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Comparative Study on Efficacy, Safety and Tolerability of Oral Isotretinoin Versus Weekly Pulse Dose of Azithromycin in Treatment of Papulopustular Acne Vulgaris

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ABSTRACT

Background and Aims: Acne vulgaris is a common disorder of adolescence which may lead to many cosmetically and psychological problems so various topical and systemic therapeutic modalities have been used. This study was designed to compare the efficacy, safety and tolerability of oral Isotretinoin with thrice weekly pulse dose of Azithromycin in the treatment of papulopustular acne vulgaris.

Methods : In this study, 70 patients with mild to moderate papulopustular acne were selected and randomly allocated into 2 groups of 35 patients each.. One group was treated with oral Isotretinoin once daily at dose of 0.5mg-1.0mg /kg body weight according to severity of disease for four months and other group was treated with Azithromycin 500mg three days per week for 3 months.

Results :In group A, all patients responded. The clinical response was found excellent in 24(75%), good in 5(15.6%), and fair in 3 (9.4%) patient in group A. In group B, clinical response was seen in 23(76.66%) cases and it was excellent in 5 (16.7%), good in 7 (23.3%), fair in 5(16.7%) and poor in 6 (20%) cases. There was a significant difference between group A and group B.

Conclusion: Both isotretinoin and azithromycin can be useful for the treatment of moderate and severe acne but isotretinoin appears to be superior to weekly pulse dose of azithromycin.

KEYWORDS : acne vulgaris, Isotretinoin, Azithromycin

Introduction :

Acne vulgaris is a multifactorial disorder of pilosebaceous unit. The clinical picture can vary significantly, from mild comedonal acne to fulminant systemic disease. Although all age groups may be affected by its many variants, it is primarily a disorder of adolescence. There are several factors that contribute to acne, including Propionibacterium acne activity, increased sebum production, androgenic stimulation, increased keratosis of follicular channel inflammatory response and cytokinetic activity (Stathkis,1997)1. Acne is the commonest cutaneous disorder affecting nearly 80% of persons at sometime between the ages of 11-30 years. It is a chronic inflammatory disorder of pilosebaceous follicles and this can occur anywhere on the body apart from palms and soles, but frequently affects face, back, chest, neck and upper arms2,3. On the contrary, hormones such as estrogens and progesterones are involved in acne (Bolognia , 2008)4. The cause of acne inflammation before menstruation is the changes in the hydration of pilosebaceous epithelium. Acne vulgaris lesions include –comedones , papules , pustules , nodules and cysts.

Regarding the treatment of acne, four major principles govern the therapy: a) decrease sebaceous gland activity, b) correct the altered pattern of follicular keratinization, c) decrease the follicular bacterial population, and d) anti-inflammatory effects.5,6

The severity of acne is categorized into four groups: mild, moderate, severe and very severe. This categorization is base on the number of inflammatory lesions (papules + pustules), and not Comedones, in a half of the face; so acne is considered as mild if the number of lesions is between 1 to 5, moderate if between 6 to 20, sever if between 21 to 50, and very severe if more than 50 (Noakazu, 2008)7.

There are many topical and systemic modalities for acne. These include topical retinoids, benzoyl peroxide, antibiotics, salicylic acid, azelaic acid, intralesional steroid infiltration, black light, laser etc. and systemic antibiotics, hormones, retinoid, low dose steroid, fenasteride etc.8,9

The use of oral retinoid (isotretinoin) has revolutionized the management of severe and treatment-resistant acne. The remarkable aspects of isotretinoin therapy are the completeness of the remission in almost all cases and the longevity of the remission which lasts for months to years in the great majority of the cases at a dose of 0.5 to 1mg/kg body weight for a period of 16-20 weeks.2,8

Azithromycin belongs to the azalide group of antibiotics and is closely related structurally to macrolides like erythromycin. It is more tissue stable, penetrates deeply into tissues and has a higher terminal half life than erythromycin.8 Azithromycin has recently been introduced to treat acne at a weekly pulse dose schedule for a period of 3 months. Pulse regimes significantly increase patients' compliance because of the reduced total number of administered drugs.9

The present study was undertaken with a view to compare the efficacy of isotretinoin and weekly pulse azithromycin in the treatment of acne. Antibiotics act by decreasing neutrophil chemotaxis and regulating the complement pathway and inhibiting the production of lipase and Propionibacterium acnes10.

Since several studies have been conducted on the use of various topical antibiotics and other topical drugs for treatment of inflammatory acne lesions in the research centers around the world, and on the other hand, no such study has been conducted on the patients in our area, so,we intended to evaluate and study therapeutic effects of oral Isotretinoin and Azithromycin in affected patients.

Material and Methods:

In a randomized clinical trial, therapeutic effects of Isotretinoin versus Azithromycin were studied in patients with papulopustular acne vulgaris. After selection , the patient underwent the intended treatment and were followed up for a period of 3 months . In a randomized clinical trial , 80 patients diagnosed with mild to moderate papular and pustular acne attending our skin OPD and qualified with the inclusion criteria were included in this study. Patients were categorized in two groups namely A& B. Group A were treated with oral Isotretinoin at a dose of 0.5-1.0mg/kg body weight according to severity of disease once daily for 20 weeks and group B was given oral Azithromycin 500mg once daily for three days in a week for 12 weeks. Both of the treatment methods were explained to patients and their informed consent were taken. Also in this study , no additional cost was imposed to the patient and no

interference was was taken place in the treatment or prevention of disease. Response to treatment was compared by consecutive evaluation of the patient's treatment and their satisfaction , and improvement of the lesions. During study , the patients were not allowed to use any cosmetics or other topical medications other than the prescribed drugs. Every 4 weeks, patients underwent a physical examination to see the response of treatment. Number of inflammatory lesions (papules and pustules) and non-inflammatory lesions (Comedones) were recorded at the beginning of and during the study. The effectiveness of medications was identified with the loss or reduction of inflammatory and noninflammatory lesions during the study. Patient's satisfaction with each of the medications was also recorded. During the treatment, side effects such as erythema, burning, itching, allergy to sunlight, patient's intolerance of the medication and other possible complications and reduction of the lesions were evaluated through the records and clinical examination. Cases having moderate to severe acne are categorized by the global acne grading score (GAGS).

Inclusion criteria:
Included patients with mild and moderate acne with age from 16 to 30 years.

Exclusion criteria:
1 - Pregnant and lactating women
2 - Use of topical medications in the past one month
3 - Use of anti-acne oral medications in the past 2 months
4 - Infection by any skin disease other than acne
5 - Concomitant use of drugs that cause acne such as lithium , oral steroid , Vit B12 Medications
containing iodine and bromine
6 - Presence of more than 20 inflammatory lesions or three nodules or cysts in one side of face.

***Note:** 03 patients from group A and 05 patients from group B left the treatment.

Table-1 demographic data and disease characteristics in two groups

		Group A (n=32)	Group B (n=30)
SEX	Male	18 (56.25%)	17(56.7%)
	Female	14 (43.75%)	13(43.3%)
AGE	16-20 yrs	15(46.8%)	14 (46.66%)
	21-25 yrs	11 (34.3%)	11 (36.66%)
	26-30 yrs	06 (18.7%)	05 (16.66%)
	Mean (years)	21.03 ±4.21	21.50±4.16
Severity of acne	Moderate	24 (75%)	21 (70%)
	Severe	08 (25%)	09 (30%)
Duration of disease	3-6 months	10(31.2%)	13(43.3%)
	6-12 months	15(46.8%)	12(40%)
	12-24 months	07 (21.8%)	05 (16.7%)
	Mean (months)	9.57 ±5.52	12.93± 6.20

Results
In total, 62 cases (32 in group A and 30 in group B) were included in the study (Table 1). 35 (56.5%) patients were male and 27(43.5%) were females. The age in both the groups ranged from 16 to 30 years. The mean age of group A was 21.03±4.21 years and in group B was 21.5±4.16 years. In both the groups, the maximum numbers of patients were in the age group of 16 to 20 years. Maximum number of patients had moderate type of acne, 24(75%) in group A and 21(70%) in group B.

The duration of disease ranged from less than 6 months to more than 12 months whereas the mean duration of the disease was 9.57±5.52 months in group A and 12.93±6.20 months in group B.

Data represented in Table 2 assessed the efficacy of both drugs. In group A, all patients responded. The clinical response was found excellent in 24(75%), good in 5(15.6%), and fair in 3 (9.4%) patient in group A. In group B, clinical response was seen in 23(76.66%) cases and it was excellent in 5 (16.7%), good in 7 (23.3%), fair in 5(16.7%) and poor in 6 (20%) cases.

Clinical response in patients with different disease severity is also shown in Table 2. In group A, out of 24 patients with moderate type of acne the response was excellent in 18(75%), good in 4(16.7%) and fair in 2(8.3%) whereas in 08 cases with severe type of acne, it was excellent in 6 (75%), good in 1(12.5%), and fair in 1(12.5%). In contrast, in group B, clinical improvement, in 21 patients with moderate acne, was rated as excellent in 4(19%), good in 6(28.6%), fair in 4 (19%), poor in 3(14.3%) and no response in 4(19%) cases. In 9 patients with severe acne in group B, response was rated as excellent in 1(11.1%), good in 1 (11.1%), fair in 1 (11.1%), poor in 3 (33.3%) and nil in 3 (33.3%) cases. There was a significant difference between group A and group B.

In group A, dryness especially on lips and face associated with mild peeling was noted in almost all the cases and controlled easily by liberal use of moisturizers and increased water intake. 3 patients showed a transient rise in serum lipids especially triglycerides but none of the patient had levels enough to warrant stoppage of the drugs. In group B, none of the patient had shown serious side effects except 2 patients complained of mild nausea and abdominal discomfort.

5 (15.6%) patients in group A and 9(30%) in group B experienced relapse during follow up period.

Table -2 Clinical response in moderate and severe disease, group A (n=32) and group B (n=30)

Clinical response	Group A (n=32)			Group B (n=30)		
	Total	Moderate acne	Severe acne	Total	Moderate acne	Severe acne
Excellent	24(75%)	18(75%)	06(75%)	05(16.7%)	04(19%)	01(11.1)
Good	05(15.6%)	04(16.7%)	01(12.5%)	07(23.3%)	06(28.6%)	01(11.1%)
Fair	03(9.4%)	02(8.3%)	01(12.5%)	05(16.7%)	04(19%)	01(11.1%)
Poor	-	-	-	06(20%)	03(14.3%)	03(33.3%)
No response	-	-	-	07(23.3%)	04(19%)	03(33.3%)
Relapse	5(15.6%)	03(12.5%)	02(25%)	09(30%)	05(23.8%)	04(44.4%)

Discussion
In the present study, the mean age of patients in group A was 21.03±4.21 years and in group B 21.5±4.16 years. The age ranged from 16 to 30 years. Out of total 62 patients 29(46.8%) were in the age group of 16 to 20 years. The age distribution in the present study is in accordance with an earlier study.10 There were 35(56.5%) males and 27 (43.5%) females in our study. In group A, 18 (56.25%) cases were males and 14(43.75%) were females. On the other hand in group B 17 (56.7%) cases were males and 13(43.3%) were females. So, in both groups male preponderance was found. This differs from earlier studies which showed female preponderance.7 In the present study, duration of the disease varied from less than 6 months to more than 12 months. The mean duration of the disease in group A was 9.57±5.52 months and in group B 12.93±6.20 months. The maximum number of patients had acne for 6 to 12 months. This finding is consistent with the study done earlier.3

For the treatment of moderate and severe type of acne, topically applied drugs are not effective hence systemic drugs always should be considered.8,11

A study by Ghaffarpour et al.11 reported a cure rate of 96.7% with oral isotretinoin. Another study done by Nawaf Al-Mutairi et al.6 found 95.5% improvement with isotretinoin.

In our study, cure rate with isotretinoin (group A) was 100%.

Kapadia et al.12 with pulse dose azithromycin in the treatment of acne showed a cure rate of 80%. Another study by Singhi et al.13 with pulse dose azithromycin found 77.3% improvement. In this present study, the cure rate with pulse dose azithromycin in group B was 76.66%.

Isotretinoin works on all four factors that predispose a person to acne i.e. excess sebum production, clogged skin pores, P. acnes and inflammation. On the other hand azithromycin acts by penetrating cells of susceptible bacteria and reversibly binding to the 50-S subunit of the ribosome, inhibiting RNA dependant protein synthesis.13,14

Side effects of isotretinoin include dryness of skin, chapped lips, increased serum lipid level, bone pain, joint pain, depression, thinning of hair, headache, blurred vision etc.15 In our study only dryness of skin was found in all cases and transient elevation of serum lipid was found in only 3 cases that did not hamper the study in group A. In group B, no serious side effect was noted. In group A, only 5 (16.7%) cases relapsed mildly and were treated topically. In group B, 9(30%) cases relapsed and those required alternate regime.

Conclusion:

Our study concluded that both isotretinoin and azithromycin can be useful for the treatment of moderate and severe type of acne. However, isotretinoin is superior to weekly pulse dose of azithromycin because isotretinoin works on all factors causing acne.

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