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Oral Azithromycin Pulse Therapy and Daily Topical Benzoyl Peroxide in the Treatment of Acne Vulgaris: An Open Clinical Trial Study

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Summary:

Introduction: Combination therapy is an effective approach to simultaneously target multiple pathogenic factor of acne. A unique combination of oral azithromycin pulse therapy and daily topical benzoyl peroxide has been developed for treatment of acne.

Material & Methods: It was an open, controlled, clinical trial, conducted on 37 out patients with acne vulgaris. Patients were clinically assessed at baseline &at week 0,4, 8 and 12.

Evaluation included success rate (subjects clear or excellent improvement, good response), lesion count & percentage change in lesion count from baseline, cutaneous tolerability & adverse events.

Results: The combination of oral azithromycin pulse therapy & daily topical benzoyl peroxide was very safe & effective with significant differences in percentage of lesion count change observed as early as 1-4 weeks .Adverse events were more frequent with the combination therapy that occurred early in the study &were transient.

Conclusion: This study revealed that combination regimen of azithromycin &benzoyl peroxide (4%) is indeed very much efficacious & safe in the management of acne vulgaris.

Key words: "To evaluate the efficacy & safety of oral azithromycin pulse therapy & daily topical benzoyl peroxide (4%) combination in the treatment of acne vulgaris."

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Introduction:

Acne vulgaris is an exclusively a follicular disorder of the pilosebaceous unit, characterized by comedones, papules, pustules, nodules and often scars. The condition usually starts in adolescence and frequently resolved by the mid-twenties. A peak in prevalence and severity occurs between 14 & 17 years in females, 16 & 19 years in males. However some levels of disease activity may persist into the 30-40 years range.[1] It can lead to significant psychological distress and cosmetic disfigurement.

The pathogenesis of acne is multifactorial. lt involves excessive sebum production, abnormal epithelial hyperkeratinization of sebaceous follicles, the presence of microbial organisms, notably the anaerobic *Propionibacterium Acnes* (P.acnes) and inflammation.[2]

The treatment armamentarium of acne contains many different therapeutic options, including topical and oral antibiotics, topical and oral retinoids, topical benzoyl peroxide, azelaic acid, hormonal agents and surgical modalities.[3]

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Benzoyl peroxide is safe & effective antimicrobial agent for the treatment of acne .It acts through oxidation and die formation of free radicals causing a reduction of Propionibacteria. The mechanism helps to prevent an induction of resistance of Propionibacterium acnes often observed in long term acne treatment with antibiotic. Systemically absorbed benzoic acid so rapidly cleared by the kidneys that no systemic toxicity due to drug accumulation can be expected. The widespread use of topical formulations of erythromycin and clindamycin to treat acne has resulted in significant dissemination of cross resistant strains of Propionibacteria. But benzoyl peroxide has distinctive advantage that, so far, no resistance has been detected against it.[4]

Systemic antibiotic most commonly used in acne vulgaris to act against P. acnes are tetracycline, erythromycin, clindamycin and doxycycline. The widespread and long-term use of antibiotics over the years have unfortunately led to the emergence of resistant bacteria. Resistance to tetracycline and cross-resistance to doxycycline are also common the incidence of P. acnes resistance in the UK is estimated to be approximately 65% for erythromycin & clindamycin and 40% for tetracycline& doxycycline[5] whereas there are no reports on resistance to azithromycin.[6-8]

Material and method:
It was an open controlled clinical trial study which was conducted in the department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka.

Duration of the study was from July 2016 to December 2016.

A total number of 37 patients were primarily selected. Complete history, general physical and dermatological examinations were done for all enrolled patients. For women of reproductive age reproductive history, lactation and pregnancy plan was careftilly judged. History and physical findings were recorded in a structured questionnaire. Finally those patients, who matched the inclusion and exclusion criteria, were selected for the study.

Inclusion criteria were:
Patients clinically diagnosed as acne vulgaris, Having age >12 years and of both sexes,

Patients with non inflammatory (comedones) lesions and inflammatory (papules, pustules) lesions on the face

Patients suffering from nodulocystic acne,

Exclusion criteria were:
Pregnant and lactating mother,

Female who were not on oral contraceptive pill.

Person having hypersensitivity to benzoyl peroxide and

Patients with other dermatological conditions interfering with the treatment of acne vulgaris

Scoring of acne vulgaris:
In all the cases the acne lesions will be graded according to the severity index described by Michaelsson et al[9] by counting the number of open or closed comedones, papules, pustules, and cystic lesions. Michaelsson described the severity index as 0.5 for comedones, l for papule, 2 for pustules and 3 for cystic lesions. The total severity score of disease will be calculated by multiplying each type of lesion with its severity index and adding them together.

Study 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, when 75% or greater reduction observed; moderate, when 50-74% reduction in total score occurred; poor, when <50% reduction observed and worse, if exacerbation of disease occurred.

Data processing and analysis:
All collected data was checked and rechecked for omissions, inconsistencies and improbabilities. Data analysis was performed by Statistical Package for Social Science (SPSS), version-12. Data was edited, coded and entered into the computer. Statistical analyses were done and level of significance was measured by using appropriate procedures like chi square lest (X^2), relative risk (RR) measurement, t-test, proportion test, ANOVA test and others where applicable. Level of significance (p value) was set at 0.05 and confidence interval at 95%.

Results:
Socio-demographic data

Table-I

Shows the age group of study population (N=37)

Age group	Total N (%)	Mean ± SD (Range)
13-15 years	7(18.9)	
16-20 years	24 (64.9)	18.7±4.0 years
21-25 years	3 (8.10)	(13-30 years)
26-30 years	3(8.10)	
Total	37 (100.0)	

Age distributions 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 female.

Clinical data

Table-II

Shows age at onset of acne vulgaris (N=37).

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

Distribution of patients by age at the onset of acne vulgaris are presented in Table-2. The lowest age 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.

Occupation:

Occupation of study population is illustrated in Figure-1. More than three quarter of the patients evaluated was students (81.1 %).

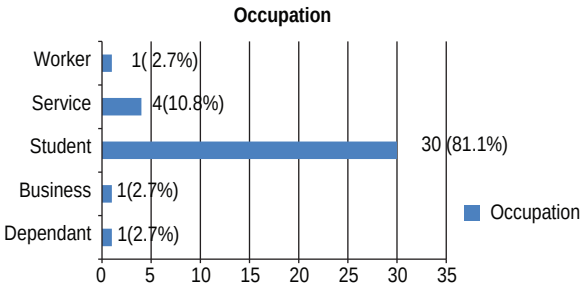

Fig.-1: *Occupation of the study patients with acne vulgaris.*

Site of involvement:

Table-III

Shows site of involvement (N=37).

Site of acne involvement	N	Present (%)
Cheek	37	(100.0)
Chin	34	(91.9)
Forehead	34	(91.9)
Nose	19	(51.4)
Back of the Neck	2	(5.4)
Shoulder	5	(13.5)
Chest	3	(8.1)
Upper back	9	(24.3)

Most of the patients had cheek, chin and forehead involvement and only few patients had upper back, shoulder, chest and back of the neck involvement.

Reduction in the number of acne:

Table-IV

Reduction in the number of different types of acne lesions in response to acne regimens.

Types of acne lesions	Number of lesion Mean±SD			
	Week O	Week 4	Week 8	Week 12
Comedones	41.0±18.0	16.8±9.8	4.6±5.1	0.6±l.5
Papular lesion	30.7±10.9	20.2±9.1	9.8±5.6	1.841.6
Pustular lesion	22.1±10.9	7.65±5.0	0.8±1.3	0.240.5
Cystic lesion	4.1±5.3	4.1±5.3	3.544.8	3.344.7

At the end of first 4 weeks there were significant reduction in the number of comedones and this reduction remained significant throughout the treatment period. Similarly popular acne significantly reduced in number throughout the treatment period. Treatment regimen also reduced the number of pustular acne in same fashion. Cystic lesions showed no improvement throughout the treatment period.

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 lesions throughout the treatment period but cystic lesion showed no significant improvement.

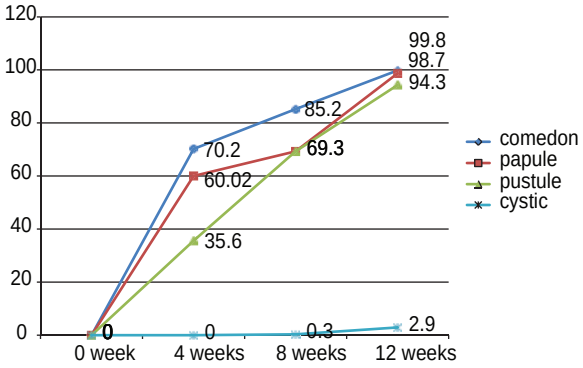

Fig.-2: *Percent reduction in the number of different types of acne lesion in response to study regimen*

Michaelsson Acne Severity Index:

Percent reduction of Michaelsson Acne Severity Index in response to study regimens is illustrated in Figure-3. The study regimens showed highly significant percent reduction of Michaelsson Acne Severity Index throughout the treatment period.

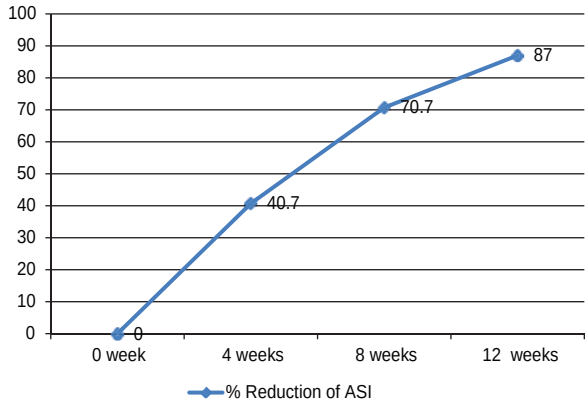

Fig.-3: *Changes in the Michaelsson Acne Severity Index and its percent reduction during treatment*

Overall assessment:

Presented in Figure -4, investigator's evaluation carried on 37 patients who have completed the study with compliance. Among them acne lesion cleared in 22% cases, excellent improvement observed in 65% cases and 13% showed good response.

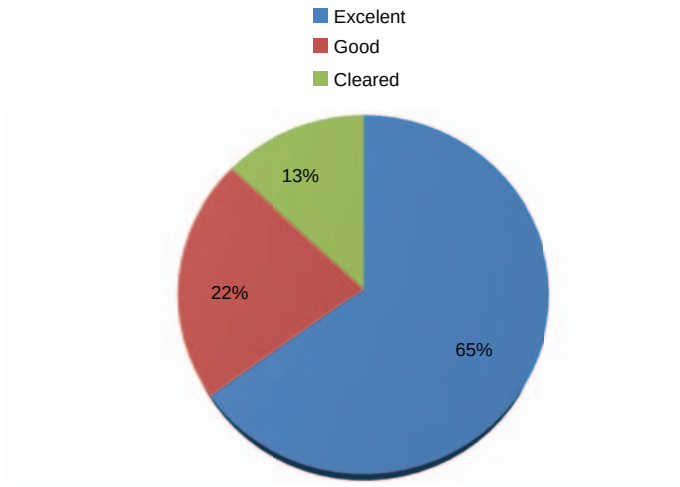

Fig.-4: *Overall evaluation of acne vulgaris at the end of 12 weeks treatment with study regimen.*

Adverse effect:

Adverse effect of two drug regimens observed during treatment period illustrated in Figure-S.Of 32 patients 8 (25%) complained of heart burn during treatment period, 5 patients (15.6%) reported abdominal cramp, 4 patients (12.5%) reported tinnitus and 2 reported headache. 9 patients (6.7%) complained of mild binning sensation (irritation) on facial skin.

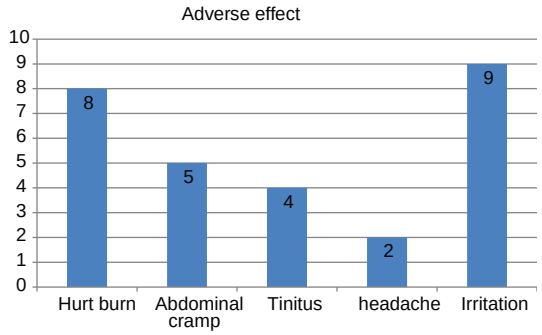

Fig.-5: *Adverse effects of study regimens observed during treatment period.*

Discussion:

Acne vulgaris is a chronic inflammatory disease typically begins at puberty and primarily a disease of adolescent with 85%of all teenagers being affected to some degree. 1 Due to multifactorial pathogenesis of acne vulgaris, combination therapy provides the opportunity to get the target multiple pathogenic causes of acne.[10] Combination therapy utilizing agents with complementary mechanisms, such as, topical benzoyl peroxide and oral antibiotics, is frequently used in the management of the disorder.[10,11,12]

As a first line systemic treatment in adolescence most authors recommend the use of systemic antibiotics, including tetracycline , doxycycline, minocycline and erythromycin.[13,14] Recently, azithromycin has been added to this list[814] Comparative clinical trials have shown that the tolerability profile of azithromycin is superior to that of erythromycin and doxycycline. 80Moreover tetracycline can cause both mucocutaneous and systemic adverse effects.[6]

In this study the concomitant use of oral azithromycin pulse therapy & daily topical benzoyl peroxide in the treatment of acne vulgaris is assessed. A total 37 patients with acne vulgaris those fulfilled the inclusions criteria were enrolled. Azithromycin 500 mg orally once daily during the first three days of 7 days cycle & topical benzoyl peroxide (4%) at night.

Patients were clinically evaluated at 4 weekly intervals. At baseline and all follow up visits, all parameters were examined & graded by using Michaelsson Acne Severity Index. Both the total scores & number of each type of acne lesions were compared to baseline scores & five comparative categories were generated i.e. cleared, excellent, moderate, poor improvement & worse.

The mean age of patients was 15 to 35 years. More than 75 % was female & most of the patients were students.

At the end of 4 weeks treatment 99.8% of comedones, 98.7% papular lesions & 94.3% pustular lesions were cleared. Only 2.9% cystic lesions responded to the regimens.

Percent reduction of Michaelsson Acne Severity Index was 40.7% after 4 weeks of treatment, 70.7% after 8 weeks & 87% after 12 weeks of treatment, which was statistically highly significant. Overall assessment revealed acne lesions cleared in 22% cases, excellent improvement observed in 65% & 13% showed good response.

The safety &efficacy of oral azithromycin and topical benzoyl peroxide in the treatment of acne have been reviewed and articles on clinical trials published in many Western Journals.[16,16,17,18,]

In this 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 Michaelsson Acne Severity Index. These findings are superior to those observed in different studies by using azithromycin[16,16] & topical benzoyl peroxide alone.

During the period of study, patients develop various side-effects such as heartburn, abdominal cramp and mild irritation of facial skin. None of these reactions were severe and most occurred within the first weeks of initiation of therapy and was observed to resolve with continued use of the drugs.

So, azithromycin pulse therapy and topical benzoyl peroxide is indeed effective and safe in the treatment of acne vulgaris.

Conclusion:

This study revealed that combination regimen of azithromycin and benzoyl peroxide (4%) 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 outcomes assess the relapse rate in clinical practice through improve compliance.

References:

1. Burton JL, Cunliffle WJ, Stafford L et al. The prevalence of acne vulgaris in adolescence. Br J Dermatol 1971; 85: 119-26.
2. Webster GF The pathophysiology of acne. Cutis. 2005; 76 (2suppl): 4-7
3. Riddle CC, Amin K, Schweiger ES, A Review of Azithromycin for the Treatment of Acne Vulgaris Cosmetic Dermatology, 2007; 20 (5); 299-302.
4. Ross JI, Snelling AM, Carnegie E, et al. Antibiotic- resistant acne: lessons from Europe. Br J Dermatol. 2003; 148: 467-478.
5. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a global alliance to improve outcomes in acne. J Am Acad Dermatol 2003, 49(Suppl l):Sl-37.
6. Kus S, Yucelten D, Aytug A.Comparison of efficacy of azithromycin vs.doxycycline inm the treatment of acne vulgaris. Clin Exp Dermatol. 2005 May; 30(3):215-20.
7. Ross JI Snelling AM,Camegie E,et al. Antibiotic-resistant acne: lessons from Europe. Br J Dermatol 2003,148: 467-478.
8. Fernandez-Obregon AC. Azithromycin for the treatment of acne. Int J dermatol. 2000 Jan; 39(l):45-50.
9. Michaelsson G, Juhlin L, Vahlquist A. Effect of oral zinc and Vitamin A in acne. Arch Dermatol 19997; 113: 31-36.1
10. Bergfeld WF. Topical retinoids in the management of acne vulgaris. J Drug Dev Clin Practl996;8: 151-160.
11. Pawin H, Beylot C, Chivot M et al. Physiopathology of acne vulgaris : recent data, new understanding of the treatments. Eur J Dermatol 2004; 14: 4-12.
12. Leyden JJ, McGinley KJ, Cavalieri S, et al. Propionibacterium Aenes resistance to antibiotic in acne patients. J Am Acad Dermatol 8(l):41-5(1983 Jan).
13. Tan AW, Tan HH. Acne vulgaris: a review of antibiotic therapy. Expert Opin Pharmacother. 2005 Mar; 6(3): 406-18.
14. Caputo R, Barbareschi M, Veraldi S. Azithromycin: a new drug for systemic treatment of inflammatory acneic lesions. G Ital Dermatol venereal. 2003; 138: 327-331.
15. Guerber F, Gribisic-Greblo H, Kastelem M, et al. Azithromycin compared with minocycline in the treatment of acne comedonica and papulo-pustulosa. J chemother 1998; 10; 269-273.
16. Adolfo C, Femandez-Obregon, Azithromycin for the treatment of acne. Int.J Dermatol 2003; 39 (I): 45.
17. Kapandia N, Talib a. Acne treated successfully with azithromycin. Int.J Dermatol 2004; 43 (10). 766.
18. Singhi MK, Ghiya BC, Dhabhai RK. Comparison of oral azithromycin pulse with daily doxycycline in the treatment of acne vulgaris. Ind. J Dermatol Venereol and Leprol 2003; 69(4): 274-276.