Original Article

Oral Azithromycin Pulse Therapy and Daily Topical Adapalene in the Treatment of Acne Vulgaris: An Open Randomized Noncomparative Study

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Abstract

The safety and efficacy of oral azithromycin and topical adapalene are well documented. In this study, concomitant use of oral azithromycin pulse therapy and daily topical adapalene in the treatment of acne vulgaris is assessed. A total of 37 patients fulfilled the inclusion criteria were enrolled. Azithromycin, 500 mg orally once daily first 3 days of 10 days' cycle for 9 cycle & topical Adapalene (0.5%) at night. Patients evaluated at 4 weeks' interval by using Michaelsson acne severity index. The overall assessment was made by percent reduction of acne lesions and severity score. At the end of 12 weeks' treatment 99.8% of comedones, 98.7% papular lesion, 94.3% pustular lesion and 88.8% infiltrated lesion were cleared. Only 2.9% cystic lesion responded to the regimens. Percent reduction of Michaelsson acne severity index was 87%, which was statistically highly significant. Overall assessment revealed acne lesion cleared in 22% cases, excellent improvement observed in 65% and 13% showed good response. Adverse effect was minimal. So, azithromycin pulse therapy and topical adapalene is indeed effective and safe in the treatment of acne vulgaris.

Key words: *Acne Vulgaris, Azithromycin, Adapalane & Michaelsson acne severity index.*

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Introduction

Acne vulgaris is the most common skin disease seen by physicians. It is a disease of the adolescent with 90% of all teenagers being affected to some degree. It may begin in the twenties or thirties or may persist in adults for many years. Like other countries a quite number of adolescents and young adults both male and female suffer from acne vulgaris in our country and many suffer from high degree of morbidity and psychological trauma due to post acne scar that develop due to lack of proper and adequate treatment. Conventional therapy for acne vulgaris includes topical agents, which act against Propionibacterium acnes or has direct effect on comedogenesis and anti - inflammatory activities. For the last one decade, topical agents mainly erythromycin, benzoyl peroxide and tretinoin and more recently cliandamycin have assumed main role in the management of acne. Resistance of P.acnesto erythromycin has been reported,[1-2] benzoyl peroxide is a strong oxidizer often irritant and topical tretinoin, which bind to retinoic acid receptors (RARs) and cytosolic retinoic acid binding protein is less stable to light and more irritant with the potential problem of patient noncompliance. Adapalene is a naphthoic acid derivative, which selectively interacts with only the b and g subtypes of nuclear RARs recently introduced in Bangladesh as a 0.1% gel (Fona®). Due to selectivity, it has lesser capacity to cause irritation and is well accepted[3]. Systemic antibiotic most commonly used in acne vulgaris to act against P.acnesare tetracycline, erythromycin and doxycycline. They often required frequent and or long-term administration. Therefore, they failed to gain acceptance, more over they are sometimes associated with side-effects contributing to reduced compliance. Azithromycin is the prototype of a group of antibiotics known as azalides, is structurally related to the macrolide erythromycin by the insertion of methyl -

substituted nitrogen at position 9a in the lactone ring. It is more tissue stable, penetrates deeply into tissue and has higher terminal life than erythromycin. Azithromycin is approved mainly for the treatment of uncomplicated upper respiratory tract and skin infection, gonococcal and genital chlamydial infection but it appears to have a broad spectrum of activity with enhanced activity in vitro against P.acnes. The efficacy and safety of azithromycin therapy in acne vulgaris has been reviewed in many Western journals[4-7]and articles on clinical trials has been published. The effect of azithromycin 3 days oral dose lasts for 10 days, which gave rationale to use as pulse therapy. So, combination of oral azithromycin pulse therapy and daily topical adapalene at night might be a good option for the treatment of acne vulgaris.

This open randomized noncomparative trial was done to evaluate the efficacy and safety of oral azithromycin pulse therapy (500 mg orally once daily during the first 3 days of a 10 days cycle for 9 cycle) and topical adapalene in the treatment of acne vulgaris.

Materials and Methods

The study required 12 months for its successful completion. A total of 30 patients having moderate to severe acne on the face as proposed by a Consensus Conference for the classification of acne[8] were needed. Considering 30% drop out in follow up visit we needed a minimum of 39 cases. A total of 48 patients who met the enrollment criteria were approached to participate in the study among them 39 (81.25%) patients agreed to participate. Two patients (5.1%) lost during follow-up. Age below 15 years and above 60 years of either sex, patients who had received topical anti-acne regimen within 2 weeks and systemic anti-acne drug within 4 weeks before the study and patients refused to give consent were excluded. Pregnant and lactating mothers, women planned for pregnancy, patient having liver and kidney function test beyond normal limit, patient with terminal illness, serious cardiac disease and any other condition which may preclude the patient from completing the study, known hypersensitivity to azithromycin or adapalene, concurrent treatment with drugs that may cause drug interaction, chronic diarrhoea, or any gastrointestinal condition which may affect absorption of trial drug were not included in the study.

All participants were randomly assigned to the treatment regimens Tab. Azithromycin 500 mg. orally once daily for 3 days of each 10 days cycle and topical Adapalene daily at night.

Assessment

Acne lesions graded according to the severity index described by Michaelsson et al[9]. Five point scaled used; 0.5 for comedone, 1 for papule, 2 for pustules, 3 for infiltrated lesions and 4 for cystic lesions. Multiplying each type of lesion with its severity index and adding them together calculate the total severity score of acne.

Patients clinically assessed at 4 weeks interval. At all follow -up visits all parameters examined and graded. Both the total scores and number of each type of acne lesions compared to the baseline scores and number and all p values calculated by Wilkinson's sign ranked test using SPSS windows version10.1.

Overall assessment

The overall evaluation made by the percent reduction of baseline total scores. Five comparative categories generated i.e. cleared, when 100% resolution occurred ; excellent improvement, when 75% or greater reduction observed ; moderate improvement, when 50% -74% reduction in total score occurred ; poor, when <50% reduction observed and worse, if exacerbation of disease occurred.

Results

Socio-Demographic Data

Table-I: Distribution of study patients with acne vulgaris.

Socio-Demographic Data	Total		Mean ± SD
	N	(%)	(Range)
Age Group			
< 15 years	7	(18.9)	10.4 ± 3.1 years
16 – 20 years	24	(64.9)	(3 - 15 years)
21 – 25 years	3	(8.1)	
26 – 30 years	3	(8.1)	
Gender			
Female	28	(75.7)	
Male	9	(24.3)	
Years of Education			
1 – 5 years	3	(8.1)	10.4 ± 3.1 years
6 – 10 years	17	(45.9)	(3 - 15 years)
11 – 15 years	17	(45.9)	
Occupation			
Student	30	(81.1)	
Business	1	(2.7)	
Service	4	(10.8)	
Worker	1	(2.7)	
Dependent	1	(2.7)	

Socio-demographic data of patients with acne vulgaris are presented in Table-1. The youngest patient was of 13 years while the oldest one aged 30 years. The average age was 18.7 ± 4.0 years and most of the patients were belonged to 20 years age groups (83.8%). Among the Study population 28 (75.7%) were female and 9 (24.3%) were male. Nearly half i.e. 45.9 % of the evaluated patients attended college level education, the average years of education was 10.4 ± 3.1 years. More than three quarter of the patients evaluated was Student (81.1%). Most of the patients (45.9%) came from upper middle socioeconomic class followed by 37.8% from lower middle socioeconomic class. None from poor socioeconomic class agreed to participate in the study.

Clinical Data

Age at Onset of Acne Vulgaris

Table-II: Distribution of study patients by age at onset of acne vulgaris

Age Group	Total		Mean ± SD
	N	(%)	(Range)
< 15 years	19	(51.4)	15.8 ± 2.5 years
16 – 20 years	16	(43.2)	(11 - 21 years)
21 – 25 years	2	(5.4)	
Total	37	(100.0)	

Distributions of patients by age at the onset of acne vulgaris are presented in Table-II. The lowest age was of 11 years while the highest age was 21 years. The average age was 15.8 ± 2.5 years when most of the patients experienced acne vulgaris.

Site of Involvement

Table-III: Site of involvement of acne lesion in patients with acne vulgaris

Site of Acne Involvement	Yes		No		Total	
	N	(%)	N	(%)	N	(%)
Cheek	37	(100.0)	0	(0.0)	37	(100.0)
Chin	34	(91.9)	3	(8.1)	37	(100.0)
Forehead	34	(91.9)	3	(8.1)	37	(100.0)
Nose	19	(51.4)	18	(48.6)	37	(100.0)
Back of the neck	2	(5.4)	35	(94.6)	37	(100.0)
Shoulder	5	(13.5)	32	(86.5)	37	(100.0)
Chest	3	(8.1)	34	(91.9)	37	(100.0)
Upper back	9	(24.3)	28	(75.7)	37	(100.0)

Most of the patients had Cheek, chin and forehead involvement. More than half of the patient showed nose involvement and only few patients had upper back, shoulder, chest and back of the neck involvement.

Assessment

Reduction in the number of acne.

Table-IV: Reduction in the number of different type of acne lesion in response to study regimens

Site of Acne Involvement	Number of Lesion Mean ± SD			
	$Week_0$	$Week_4$	$Week_8$	$Week_{12}$
Comedones	41.0 ± 18.0	16.8 ± 9.8	4.6 ± 5.1	0.6 ± 1.5
Papular lesion	30.7 ± 10.9	20.2 ± 9.1	9.8 ± 5.6	1.8 ± 1.6
Pustular lesion	22.1 ± 10.9	7.6 ± 5.0	0.8 ± 1.3	0.2 ± 0.5
Infiltrated lesion	9.2 ± 4.9	7.8 ± 4.0	4.4 ± 3.2	1.3 ± 1.8
Cystic lesion	4.1 ± 5.3	4.1 ± 5.3	3.5 ± 4.8	3.3 ± 4.7

At the end of first four weeks there was significant reduction in the number of comedones (95% CI of the difference= 20.7-27.8, P=0.000) and these reduction remained significant throughout the treatment period (week8: 95% CI of the difference=30.8-42.5, P=0.000 and week12: 95% CI of the difference=34.2-47.3, P=0.000). Similarly Papular acne significantly reduced in number throughout the treatment period (week4: 95% CI of the difference=8.2-12.7, P=0.000, week8: 95% CI of the difference=18.1-24.7, P=0.000 and week12: 95% CI of the difference=25.4-33.1, P=0.000). Treatment regimen also reduced the number of pustular acne in same fashion (week4: 95% CI of the difference=12.4-17.3, P=0.000, week8: 95% CI of the difference=18.3-25.7, P=0.000 and week12: 95% CI of the difference=18.9-26.7, P=0.000). In case of infiltrated lesion the reduction was gradual but significant in all follow-ups (week4: 95% CI of the difference=0.9-1.9, P=0.000, week8: 95% CI of the difference=3.6-5.6, P=0.000 and week12: 95% CI of the difference=6.2-9.3, P=0.000), but cystic lesion showed no improvement through out the treatment period (week4: P=1.000, week8: P=0.325 and week12: P=0.161).

Percent reduction in the number of acne

Percent reduction in the number of acne lesion showed highly significant improvement in case of comedones, papular and pustular lesion throughout the treatment period(Fig I) Infiltrated lesion also showed significant response to the treatment regimen but cystic lesion showed no significant improvement.

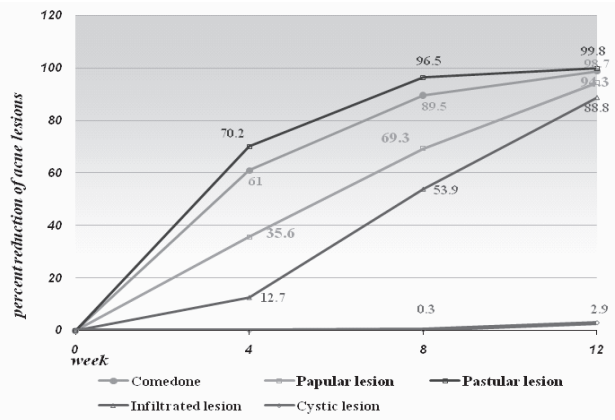
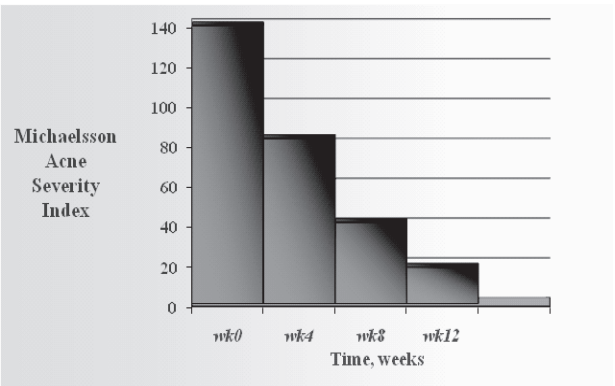


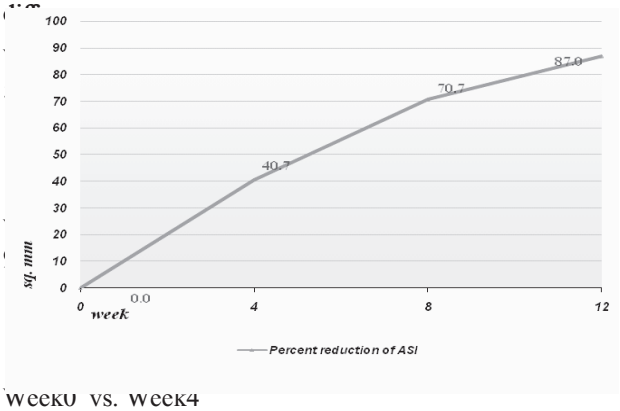
Figure I: Percent reduction in the number of different type acne lesion in response to study regimen.

Michaelsson Acne Severity Index

The study regimens showed significant reduction in the severity score throughout the treatment period.(Fig II)



Time of assessment	Mean difference	95% CI	of P value



Week0 vs. Week4
118.8

107.6 - 130.0 0.000

Figure-II: Changes in the Michaelsson Acne Severity Index during treatment with study regimens.

Michaelsson Acne Severity Index

The study regimens showed highly significant percent reduction of throughout the treatmen

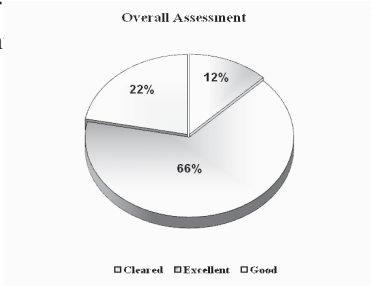


Figure-III: Changes in the Michaelsson Acne Severity Index and its percent reduction during treatment.

Overall Assessment

Presented in Figure-IV. Investigator's evaluation carried on 32 patients who have completed the study with compliance. Among them Acne lesion cleared in 22.0% patients (6.7%) complained of mild burning sensation (irritation) on facial skin.

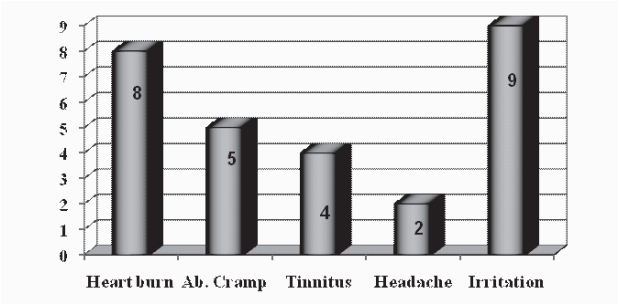


Figure-V: Adverse effects of study regimens observed during treatment period.

Discussion

The number of patient enrolled in the study is not sufficient to describe the epidemiology of Acne vulgaris. However the socio- demographic characteristics observed among the patient is similar to those described in different textbook. Topicalretinoides have been a mainstay of acne therapy for approximately a quarter of century. Their clinical effectiveness in treating comedones and micro-inflammatory acne remains unequalled by other topical retinoides in the treatment of acne has been the typical irritation that accompanies their use. The development of adapalene signifies the onset of a new era in topical retinoid therapy an era of "low irritancy retinoides[3]".

Systemic antibiotic most commonly used are tetracycline, erythromycin and doxycycline. They often required frequent or long- term administration. Therefore they failed to gain acceptance. In many Western journals, the efficacy and safety of azithromycin in treatment of acne have been reviewed and articles on clinical trials published [4,5,6,7].

Adapalene affect keratinization and differentiation of epithelial tissues. It also possesses anti-inflammatory and comedolytic properties. On the other hand, Azithromycin has bactericidal activity against P. acne. So, concomitant use of these two drugs might have synergistic effect in the management of acne vulgaris. As these two drugs have two different route of administration, there is no possibility of drug antagonism. These facts suggest that the use of oral azithromycin and topical adapalene at the same time may improved the cure rate of acne vulgaris.

In our study, the treatment regimens showed highly significant improvement from the first follow- up visit. At the end of 12 weeks treatment 87% improvement observed in term of percent reduction of MichaelssonAcne Severity Index.These findings are more superiortothose observed in different studies by using azithromycin[4,5,7] and topicaladapalene[3,1011,12,13]alone.

Nearly 90% of comedones and popular lesion and more than half of the pustular and infiltrated lesion healed after

At the end of 12 weeks nearly all of the comedones, papules and pustular lesion were cleared, but only few infiltrated lesion persist. On the other hand, the number of cystic lesion remained almost unchanged.

Therefore, the study regimen failed to show any efficacy against cystic type of acne, which is usually recalcitrant to topical and oral anti-acne drugs. It often requires surgical intervention. So, treatment failure in cystic acne doesn't mean that the regimen is not effective against acne vulgaris.During the period of study patients developed various side-effects as heart burn, abdominal cramp, tinnitus and mild irritation on the facial skin. None of these reaction were severe and most occurred within the first week of initiation of therapy and was observed to resolve with continued use of the drugs adding Ranitidine and anti-spasmodic in some patient.

In conclusion, this study revealed that combination regimen of azithromycin and adapalene is indeed more efficacious and safe in the management of acne vulgaris. Study with larger group of patients for longer period may result in superior out comes and assess the relapse rate in clinical practice through improved compliance.

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