Comparative Evaluation of Azithromycin and Doxycycline in the Management of Acne Vulgaris – A Study of 120 Cases

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ABSTRACT

Background: Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit affecting adolescents and young adults. Oral antibiotics remain the mainstay in moderate-to-severe cases. Among them, doxycycline (a tetracycline derivative) and azithromycin (a macrolide) are commonly prescribed, but comparative evidence is still evolving. **Objective:** To evaluate and compare the efficacy and safety of azithromycin versus doxycycline in patients with moderate-to-severe acne vulgaris. **Methods & Materials:** A randomized, prospective, comparative clinical study was conducted on 120 patients with moderate-to-severe acne vulgaris. Patients were divided into two groups: Group A (n=60) received azithromycin 500 mg three times a week for 12 weeks, and Group B (n=60) received doxycycline 100 mg once daily for 12 weeks. Clinical improvement was assessed at baseline, 6 weeks, and 12 weeks using the Global Acne Grading System (GAGS) and percentage reduction in lesion count. Adverse effects were recorded. **Results:** Both groups showed significant improvement from baseline ($p < 0.001$). At 12 weeks, mean GAGS reduction was 65% in the doxycycline group and 59% in the azithromycin group. The difference was not statistically significant ($p > 0.05$). Adverse effects were more common with doxycycline (gastritis, photosensitivity) compared to azithromycin (mild diarrhea, nausea). Compliance was slightly better with azithromycin due to intermittent dosing. **Conclusion:** Both azithromycin and doxycycline are effective and well-tolerated in the treatment of acne vulgaris. Doxycycline showed slightly better efficacy, while azithromycin was associated with fewer adverse effects and better compliance. The choice of drug should be individualized based on patient tolerance, compliance, and contraindications.

Keywords: *Acne vulgaris, Azithromycin, Doxycycline, Antibiotics, Randomized study*

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Introduction

Acne vulgaris is a common, chronic, inflammatory skin disorder of the pilosebaceous unit, characterized by the presence of comedones, papules, pustules, nodules, and in severe cases, cysts and scarring. It is one of the most prevalent dermatological conditions worldwide, affecting approximately 85% of adolescents and young adults to varying degrees, and often persisting into adulthood in both men and women [1]. The global burden of acne vulgaris is significant not only because of its high prevalence but also due to its psychosocial impact, which includes diminished self-esteem, depression, social withdrawal, and impaired quality of life [2].

Pathogenesis of Acne Vulgaris

The pathogenesis of acne is multifactorial and involves a complex interplay of four main processes:

1. Increased sebum production under androgenic influence.
2. Abnormal follicular keratinization, leading to obstruction of pilosebaceous follicles and comedone formation.
3. Colonization by *Cutibacterium acnes* (formerly *Propionibacterium acnes*), a Gram-positive anaerobic bacterium that plays a central role in triggering and maintaining inflammation.
4. Inflammatory response mediated by innate and adaptive immune pathways, involving pro-inflammatory cytokines such as IL-1, TNF-α, and IL-8[3,4].

These mechanisms contribute to the heterogeneous clinical spectrum of acne vulgaris, ranging from mild comedonal lesions to severe nodulocystic disease with potential for permanent scarring.

Systemic Antibiotic Therapy

While topical therapies such as retinoids, benzoyl peroxide, and topical antibiotics remain first-line treatments for mild acne, systemic therapy is often required for moderate-to-severe acne, especially when there is widespread involvement of the trunk, risk of scarring, or inadequate response to topical regimens.

Systemic antibiotics have been the cornerstone of acne management for decades. Their therapeutic efficacy stems from a dual mechanism of action:

- Antimicrobial effect: inhibition of *C. acnes* proliferation, leading to reduced bacterial-driven inflammation.
- Anti-inflammatory effect: inhibition of neutrophil chemotaxis, suppression of inflammatory cytokines, and downregulation of matrix metalloproteinases [5].

Among oral antibiotics, the most widely used include the tetracyclines (doxycycline, minocycline, tetracycline), macrolides (erythromycin, azithromycin), and less commonly, clindamycin and trimethoprim-sulfamethoxazole.

However, increasing concerns about antibiotic resistance, particularly with long-term use, necessitate judicious prescribing practices and comparative studies to optimize therapeutic outcomes [6].

Doxycycline in Acne Management

Doxycycline, a second-generation tetracycline derivative, has long been considered one of the most effective systemic antibiotics for acne. It is widely preferred due to:

- Potent anti-inflammatory activity, independent of its antimicrobial action.
- Favorable pharmacokinetics with good bioavailability.
- Once-daily dosing convenience [7].

Doxycycline reduces the number of inflammatory lesions, decreases sebaceous gland activity, and suppresses pro-inflammatory mediators. Several randomized controlled trials have demonstrated its superior efficacy compared to placebo and comparable efficacy to minocycline [8]. However, its use is not without drawbacks. Adverse effects such as gastrointestinal intolerance, esophagitis, photosensitivity, and in rare cases, hepatotoxicity or intracranial hypertension, can limit compliance. Importantly, doxycycline is contraindicated in pregnancy and in children under 8 years due to its effects on teeth and bone growth [9].

Azithromycin in Acne Management

Azithromycin, a macrolide antibiotic, has gained attention as an alternative to tetracyclines in acne treatment. Unlike erythromycin, which has largely fallen out of favor due to high resistance rates, azithromycin offers several advantages:

- Favorable pharmacokinetics, including a long half-life and extensive tissue penetration, allowing for intermittent pulse dosing regimens (e.g., three times weekly).
- Anti-inflammatory properties, including inhibition of neutrophil migration and modulation of cytokine production.
- Better gastrointestinal tolerability compared to erythromycin [10].

Clinical studies have shown that azithromycin, administered either as pulse therapy (500 mg three times per week) or short courses repeated monthly, achieves significant reduction in acne severity, with efficacy comparable to doxycycline or minocycline [11,12].

Azithromycin is particularly valuable in patients who cannot tolerate tetracyclines, such as pregnant women, lactating mothers, and those with contraindications to doxycycline. Furthermore, its intermittent dosing regimen may improve patient adherence compared to daily therapy.

Comparative Considerations: Azithromycin vs. Doxycycline

Despite the widespread use of both doxycycline and azithromycin, there is no clear consensus regarding which antibiotic is superior in terms of efficacy, safety, and compliance. Most clinical guidelines still recommend doxycycline as first-line therapy, but emerging evidence suggests azithromycin may be equally effective and better tolerated in certain patient populations.

Key comparative considerations include:

- **Efficacy:** Several randomized controlled trials have reported no significant difference between doxycycline and azithromycin in terms of reduction of acne severity scores [13,14].
- **Safety:** Azithromycin is associated with fewer gastrointestinal and photosensitivity side effects, while doxycycline may cause more frequent intolerance.
- **Compliance:** Intermittent pulse therapy with azithromycin may enhance adherence compared to daily doxycycline.
- **Resistance:** Concerns exist about macrolide resistance, particularly in regions with high rates of antibiotic overuse. Nonetheless, doxycycline resistance is also an emerging issue [15].

Given these factors, head-to-head comparative studies are essential to clarify whether azithromycin can serve as a viable alternative to doxycycline in clinical practice.Despite decades of research, acne vulgaris remains a therapeutic challenge, particularly in patients with moderate-to-severe disease requiring systemic therapy. While doxycycline continues to be a first-line oral antibiotic, azithromycin's favorable safety profile and dosing schedule make it an attractive alternative. However, in many regions, including South Asia, the prescribing patterns of dermatologists are not standardized, and there is limited regional data comparing these two drugs in a randomized, prospective setting. Evaluating their relative efficacy, safety, and patient compliance in a real-world population is thus clinically relevant. Therefore, the present study was undertaken with the objective of conducting a comparative evaluation of azithromycin and doxycycline in the treatment of moderate-to-severe acne vulgaris in 120 patients. By analyzing clinical outcomes, adverse effects, and compliance, this study aims to provide evidence to guide rational antibiotic use in acne management.

Methods & Materials

Study Design

A prospective, randomized, comparative study was carried out in the Department of Dermatology & Venereology, Mymensingh Medical College & Hospital, Mymensingh, Bangladesh from July 2023 to June 2024, over a period of 12 months.

Study Population

- **Total patients:** 120
- **Age group:** 15–30 years
- **Inclusion criteria:** Patients with moderate-to-severe acne vulgaris (based on GAGS score), willing to participate.
- **Exclusion criteria:** Pregnancy, lactation, known allergy to study drugs, history of systemic antibiotic therapy in the past 1-month, chronic systemic illness, and severe cystic acne requiring isotretinoin.

Randomization and Intervention

Patients were randomly assigned into two groups:

- **Group A (Azithromycin group):** 60 patients received oral azithromycin 500 mg three consecutive days per week for 12 weeks.
- **Group B (Doxycycline group):** 60 patients received oral doxycycline 100 mg once daily for 12 weeks.

All patients received topical adapalene 0.1% once daily as adjunct therapy.

Assessment

- **Baseline:** Detailed history, dermatological examination, and GAGS scoring.
- **Follow-up:** At 6 and 12 weeks, improvement in lesion count and GAGS score was recorded.
- **Safety assessment:** Adverse effects were documented.
- **Compliance:** Monitored by patient diary and pill count.

Statistical Analysis

Data were analyzed using SPSS software 25. Mean values were compared with Student's t test, and categorical variables with Chi-square test. A p-value <0.05 was considered statistically significant.

Results

Demographic and Baseline Characteristics

A total of 120 patients diagnosed with moderate-to-severe acne vulgaris were enrolled in the study and randomly assigned to two treatment groups: Group A (Azithromycin, n = 60) and Group B (Doxycycline, n = 60). The two groups were comparable at baseline, with no statistically significant differences in demographic or clinical parameters.The mean age of patients in the azithromycin group was 20.3 ± 3.5 years, while in the doxycycline group it was 20.7 ± 3.0 years (p = 0.48). Gender distribution was similar between the two groups (Azithromycin: 32 males/28 females; Doxycycline: 34 males/26 females, p = 0.72). The mean duration of acne was 18.2 ± 5.6 months in Group A and 17.9 ± 6.1 months in Group B (p = 0.81). Baseline Global Acne Grading System (GAGS) scores were also comparable (28.4 ± 5.7 vs 29.1 ± 6.0, p = 0.59), confirming adequate randomization and baseline homogeneity (*Table I*).

Table I
Baseline Characteristics of Study Participants.

Parameter	Azithromycin (n=60)	Doxycycline (n=60)	p-value
Mean Age (years)	20.3 ± 3.5	20.7 ± 3.0	0.48
Gender (Male/Female)	32/28	34/26	0.72
Duration of acne (months)	18.2 ± 5.6	17.9 ± 6.1	0.81
Baseline GAGS score	28.4 ± 5.7	29.1 ± 6.0	0.59

No statistically significant differences were observed at baseline between groups.

Reduction in Acne Severity (GAGS Score)
Both treatment groups demonstrated a statistically significant reduction in mean GAGS scores from baseline to week 6 and week 12 ($p < 0.001$ *within groups*).At week 6, the mean GAGS score decreased to 18.5 ± 4.9 in the azithromycin group and 17.9 ± 5.2 in the doxycycline group ($p = 0.62$). By week 12, further improvement was observed, with mean GAGS scores of 11.6 ± 3.8 and 10.2 ± 3.5, respectively ($p = 0.08$).The percentage reduction in GAGS score at the end of 12 weeks was 59.1% in the azithromycin group and 65.0% in the doxycycline group. Although doxycycline showed a slightly greater reduction, the difference between the two groups was not statistically significant ($p > 0.05$) (*Table II*).

Table II
Mean GAGS Score Reduction Over 12 Weeks.

Time Point	Azithromycin	Doxycycline	p-value
Baseline	28.4 ± 5.7	29.1 ± 6.0	0.59
Week 6	18.5 ± 4.9	17.9 ± 5.2	0.62
Week 12	11.6 ± 3.8	10.2 ± 3.5	0.08
% Reduction	59.1%	65.0%	>0.05

Both groups showed significant reduction in acne severity from baseline to 6 and 12 weeks ($p < 0.001$ *within groups*).

Lesion Count Reduction
Both treatment regimens resulted in substantial improvement across all lesion types. The mean percentage reduction in comedones was 54% in the azithromycin group and 58% in the doxycycline group ($p = 0.21$). Reduction in papules was 63% versus 68% ($p = 0.18$), and pustules decreased by 67% and 70%, respectively ($p = 0.27$). Nodular lesions showed a reduction of 52% in the azithromycin group and 56% in the doxycycline group ($p = 0.33$). Although the doxycycline group consistently showed slightly higher lesion reduction percentages, none of these differences reached statistical significance, indicating comparable efficacy between the two treatments (*Table III*).

Table III
Mean Percentage Reduction in Lesion Counts.

Lesion Type	Azithromycin	Doxycycline	p-value
Comedones	54%	58%	0.21
Papules	63%	68%	0.18
Pustules	67%	70%	0.27
Nodules	52%	56%	0.33

Adverse Events and Tolerability
Adverse events were reported in both groups, but were more frequent in the doxycycline group. In the azithromycin group, 12 patients (20%) experienced adverse effects, compared to 23 patients (38.3%) in the doxycycline group.Gastrointestinal disturbances were the most commonly reported adverse events. Gastrointestinal upset occurred in 6.7% of azithromycin-treated patients and 16.7% of doxycycline-treated patients. Nausea was reported by 3.3% and 6.7%, respectively. Diarrhea was more common in the azithromycin group (10.0%) compared to the doxycycline group (3.3%). Photosensitivity and esophagitis were observed exclusively in the doxycycline group, affecting 8.3% and 3.3% of patients, respectively (*Table IV*).

Table IV
Adverse Events in Both Groups.

Adverse Effect	Azithromycin	Doxycycline
Gastrointestinal upset	4 (6.7%)	10 (16.7%)
Nausea	2 (3.3%)	4 (6.7%)
Diarrhea	6 (10.0%)	2 (3.3%)
Photosensitivity	0	5 (8.3%)
Esophagitis	0	2 (3.3%)
Total adverse events	12 (20%)	23 (38.3%)

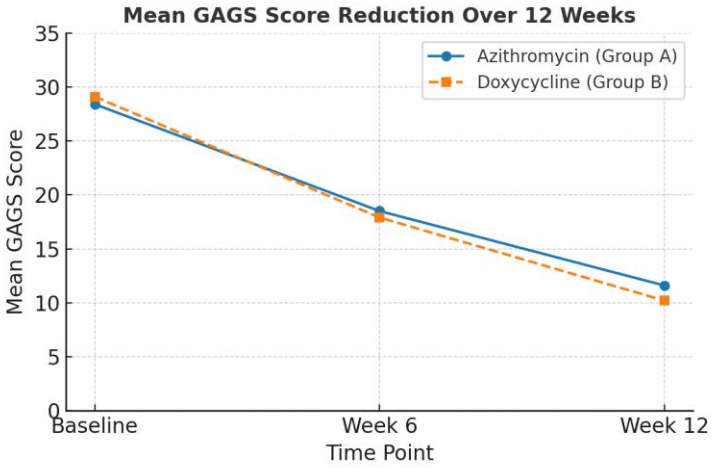

Figure 1 Mean GAGS Score Reduction Over 12 Weeks.

Treatment Compliance

Treatment adherence was slightly higher in the azithromycin group (95%) compared to the doxycycline group (88%). The improved compliance in the azithromycin group may be attributed to its intermittent dosing schedule and better overall tolerability.

Figure 1 illustrates the progressive reduction in mean GAGS scores over the 12-week treatment period in both groups. A steady and comparable decline in acne severity is evident in both treatment arms, with a slightly steeper reduction observed in the doxycycline group by week 12.

Discussion

Acne vulgaris is one of the most prevalent dermatological conditions globally, affecting nearly 85% of adolescents and a significant proportion of adults [1]. Despite being perceived by some as a "cosmetic problem," acne is a chronic inflammatory disease of the pilosebaceous unit, with profound psychosocial and quality-of-life implications [2]. Moderate-to-severe acne often requires systemic therapy, and oral antibiotics remain the cornerstone of treatment when topical measures prove inadequate. Among the most commonly used oral agents, doxycycline (a tetracycline derivative) and azithromycin (a macrolide) are widely prescribed. This study compared the efficacy, safety, and tolerability of azithromycin versus doxycycline in 120 patients with moderate-to-severe acne vulgaris over a 12-week treatment period. Both antibiotics were effective, with significant reductions in acne severity scores, but doxycycline showed slightly greater efficacy, while azithromycin demonstrated a better safety profile and compliance due to its pulse-dosing regimen.

Efficacy of Doxycycline and Azithromycin

The results of our study demonstrated that both doxycycline and azithromycin significantly reduced acne severity as measured by the Global Acne Grading System (GAGS). At week 12, the mean reduction in GAGS scores was 65% in the doxycycline group and 59% in the azithromycin group. While doxycycline showed a numerically greater reduction, the difference did not reach statistical significance. These findings are consistent with multiple prior studies. Singh et al [13] conducted a randomized controlled trial comparing azithromycin pulse therapy with daily doxycycline in Indian patients and reported comparable efficacy between the two regimens. Similarly, Nagpal et al [14] and Parsad et al [12] observed no significant differences in clinical outcomes between these antibiotics, suggesting that azithromycin can be considered an alternative to doxycycline in appropriate patients. However, some studies have suggested a slight superiority of doxycycline. Del Rosso et al [8] highlighted that doxycycline has more potent anti-inflammatory properties than macrolides, which may explain the marginally better results observed in our trial. Doxycycline inhibits neutrophil chemotaxis, suppresses cytokines such as IL-1 and TNF-α, and reduces activity of matrix metalloproteinases, all of which are implicated in acne pathogenesis. Azithromycin also possesses anti-inflammatory properties, but its effects are less robust in this context (Gollnick, 2015)[4].

Safety and Tolerability

A major finding of this study was the difference in adverse event profiles between the two antibiotics. In our study, 38.3% of patients on doxycycline experienced side effects, compared to 20% in the azithromycin group. The most common adverse effects with doxycycline were gastrointestinal intolerance (16.7%) and photosensitivity (8.3%), while azithromycin was more commonly associated with mild diarrhea (10%) and nausea (3.3%). These results align with earlier reports. Shalita et al [9] and Leyden [5] described gastrointestinal symptoms and photosensitivity as typical side effects of doxycycline. In contrast, azithromycin has generally been associated with fewer and milder adverse events, with diarrhea being the most commonly reported [10,11]. Importantly, no severe or life-threatening side effects were reported in our cohort, underscoring the overall safety of both regimens.The tolerability advantage of azithromycin makes it particularly useful in patients who are unable to tolerate doxycycline or have contraindications, such as pregnancy, lactation, or history of photosensitivity reactions. This makes azithromycin an important alternative option in clinical practice.

Patient Compliance and Dosing Convenience

Compliance is a crucial determinant of therapeutic success in chronic diseases like acne. In our study, compliance was higher in the azithromycin group (95%) compared to the doxycycline group (88%). This difference likely stems from azithromycin's pulse dosing regimen (500 mg three times weekly), which reduces pill burden and improves adherence compared to daily doxycycline dosing.This observation has also been highlighted in prior studies. Parsad et al[12] noted that the pulse dosing schedule of azithromycin not only improved compliance but also reduced gastrointestinal intolerance by limiting continuous exposure. Moreover, azithromycin's long half-life and excellent

tissue penetration allow effective drug levels to be maintained between doses[14]. Doxycycline, despite requiring daily administration, remains popular due to its well-established efficacy. However, patients with poor adherence to daily regimens may benefit from azithromycin, especially in resource-limited settings where follow-up and monitoring are challenging.

Antibiotic Resistance Considerations

One of the most pressing concerns in acne management is the emergence of antibiotic resistance. Long-term use of oral antibiotics has contributed to increasing resistance rates in *Cutibacterium acnes* and other commensal bacteria, leading to reduced efficacy of treatments and concerns about broader public health implications [15]. Resistance rates to macrolides, particularly erythromycin, are already high in many regions, while tetracycline resistance is increasing but generally remains lower [6]. Azithromycin, being a macrolide, may be subject to similar resistance patterns. However, the intermittent dosing regimen may mitigate some selection pressure compared to continuous daily therapy. Clinical guidelines, including those by the American Academy of Dermatology [7], emphasize the importance of limiting the duration of systemic antibiotic use, avoiding monotherapy, and combining oral antibiotics with topical agents such as benzoyl peroxide or retinoids to reduce resistance risk. In our study, all patients were prescribed topical adapalene, which aligns with best practice recommendations. Future studies should focus on molecular surveillance of *C. acnes* resistance patterns in different regions to better guide antibiotic selection.

Psychosocial Impact and Clinical Relevance

Beyond clinical outcomes, the choice of antibiotic must also consider the psychosocial impact of acne. Even moderate disease can cause significant distress, impair social functioning, and contribute to depression or anxiety [2]. Rapid and visible improvement is therefore critical, and both doxycycline and azithromycin provided significant lesion reduction within 6 weeks in our study. While doxycycline may provide slightly superior efficacy, azithromycin's favorable safety and compliance profile may improve overall patient satisfaction and adherence. Thus, the choice of therapy should be individualized, taking into account not only efficacy but also side effect profiles, patient preferences, and comorbidities.

Comparison with Previous Studies

Our study reinforces the findings of multiple comparative trials:

- Parsad et al [12]: Compared azithromycin pulse with daily doxycycline and found no significant difference in efficacy.
- Singh et al [13]: Reported similar outcomes in Indian patients, with better tolerability in azithromycin.
- Nagpal et al [14]: Concluded that both regimens are effective, but azithromycin may be more suitable in patients intolerant to tetracyclines.
- Dogra & Kumar [10]: Highlighted azithromycin as an emerging therapeutic option due to its tolerability.

These studies, combined with our findings, suggest that azithromycin is not inferior to doxycycline and may be a viable alternative, especially in specific subgroups of patients.

Strengths & Limitations

Strengths of our study include its prospective randomized design, adequate sample size (120 patients), and standardized assessment using the Global Acne Grading System (GAGS). The inclusion of both efficacy and safety outcomes provides a holistic comparison of the two antibiotics.

Limitations must also be acknowledged:

1. The duration of follow-up (12 weeks) was relatively short. Acne is a chronic disease, and longer-term data on relapse rates and sustained efficacy would provide more comprehensive insights.
2. The study was conducted in a single center, limiting generalizability to broader populations.
3. Microbiological assessment of *C. acnes* resistance was not performed, which would have provided valuable information on local resistance patterns.
4. We did not formally assess quality of life improvements using validated tools such as the Dermatology Life Quality Index (DLQI), which could have strengthened the psychosocial dimension of the study.

Clinical Implications

The findings of this study have practical clinical implications:

- **Doxycycline** remains the preferred first-line systemic antibiotic due to its slightly greater efficacy and well-established clinical track record.
- **Azithromycin** should be considered a valuable alternative, particularly for patients who:
    - Cannot tolerate doxycycline (GI intolerance, photosensitivity).
    - Have contraindications (pregnancy, lactation, children under 8 years).
    - Are unlikely to adhere to daily regimens.
- Clinicians should always combine systemic antibiotics with topical agents to reduce the risk of resistance.
- Treatment duration should be limited, and patients should be reassessed regularly to minimize unnecessary prolonged antibiotic exposure.

Future Directions

Future research should focus on:

1. Long-term comparative trials evaluating relapse rates after discontinuation of therapy.
2. Microbiological studies assessing resistance trends to guide rational prescribing.
3. Combination regimens, such as low-dose doxycycline with topical retinoids or azithromycin combined with benzoyl peroxide.
4. Pharmacogenetic studies to identify which patients may respond better to specific antibiotics.
5. Quality of life assessments, to integrate psychosocial outcomes with clinical efficacy.

Conclusion

In conclusion, both doxycycline and azithromycin are effective in the treatment of moderate-to-severe acne vulgaris. Doxycycline demonstrated slightly superior efficacy in reducing GAGS scores and lesion counts, while azithromycin was associated with fewer adverse effects and higher compliance. The results of this study suggest that doxycycline remains the gold standard, but azithromycin represents a safe and effective alternative in patients where tetracyclines are contraindicated or poorly tolerated.The choice of therapy should therefore be individualized, balancing efficacy, safety, patient compliance, and the broader context of antibiotic resistance.

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