of acne vulgaris, particularly in pigmented skin.¹³ Adityan B, Thappa DM¹⁴ noticed 24.6% of their patients with, post-acne hyperpigmentation. The incidence of pigmentation in our study was very low as compared to earlier studies.

Oral isotretinoin produces significant and faster reduction of lesions in moderate to severe type of acne vulgaris. It is well tolerated in low dose continuous therapy, which produce better anti-inflammatory effect in reducing papules, pustules, nodule and cystic lesions. Drug compliance is better even after more than 8 weeks; therefore it shows excellent tolerability, efficacy and patient satisfaction.

CONCLUSION

Isotretinoin is used in low dose (20mg/day for 4 months) and interrupted dose (20mg/day for one week out of every four week for 16 weeks) in moderate to severe acne vulgaris. Continuous low dose regimen has better clinical efficacy, lesser side effects and excellent patient satisfaction.

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