

Comparative Evaluation of Oral Azithromycin and Doxycycline in Patients with Acne Vulgaris

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Abstract

Background: Acne vulgaris is a common chronic inflammatory disorder of the pilosebaceous unit affecting a large proportion of adolescents and young adults. Systemic antibiotics remain an important component in the management of moderate inflammatory acne due to their antimicrobial and anti-inflammatory properties. Among the commonly prescribed antibiotics, doxycycline and azithromycin are widely used in clinical practice. However, comparative data regarding their efficacy and safety in Indian patients remain limited. The objective is to evaluate the age-specific efficacy of oral azithromycin in mild and moderate acne vulgaris. To evaluate the age-specific efficacy of oral doxycycline in mild and moderate acne vulgaris. **Subjects and Methods:** A prospective randomized parallel-group study was conducted in the Department of Pharmacology at Saraswathi Institute of Medical Sciences, Hapur, from March 2024 to February 2026. A total of 160 patients aged 15–25 years with mild to moderate acne vulgaris were included. Patients were divided into two groups based on disease severity (mild and moderate acne). Each group was further subdivided into four subgroups according to age and systemic antibiotic therapy. Subgroups receiving doxycycline were treated with oral doxycycline 100 mg once daily, while those receiving azithromycin were given oral azithromycin 500 mg three times weekly for six weeks. All patients received topical benzoyl peroxide 5% as adjunct therapy. Acne severity scores were recorded at baseline and at weekly follow-up visits for six weeks. Data were analysed using repeated measures ANOVA and independent sample t-test. **Results:** Both doxycycline and azithromycin produced a significant reduction in acne severity scores across all study subgroups over the six-week treatment period ($p < 0.001$). Doxycycline demonstrated slightly faster early improvement in inflammatory lesion counts, whereas azithromycin showed comparable efficacy by the end of the treatment period. Both drugs were well tolerated, and no serious adverse effects were reported. **Conclusion:** Both oral doxycycline and oral azithromycin are effective and safe options for the management of mild to moderate acne vulgaris. While doxycycline may produce a faster initial response, azithromycin pulse therapy provides comparable overall efficacy with good tolerability and may serve as a suitable alternative in selected patients.

Keywords: Acne vulgaris, Azithromycin, Doxycycline, Systemic antibiotics, Acne severity score.

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Introduction

Acne vulgaris is a chronic inflammatory skin disorder that affects the pilosebaceous unit. The disease typically manifests as papules, pustules, or nodules on the face, but it can also affect the back, upper arms, and upper body. The acne vulgaris etiology includes the interplay of many variables that ultimately result in developing of its main lesion, known as a "comedo". The condition acne vulgaris is most typically seen in adolescence, it may afflict people of all ages. The level of seriousness of this illness may vary from a moderate appearance with only some comedones to the more severe types marked by disfiguring inflammatory symptoms, which may contribute to excessive pigmentation, scarring, and negative cognitive repercussions.^[1,2,3]

Acne vulgaris is widespread among teenagers and young

adults. Their prevalence levels are predicted to vary between 35% and over 90% across adolescents.^[4] This disease's normal progression can begin as early as ages 7-12 (preadolescent acne) and end in the third decade of life. Acne may, however, occasionally persist into adulthood or even manifest for the first time during adulthood. Boys experience adolescent acne more frequently than girls do. Females are more likely than guys to suffer from postadolescent acne. It affects urban people more than rural populations. Around twenty percent of those impacted have severe acne, which leaves scarring. According to some data, the severity and frequency of acne vulgaris can differ among various ethnic and racial populations. Asians and Africans have a higher risk of developing serious acne. A mild form of acne is more frequent among the White population. In general, those having darker complexion likely to acquire excessive pigmentation.^[5] When normal levels of circulating

dehydroepiandrosterone are present during adolescence, it is frequently caused by the bacterial species *Cutibacterium acnes*. This common skin condition can result in both non-inflammatory and inflammatory lesions.

Acne vulgaris has several forms, including:

- Acne conglobata: In young men, acne conglobata is a rare but severe form of nodulocystic acne. On the face, shoulders, back, chest, upper arms, buttocks, and thighs, it frequently appears as sensitive, deforming comedones, cysts, inflammatory nodules, and deep burrowing abscesses. Usually, there are no systemic symptoms.
- Acne fulminans, sometimes referred to as acne maligna, is a rare skin condition that results in acute, severe, hemorrhagic, and ulcerative acne. Fever and polyarthritides are examples of systemic symptoms that may or may not be connected to it. Test issues and bone lesions may result from acne fulminans.
- Young women with underlying psychological conditions frequently experience acne excoriée. It appears as mild acne, including comedones that are overly removed and excoriated, leaving scars.
- Due to increased androgens produced by the immature adrenal gland in girls and the immature adrenal gland and testes in boys, infantile acne typically begins between three and six months of age. A child's androgen levels returned to normal by the time they were one or two years old, and their acne improved as a result.

Acne vulgaris can be connected with specific uncommon disorders, such as:

- Inflammatory arthritis or osteitis, particularly in the anterior chest wall, is a characteristic of SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis).
- Acne, pyoderma gangrenosum, and sterile pyogenic arthritis are all part of the PAPA syndrome.

This study was conducted to assess the efficacy of a low dosage oral clindamycin and azithromycin in patients of acne vulgaris.

Subjects and Methods

Study design and setting

A prospective comparative parallel-group study was conducted from March 2024 to February 2026 in the Department of Pharmacology, Saraswathi Institute of Medical Sciences, Hapur. The study protocol was approved by the Institutional Scientific Review Board and Ethics Committee.

Ethical considerations

Written informed consent was obtained from all patients (or their guardians) prior to enrolment in the trial.

Source of data

Patients diagnosed with Acne Vulgaris, recruited from the outpatient department of Dermatology at Saraswathi Institute of Medical Sciences, NH-24, Pilkhuwa, Hapur, Uttar Pradesh, over a period of 24 months.

Sample size and basis of calculation

The sample size for the study was determined using the statistical formula:

$$n = Z^2 PQ / E^2$$

Where:

- P (Prevalence) = 73.3% (0.733), derived from a previous study by Collier CN et al.^[6]
- Q = 1 – P = 0.267
- Z (Score) = 1.96 at 95% Confidence Interval
- E (Allowable error) = 10% (0.10)

Substituting the values:

$$n = (1.96)^2 \times 0.733 \times 0.267 / (0.10)^2$$

$$n = 75.15$$

The calculated sample size was 75.15.

To improve statistical power and allow equal distribution between treatment groups, the sample size was rounded to 80 participants per group.

Criteria for selection

A total of 160 patients with mild to moderate acne vulgaris were enrolled. The inclusion and exclusion criteria were as follows:

Inclusion Criteria:

1. Individuals diagnosed clinically with mild to moderate acne vulgaris.
2. Lesions present on the face (cheeks, forehead, chin, nose) and/or neck (above the collarbone).
3. Both male and female patients
4. Age 15-25 years

Exclusion Criteria

1. Patients with severe acne vulgaris (predominantly cysts, abscesses, widespread scarring).
2. Patients aged below 15 or above 25 years.
3. Patient with known hypersensitivity to tetracyclines, macrolides, or benzoyl peroxide.
4. Patients suffering from comorbidities like diabetes mellitus, hypertension and women with pregnancy, lactation, and not on effective contraception.

Study Groups and Randomization:

Patients were first stratified into two major groups based on clinical severity:

- **Group 1 (Mild Acne Vulgaris):** 80 patients.
- **Group 2 (Moderate Acne Vulgaris):** 80 patients.

Each severity group was then further subdivided into four subgroups (A, B, C, D; n=20 each) based on age and the assigned systemic antibiotic, resulting in a total of eight subgroups.

Severity Group	Subgroup	Age Range (Years)	Systemic Antibiotic (Oral)	Topical Adjunct
Group 1 (Mild)	A	15 – 18	Doxycycline	Benzoyl Peroxide 5%
	B	18 – 25	Doxycycline	Benzoyl Peroxide 5%
	C	15 – 18	Azithromycin	Benzoyl Peroxide 5%
	D	18 – 25	Azithromycin	Benzoyl Peroxide 5%
Group 2 (Moderate)	A	15 – 18	Doxycycline	Benzoyl Peroxide 5%
	B	18 – 25	Doxycycline	Benzoyl Peroxide 5%

C	15 – 18	Azithromycin	Benzoyl Peroxide 5%
D	18 – 25	Azithromycin	Benzoyl Peroxide 5%

Acne severity grading:

Acne severity was classified at baseline using a clinical grading system based on lesion morphology and inflammatory lesion count:

- Grade 1 (Mild): Comedones and occasional papules.
- Grade 2 (Moderate): Papules, comedones, and few pustules.
- Grade 3 (Moderately Severe): Predominant pustules, nodules, and abscesses.
- Grade 4 (Severe): Mainly cysts, abscesses, and widespread scarring.

Patients with Grades 1 and 2 were included as Mild and Moderate groups, respectively.

Therapeutic Intervention: All patients received a standard adjunct therapy of topical 5% Benzoyl Peroxide, applied once daily at bedtime for the entire 6-week study period. In addition to topical therapy, they received two oral antibiotic regimens based on their subgroup:

- Doxycycline Subgroups (A & B): Oral Doxycycline 100 mg, once daily in the morning after breakfast, for 6 weeks.
- Azithromycin Subgroups (C & D): Oral Azithromycin 500 mg, administered three times per week (e.g., Monday, Wednesday, Friday) in the morning after breakfast, for 6 weeks.

No other anti-acne treatments were permitted during the study.

Clinical Assessments and Efficacy Measures:

Patients were evaluated at baseline (Visit 0, Week 0) and subsequently at the end of Weeks 1, 2, 3, 4, 5, and 6 (Visits 1-6). At each visit, the following were recorded:

- Acne Severity Score: A quantitative lesion count (comedones, papules, pustules, nodules) was performed on standardized facial areas.
- Safety Evaluation: Patients were questioned about any adverse events (e.g., gastrointestinal upset, photosensitivity, headache, skin irritation).

Statistical Analysis

Data were compiled in Microsoft Excel and analyzed using SPSS software (Version 29.0). Descriptive statistics were presented as mean $\pm$ standard deviation (SD) for continuous variables and as proportions/percentages for categorical variables.

- Primary Efficacy Analysis: Intragroup changes in acne severity scores across the 7 visits were analyzed using

Repeated Measures Analysis of Variance (ANOVA).

- Comparative Endpoint Analysis: The final (Week 6) acne scores between Doxycycline and Azithromycin subgroups within the same age and severity category were compared using an Independent Samples t-test. A p-value of less than 0.05 was considered statistically significant.

Results

Study Population and Demographic Profile

The results of the study conducted to evaluate the safety and efficacy of oral azithromycin administered at a dose of 500 mg three times per week for a duration of six weeks, in comparison with oral doxycycline 100 mg once daily for six weeks, are presented and analysed. All patients additionally received topical benzoyl peroxide 5% as adjunct therapy.

A total of 160 patients with acne vulgaris were enrolled in the study and divided into two major groups based on clinical severity: Group 1 (Mild Acne Vulgaris, n = 80) and Group 2 (Moderate Acne Vulgaris, n = 80).

Each group was further subdivided into four subgroups (A–D) according to age and systemic antibiotic therapy. Subgroups A and B received oral doxycycline, while subgroups C and D received oral azithromycin. Age-wise stratification included patients aged 15–18 years and 18–25 years.

All patients in every subgroup received topical benzoyl peroxide as adjunct therapy. Clinical assessments were recorded at baseline and during follow-up visits from Visit 0 to Visit 6.

- Group 1 (Mild Acne Vulgaris): 80 patients
- Group 2 (Moderate Acne Vulgaris): 80 patients

Each of these major groups was further stratified by age and therapeutic intervention, resulting in four distinct subgroups per severity group to facilitate a granular analysis. Treatment efficacy was evaluated using acne severity scores recorded at each visit. Intragroup changes in acne severity scores over successive visits were analysed using repeated measures ANOVA. Intergroup comparisons between doxycycline and azithromycin at the end of six weeks (Visit 6) were performed using an independent samples t-test. A p-value of <0.05 was considered statistically significant.

The distribution and baseline demographic characteristics of the study population are summarized in [Table 1.1].

Table 1: ?

Characteristic	Group 1: Mild Acne (n=80)	Group 2: Moderate Acne (n=80)
Age (years)		
- Mean $\pm$ SD	19.8 $\pm$ 3.1	20.1 $\pm$ 3.3
- Range	15-25	15-25
Gender, n (%)		
- Male	42 (52.5%)	44 (55.0%)
- Female	38 (47.5%)	36 (45.0%)
Subgroup Distribution		
- Subgroup A (15-18Y, on tab doxycycline)	20	20
- Subgroup B (18-25Y, on tab doxycycline)	20	20

- Subgroup C (15-18Y, on tab azithromycin)	20	20
- Subgroup D (18-25Y, on tab azithromycin)	20	20
Baseline Acne Score, Mean $\pm$ SD		
- Subgroup A	9.45 $\pm$ 0.51	13.50 $\pm$ 1.15
- Subgroup B	9.55 $\pm$ 0.51	13.50 $\pm$ 1.15
- Subgroup C	9.45 $\pm$ 0.51	14.05 $\pm$ 0.82
- Subgroup D	9.65 $\pm$ 0.59	13.55 $\pm$ 1.14

[Table 1.1] Baseline demographic and clinical characteristics of the study population, comparing mild acne and moderate acne groups before initiation of treatment.

Therapeutic Regimens and Adherence

All enrolled patients completed the full 6-week study protocol, resulting in excellent adherence with no loss to follow-up. The specific treatment regimens were as follows:

- Doxycycline Subgroups (A & B): Received oral doxycycline 100 mg once daily post-breakfast.
- Azithromycin Subgroups (C & D): Received oral azithromycin 500 mg three times per week (e.g., Monday, Wednesday, and Friday) post-breakfast.

All 160 patients concurrently applied topical 5% benzoyl peroxide once daily in the evening as a standard adjunct therapy. No other topical or systemic acne treatments were permitted during the study period. Pill counts and patient diaries confirmed excellent adherence to the prescribed protocols in all subgroups.

Response in Mild Acne Vulgaris (Group 1)

80 patients with mild acne vulgaris were included in Group 1 and were equally distributed into four subgroups (A–D) based on age and systemic antibiotic therapy. Each subgroup consisted of 20 patients and was followed for a total duration of six weeks, with acne severity scores recorded at baseline (Visit 0) and at subsequent follow-up visits up to Visit 6.

All four subgroups demonstrated a progressive reduction in mean acne severity scores over the treatment period, indicating a favourable response to therapy. Statistical evaluation using repeated measures ANOVA revealed a significant decrease in acne scores across visits within each subgroup ($p < 0.001$), confirming the effectiveness of both doxycycline and azithromycin in the management of mild acne vulgaris.

The longitudinal changes in mean acne severity scores for doxycycline and azithromycin in patients with mild acne vulgaris are illustrated in [Figure 1.1] for the 15–18year age group and [Figure 5.2] for the 18–25year age group.

Table 2: ?

Subgroup	Baseline (V0)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 (Final)	p-value (ANOVA)
B (18-25, Doxy)	9.55 $\pm$ 0.51	8.25 $\pm$ 0.91	7.80 $\pm$ 0.89	7.70 $\pm$ 0.97	7.10 $\pm$ 0.85	7.40 $\pm$ 0.50	7.05 $\pm$ 0.99	<0.001

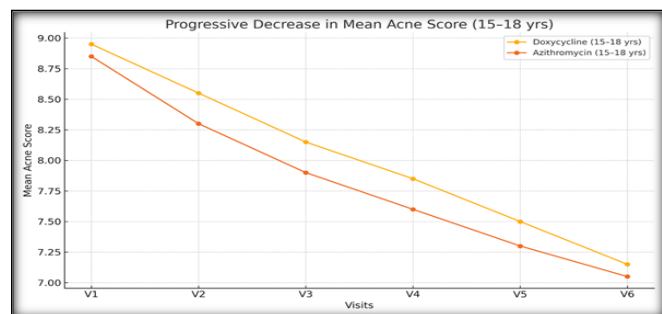


Figure 1.1: Mean Acne Severity Scores over Time for Doxycycline and Azithromycin in Mild Acne (15-18 years)

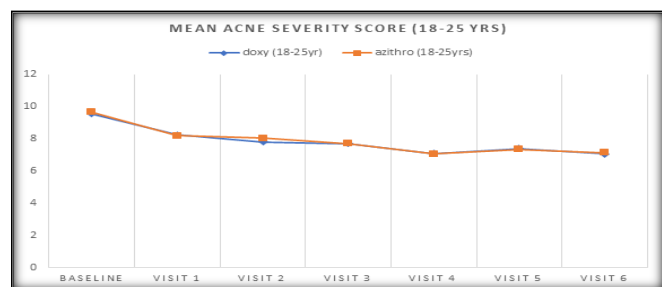


Figure 1.2: Mean Acne Severity Scores over Time for Doxycycline and Azithromycin in Mild Acne (18-25 years)

Table 3: ?

Subgroup	Baseline (V0)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	p-value
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							(Final)	(ANOVA)
C (15-18, Azithro)	9.45 ± 0.51	8.35 ± 0.81	8.00 ± 1.07	7.80 ± 1.0	7.30 ± 1.03	7.35 ± 0.74	7.25 ± 1.02	<0.001

Subgroup D: Mild Acne Vulgaris (18–25 years, Oral Azithromycin)

In Subgroup D, the baseline mean acne severity score was 9.65 ± 0.59 , which reduced progressively to 7.15 ± 0.88 at

the end of six weeks. Statistical analysis showed a significant reduction in acne severity across visits ($p < 0.001$), indicating a favourable response to azithromycin in the older mild acne cohort. Table 1.5 Mild Acne (18–25 years, Azithromycin).

Table 4: ?

Subgroup	Baseline (V0)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 (Final)	p-value (ANOVA)
D (18-25, Azithro)	9.65 ± 0.59	8.20 ± 0.89	8.05 ± 1.05	7.70 ± 0.92	7.05 ± 0.82	7.35 ± 0.58	7.15 ± 0.88	<0.001

Repeated Measures ANOVA Results for Mild Acne:

Repeated measures ANOVA demonstrated a statistically significant reduction in mean acne severity scores across successive visits in all four mild acne subgroups ($p < 0.001$ for each subgroup), confirming the effectiveness of both doxycycline and azithromycin over the six-week treatment period.

5.3.2. Response in Moderate Acne Vulgaris (Group 2)

The temporal trends in mean acne severity scores for patients with moderate acne vulgaris treated with doxycycline and azithromycin are depicted in Figure 1.3 (15–18 years) and Figure 1.4 (18–25 years).

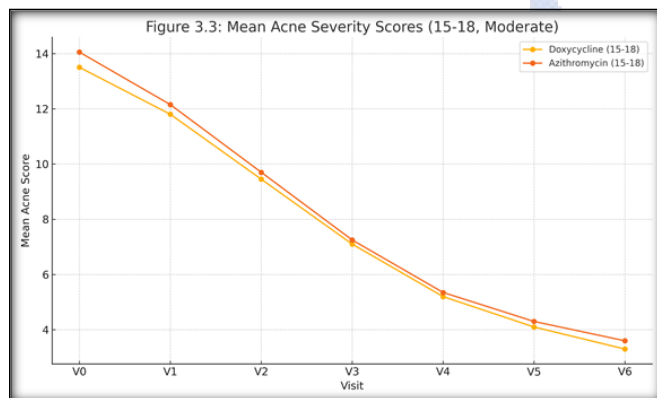


Figure 1.3: Mean Acne Severity Scores over Time for Doxycycline and Azithromycin in Moderate Acne (15-18 years)

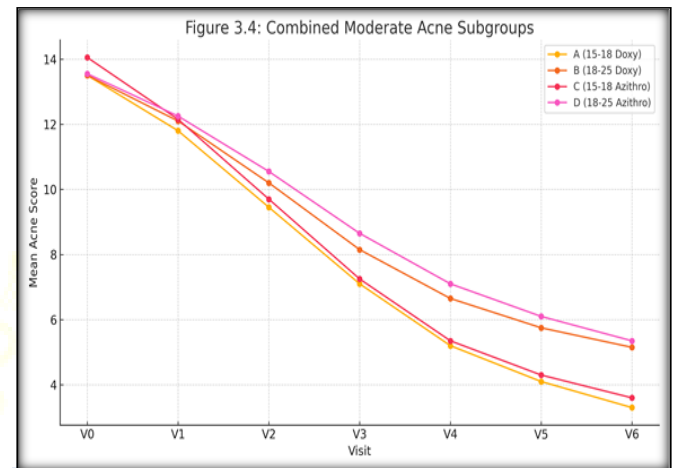


Figure 1.4: Mean Acne Severity Scores over Time for Doxycycline and Azithromycin in Moderate Acne (15-25 years)

Subgroup A: Moderate Acne Vulgaris (15–18 years, Oral Doxycycline)

In Subgroup A, the baseline mean acne severity score was 13.50 ± 1.15 . A gradual decline in mean scores was observed over successive visits, reaching 3.30 ± 0.47 at the end of six weeks. Repeated measures ANOVA demonstrated a statistically significant reduction in acne severity across visits ($p < 0.001$), indicating sustained clinical improvement with oral doxycycline therapy in this age group. Table 1.6 Moderate Acne (15–18 years, Doxycycline).

Table 5: ?

Subgroup	Baseline (V0)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 (Final)	p-value (ANOVA)
A (15-18, Doxy)	13.50 ± 1.15	12.50 ± 1.05	10.75 ± 0.85	8.50 ± 0.51	6.50 ± 0.51	4.50 ± 0.51	3.30 ± 0.47	<0.001

Subgroup B: Moderate Acne Vulgaris (18–25 years, Oral Doxycycline)

Patients in Subgroup B showed a similar pattern of improvement. The mean acne severity score decreased from 13.50 ± 1.15 at baseline to 5.15 ± 0.81 at Visit 6. The

reduction in scores over time was statistically significant on repeated measures ANOVA ($p < 0.001$), demonstrating effective response to doxycycline among older patients with mild acne vulgaris. Table 1.7 Moderate Acne (18–25 years, Doxycycline).

Table 6: ?

Subgroup	Baseline (V0)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 (Final)	p-value (ANOVA)
B (18-25, Doxy)	13.50 ± 1.15	13.50 ± 1.15	12.10 ± 1.33	10.55 ± 1.19	8.65 ± 0.988	7.05 ± 0.82	5.15 ± 0.81	<0.001

Subgroup C: Moderate Acne Vulgaris (15–18 years, Oral Azithromycin)

Subgroup C exhibited a consistent reduction in acne severity throughout the study period. The mean score declined from 14.05 ± 0.83 at baseline to 3.60 ± 0.50 at the final visit.

Repeated measures ANOVA confirmed that the decrease in acne severity was statistically significant ($p < 0.001$), reflecting effective disease control with azithromycin in adolescent patients. Table 1.8 Moderate Acne (15–18 years, Azithromycin).

Table 7: ?

Subgroup	Baseline (V0)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 (Final)	p-value (ANOVA)
C (15-18, Azithro)	14.05 ± 0.82	13.00 ± 0.85	11.00 ± 0.85	9.15 ± 0.87	7.30 ± 0.65	5.60 ± 0.59	3.60 ± 0.50	<0.001

Subgroup D: Moderate Acne Vulgaris (18–25 years, Oral Azithromycin)

In Subgroup D, the baseline mean acne severity score was 13.55 ± 1.14 , which reduced progressively to 5.35 ± 0.74 at the end of six weeks. Statistical analysis showed a significant

reduction in acne severity across visits ($p < 0.001$), indicating a favourable response to azithromycin in the older mild acne cohort. Table 1.9 Moderate Acne (18–25 years, Azithromycin).

Table 8: ?

Subgroup	Baseline (V0)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 (Final)	p-value (ANOVA)
D (18-25, Azithro)	13.55 ± 1.14	12.60 ± 1.27	12.10 ± 1.41	10.40 ± 1.27	8.85 ± 1.82	7.25 ± 0.91	5.35 ± 0.74	<0.001

The reduction in acne severity was more pronounced in the moderate acne group, reflecting the greater room for improvement from a higher baseline.

Repeated Measures ANOVA Results for Moderate Acne: Repeated measures ANOVA revealed a highly significant reduction in acne severity scores across follow-up visits in all moderate acne subgroups ($p < 0.001$). The reduction was more pronounced due to higher baseline severity, indicating substantial clinical improvement with both treatment

regimens.

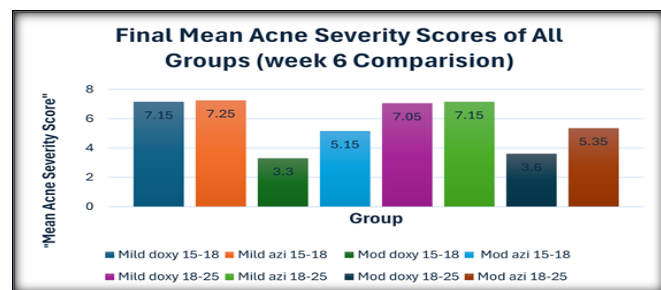
5.4. Final Endpoint Comparative Analysis

To directly compare the efficacy of the two antibiotics at the completion of therapy, an independent samples t-test was conducted on the final (Visit 6) acne scores for each age and severity subgroup. The intergroup comparison of final (Visit 6) acne severity scores using an independent samples t-test is summarized in [Table 1.10].

Table 5.10: Statistical Comparison of Efficacy at Week 6 (Independent t-test)

Severity	Age Group (years)	Doxycycline (Mean $\pm$ SD)	Azithromycin (Mean $\pm$ SD)	Mean Difference	95% Confidence Interval	t-value	p-value	Interpretation
Mild	15–18	7.15 ± 0.93	7.25 ± 1.02	-0.10	(-0.71 to 0.51)	-0.32	0.748	Not Significant
Mild	18–25	7.05 ± 0.99	7.15 ± 0.88	-0.10	(-0.69 to 0.49)	-0.33	0.738	Not Significant
Moderate	15–18	3.30 ± 0.47	5.15 ± 0.81	-1.85	(-2.27 to -1.43)	-8.81	<0.000001	Highly Significant
Moderate	18–25	3.60 ± 0.50	5.35 ± 0.75	-1.75	(-2.18 to -1.32)	-8.00	<0.001	Highly Significant

The results of this final comparison are powerfully visualized in the bar chart below [Figure 1.5], which succinctly summarizes the key finding of the study.

**Figure 1.5: Final Mean Acne Severity Scores at Week 6 for All Treatment Groups**

Bar chart comparing the final mean acne severity scores for

all subgroups. The bars for moderate acne clearly show that both doxycycline groups achieved significantly lower final scores compared to their respective azithromycin groups, while the bars for mild acne are nearly identical between treatments.

Comparative Endpoint Analysis (Week 6):**Mild Acne**

An intergroup comparison between oral doxycycline and oral azithromycin was performed at the end of six weeks using an independent samples t-test within each age subgroup.

Among patients aged 15–18 years, the mean acne severity score at Visit 6 was 7.15 ± 0.93 in the doxycycline group and 7.25 ± 1.02 in the azithromycin group. The difference between the two groups was not statistically significant ($p > 0.05$).

Similarly, among patients aged 18–25 years, the mean acne severity score at Visit 6 was 7.25 ± 1.02 in the doxycycline

group and 7.15 ± 0.88 in the azithromycin group. The difference between groups was not statistically significant ($p > 0.05$).

Moderate Acne

Among patients aged 15–18 years, the mean acne severity score at Visit 6 was 3.30 ± 0.47 in the doxycycline group and 5.15 ± 0.81 in the azithromycin group. The difference between groups was statistically significant ($p < 0.001$).

Similarly, among patients aged 18–25 years, the mean acne severity score at Visit 6 was 3.60 ± 0.50 in the doxycycline group and 5.35 ± 0.75 in the azithromycin group. The difference between groups was statistically significant ($p < 0.001$).

Analysis of Trend Patterns and Trajectory of Response

A deeper analysis of the within-subject contrasts from the Repeated Measures ANOVA provides insight into the pattern of improvement.

- Doxycycline in Moderate Acne: The highly significant linear trends ($F > 800$) indicate a steady, relentless decline in acne scores throughout the 6 weeks, as seen in Figure 3.4. The therapy demonstrates consistent and cumulative efficacy.
- Azithromycin in Moderate Acne: Azithromycin subgroups demonstrated a slightly faster initial reduction in mean acne severity scores during the early visits, whereas final scores at Visit 6 were comparable between treatment groups.

Tolerability and Safety Profile

Both oral antibiotic regimens were well-tolerated. No serious adverse events were reported during the study period. Minor, self-limiting side effects were reported in a small number of patients:

- Doxycycline groups: 3 patients reported transient gastrointestinal upset (nausea), and 2 patients reported mild photosensitivity, which was managed with sunscreen use.
- Azithromycin groups: 2 patients reported mild, transient abdominal discomfort.

There were no dropouts due to adverse effects. The combination with topical benzoyl peroxide did not lead to any significant cutaneous irritation reported beyond mild, initial dryness.

The distribution of adverse events observed during the study period is summarized in [Table 1.11]

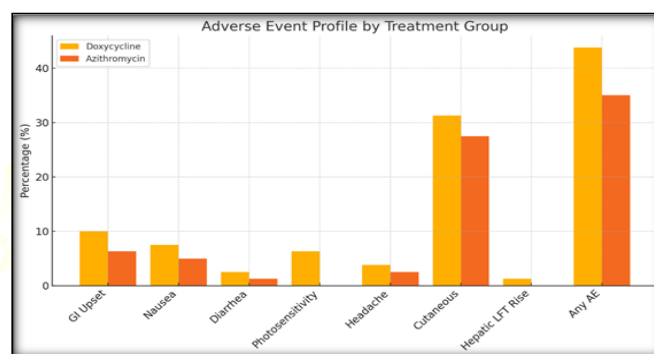


Table 1.11: Adverse Event Profile by Treatment Group (n, %)

Adverse Event	Doxycycline (n=80)	Azithromycin (n=80)
Gastrointestinal Upset	8 (10.0%)	5 (6.3%)
- Nausea	6 (7.5%)	4 (5.0%)
- Diarrhoea	2 (2.5%)	1 (1.3%)
Photosensitivity	5 (6.3%)	0
Headache	3 (3.8%)	2 (2.5%)
Cutaneous (Dryness/Redness) *	25 (31.3%)	22 (27.5%)
Hepatic (LFT Rise)	1 (1.3%)	0
Any Adverse Event	35 (43.8%)	28 (35.0%)
Discontinuation due to AE	0	0

[Table 1.11]: Adverse Event Profile by Treatment Group (n, %).

Discussion

Overview and Rationale of the Study

The present prospective, randomized study was designed to evaluate and compare the efficacy and safety of oral doxycycline and oral azithromycin, both used in combination with topical benzoyl peroxide 5%, in patients with mild and moderate acne vulgaris. The study further aimed to assess whether age and disease severity influence therapeutic outcomes, thereby providing a more granular understanding of treatment response in different patient subgroups.

A total of 160 patients were enrolled and stratified into mild and moderate acne groups, with further subdivision based on age (15–18 years and 18–25 years) and antibiotic regimen. This stratified design allowed for a comprehensive assessment of both longitudinal response patterns and final endpoint efficacy, offering valuable insights into the

comparative performance of these two commonly used systemic antibiotics.

The discussion that follows critically interprets the findings of this study in the context of existing literature, explores potential pharmacological and pathophysiological explanations for observed differences in response, evaluates safety and tolerability profiles, and highlights the clinical implications of these results for evidence-based acne management.

Interpretation of Treatment Response in Mild Acne Vulgaris

In the present study, both oral doxycycline and oral azithromycin demonstrated statistically significant and clinically meaningful improvement in patients with mild acne vulgaris across all age groups. A progressive reduction in mean acne severity scores was observed from baseline (Visit 0) to the end of therapy (Visit 6), confirming the effectiveness of systemic antibiotic therapy when used in conjunction with topical benzoyl peroxide.

Repeated measures ANOVA revealed a highly significant decline in acne severity scores ($p < 0.001$) across successive visits in all four mild acne subgroups, indicating sustained therapeutic response throughout the six-week treatment period [Table 3.2A–3.2D]. The temporal reduction in acne scores is clearly illustrated in [Figure 1.1 and Figure 1.2], which demonstrate a steady downward trend irrespective of the antibiotic used.

These findings are consistent with earlier reports that systemic antibiotics provide benefit in mild inflammatory acne primarily through their anti-inflammatory effects, in addition to antimicrobial activity. Tetracyclines such as doxycycline are known to inhibit neutrophil chemotaxis and suppress inflammatory mediators, contributing to lesion reduction.^[6,7]

Similarly, macrolides like azithromycin exhibit immunomodulatory properties that downregulate pro-inflammatory cytokines involved in acne pathogenesis.^[8,9]

At the final endpoint (Visit 6), no statistically significant difference was observed between doxycycline and azithromycin in either age subgroup with mild acne vulgaris [Table 3.4]. In patients aged 15–18 years, the mean acne severity scores were 7.15 ± 0.93 in the doxycycline group and 7.25 ± 1.02 in the azithromycin group ($p = 0.748$). Comparable results were also noted in the 18–25 year age group ($p = 0.738$). This confirms that both drugs achieve equivalent clinical outcomes in mild acne at six weeks.

Comparable efficacy between doxycycline and azithromycin in mild acne has been reported in multiple previous studies. Gruber et al,^[10] and Fernandez-Obregon,^[11] observed similar reductions in inflammatory lesion counts with both agents over short treatment durations. Indian studies by Singhi et al,^[12] and Ghafoor et al,^[13] also demonstrated no statistically significant difference in final acne severity between macrolides and tetracyclines in mild acne vulgaris. These findings support the results of the present study and reinforce the concept that in mild disease, therapeutic outcomes between different systemic antibiotics tend to converge.

A subtle trend toward faster initial improvement was observed in the azithromycin subgroups during early follow-up visits, as reflected by slightly lower mean acne scores from Visit 1 to Visit 3 [Figure 1.1 and Figure 1.2]. This early response may be attributed to the pharmacokinetic profile of azithromycin, which achieves high intracellular and tissue concentrations and exerts rapid immunomodulatory effects.^[14,15] However, this early advantage did not translate into superior final efficacy at Week 6.

From a clinical perspective, these results indicate that both doxycycline and azithromycin are equally effective options for the treatment of mild acne vulgaris. Therefore, drug selection may be guided by patient-specific factors such as dosing convenience, compliance, tolerability, and prior antibiotic exposure rather than differences in efficacy.

Interpretation of Treatment Response in Moderate Acne Vulgaris

In patients with moderate acne vulgaris, both oral doxycycline and oral azithromycin produced a statistically significant reduction in acne severity scores over the six-week treatment period. However, unlike the findings

observed in mild acne, a clear and clinically meaningful divergence in final treatment outcomes was evident between the two antibiotics in moderate disease.

Longitudinal Improvement in Moderate Acne

Repeated measures ANOVA demonstrated a highly significant decline in mean acne severity scores ($p < 0.001$) across successive visits in all four moderate acne subgroups, confirming that both treatment regimens were effective in reducing inflammatory lesion burden. The reduction was more pronounced than that observed in mild acne, reflecting the higher baseline severity and greater potential for clinical improvement.

The temporal trends illustrated in [Figure 1.3] (15–18 years) and [Figure 1.4] (18–25 years) show a steady decline in acne scores in both treatment arms. Notably, azithromycin subgroups demonstrated a relatively faster initial improvement during early visits, whereas doxycycline-treated patients exhibited a more consistent and sustained decline throughout the six-week period.

Endpoint Superiority of Doxycycline

At the final endpoint (Visit 6), doxycycline achieved significantly lower mean acne severity scores than azithromycin in both age subgroups with moderate acne vulgaris. Among patients aged 15–18 years, the mean final score was 3.30 ± 0.47 in the doxycycline group compared to 5.15 ± 0.81 in the azithromycin group ($p < 0.000001$). Similarly, in patients aged 18–25 years, doxycycline resulted in a mean final score of 3.60 ± 0.50 versus 5.35 ± 0.75 with azithromycin ($p < 0.001$) [Table 3.4]. These findings establish that while both antibiotics are effective in moderate acne, doxycycline provides superior end-of-treatment clearance, a distinction not observed in mild disease.

Comparison with Published Literature

The superior endpoint efficacy of doxycycline in moderate acne observed in the present study is in agreement with several previous reports. Tetracyclines have long been regarded as first-line systemic agents for moderate to moderately severe acne due to their sustained anti-inflammatory action and consistent suppression of *Cutibacterium* acnes.^[16,17]

Clinical trials and guideline-based reviews have demonstrated that doxycycline achieves greater reductions in inflammatory lesion counts compared to macrolides when treatment is continued for several weeks.^[18,19]

In contrast, although azithromycin has shown good efficacy in moderate acne, particularly during early treatment phases, multiple studies have reported that its pulsatile dosing regimen may limit sustained suppression of inflammation, leading to comparatively higher residual disease activity at treatment completion.^[20,21]

The findings of the present study closely mirror this pattern, wherein azithromycin showed rapid initial improvement but failed to match the final outcomes achieved with doxycycline.

Pharmacological Basis for Doxycycline Superiority

The observed superiority of doxycycline in moderate acne can be explained by its dual antimicrobial and anti-inflammatory mechanisms. Doxycycline inhibits matrix metalloproteinases, suppresses neutrophil chemotaxis, and

reduces the production of pro-inflammatory cytokines involved in acne pathogenesis.^[22,23]

Continuous daily dosing ensures stable tissue concentrations, leading to persistent inflammatory suppression over the treatment course.

Influence of Age on Treatment Response

Age-wise analysis revealed that younger patients (15–18 years) exhibited a slightly more robust response to both antibiotics compared to the older age group. However, the superior efficacy of doxycycline in moderate acne was consistent across both age strata, indicating that disease severity, rather than age alone, was the primary determinant of differential response.

Clinical Implications

The results of this study have important clinical implications. For patients with moderate acne vulgaris, doxycycline should be preferred over azithromycin when the goal is maximal lesion clearance at the end of therapy. While azithromycin may be considered in selected cases—such as patients with tetracycline intolerance or poor compliance—doxycycline remains the more reliable first-line systemic antibiotic for moderate disease.

Safety, Tolerability and Adverse Event Profile

Assessment of safety and tolerability is a critical component of systemic antibiotic therapy in acne, particularly because treatment often involves young individuals and may extend over several weeks. In the present study, both doxycycline and azithromycin were generally well tolerated, with no serious adverse events or treatment discontinuations reported during the six-week study period.

Overall Safety Profile

The overall incidence of adverse events was low and predominantly mild in nature. As summarized in Table 3.5, adverse events were reported in 43.8% of patients receiving doxycycline and 35.0% of patients receiving azithromycin. Importantly, no patient in either treatment group required discontinuation of therapy, underscoring the acceptable safety profile of both regimens. These findings align with existing literature, which consistently reports good tolerability of both tetracyclines and macrolides when used for acne vulgaris.^[24,25]

Adverse Events Associated with Doxycycline In the doxycycline-treated group, the most commonly reported adverse events were gastrointestinal disturbances and photosensitivity. Mild nausea was reported by a small proportion of patients, while photosensitivity reactions were infrequent and managed conservatively with sun-protective measures.

Adverse Events Associated with Azithromycin

Patients receiving azithromycin reported a numerically lower incidence of adverse events overall (35.0% vs. 43.8%), with mild abdominal discomfort being the most common complaint. No cases of photosensitivity, hepatic dysfunction, or serious systemic reactions were observed in the azithromycin group.^[26,27]

Role of Topical Benzoyl Peroxide in Safety

All patients in the study received topical benzoyl peroxide 5% as adjunct therapy. Mild cutaneous dryness and erythema were reported in both treatment arms; however, these effects

were transient and did not necessitate discontinuation of therapy. Beyond its therapeutic role, benzoyl peroxide is known to reduce bacterial resistance when used alongside systemic antibiotics.^[28,29]

Clinical Implications

From a clinical standpoint, the safety data suggest that both doxycycline and azithromycin can be prescribed with confidence in patients with mild to moderate acne vulgaris for short-term therapy. While doxycycline demonstrated superior efficacy in moderate acne, azithromycin may be preferred in patients with a history of photosensitivity or intolerance to tetracyclines.

Integrated Interpretation of Study Findings

The present study provides a comprehensive comparative evaluation of oral doxycycline and oral azithromycin in patients with mild and moderate acne vulgaris when used in combination with topical benzoyl peroxide. By integrating both longitudinal response patterns and final endpoint outcomes, a nuanced understanding of treatment efficacy emerges.

In patients with mild acne vulgaris, both antibiotics demonstrated comparable efficacy, with no statistically significant difference in final acne severity scores at six weeks. This finding reinforces the concept that in mild disease, systemic antibiotics primarily function as adjunct anti-inflammatory agents, and differences between drug classes tend to diminish by the end of therapy.^[30,31] The slightly faster early response observed with azithromycin did not translate into superior long-term outcomes, indicating therapeutic equivalence in this subgroup.

In contrast, patients with moderate acne vulgaris exhibited a clear divergence in final outcomes. Although azithromycin produced a rapid initial improvement, doxycycline achieved significantly greater reduction in acne severity at the completion of therapy. This pattern highlights the importance of sustained inflammatory suppression in moderate disease and supports the preferential use of doxycycline when maximal clearance is desired.^[32,33]

Taken together, these findings confirm that disease severity is the primary determinant of differential antibiotic response, rather than age alone. The consistent superiority of doxycycline across both age groups in moderate acne underscores its role as a first-line systemic agent in this population.

Conclusion

The present study provides a structured and comparative evaluation of oral doxycycline and oral azithromycin in the management of mild and moderate acne vulgaris when used in combination with topical benzoyl peroxide 5%. Both doxycycline and azithromycin produced statistically significant improvement in acne severity scores across all study groups, confirming the effectiveness of systemic antibiotic therapy as an adjunct to topical treatment. In patients with mild acne vulgaris, no statistically significant difference was observed between the two antibiotics at the end of six weeks, indicating comparable efficacy irrespective

of age group. In contrast, among patients with moderate acne vulgaris, doxycycline demonstrated significantly superior endpoint efficacy compared to azithromycin in both age categories, a finding that highlights the importance of sustained anti-inflammatory action in more severe disease. Both treatment regimens were well tolerated, with no serious adverse events or treatment discontinuations, supporting their safety for short-term use in acne vulgaris. Overall, these findings indicate that disease severity rather than age is the primary determinant of differential therapeutic response.

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