RESEARCH PAPER

Efficacy And Safety Of Topical Ketoconazole 2% Cream Plus Adapalene 0.1% Gel Versus Adapalene 0.1% Gel In The Treatment Of Facial Acne Vulgaris - a Randomised Control Trial

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Received: 24th April, 2026; Revised: 20th May 2026; Accepted: 30th June, 2026; Available Online: 10th July, 2026

ABSTRACT

Introduction: Acne vulgaris is a common chronic inflammatory disorder influenced by multiple factors, including Malassezia species, which exacerbate inflammation. Adapalene is a first-line topical retinoid effective in treating mild-to-moderate acne, while ketoconazole, an antifungal with anti-inflammatory and anti-androgenic properties, may enhance treatment outcomes. This study evaluates the efficacy and safety of combining topical ketoconazole 2% cream with adapalene 0.1% gel versus adapalene monotherapy in mild-to-moderate facial acne vulgaris.

Methodology: In a randomized controlled trial conducted from September 2025 to February 2026, 66 patients aged 12 years and above with mild-to-moderate facial acne were randomized into two groups: Group A received adapalene 0.1% gel nightly plus ketoconazole 2% cream daily; Group B received adapalene 0.1% gel alone. Treatment lasted 8 weeks with assessments at baseline and weeks 2, 4, 6, and 8. Acne severity was measured using the Global Acne Grading System (GAGS) and Investigator Global Assessment (IGA). Safety and tolerability were also evaluated.

Results: Baseline characteristics were comparable between groups. After 8 weeks, Group A showed a significantly greater reduction in mean GAGS score (15.2 ± 4.1) compared to Group B (11.4 ± 4.3; $p < 0.001$), with a higher percentage reduction (64.4% vs. 47.3%; $p < 0.001$). Treatment success (IGA 0 or 1) was achieved in 60.6% of Group A versus 30.3% of Group B ($p = 0.014$). Adverse effects were mild and similar between groups, with no significant differences in erythema, burning, dryness, or discontinuation rates.

Conclusion: The combination of ketoconazole 2% cream with adapalene 0.1% gel is more effective than adapalene alone in reducing acne severity in mild-to-moderate facial acne vulgaris, without increasing adverse effects. This dual-action regimen offers a comprehensive approach by targeting both comedogenesis and Malassezia colonization, supporting its use as an adjunctive therapy in acne management.

Keywords: Acne Vulgaris, Adapalene, Ketoconazole, Antifungal Agents, Randomized Controlled Trial

How to cite this article: Dr. M. Yashaswini, Dr. Rajashekar TS, Dr. Suresh Kumar K, Dr. Madhu Kiran C, Efficacy And Safety Of Topical Ketoconazole 2% Cream Plus Adapalene 0.1% Gel Versus Adapalene 0.1% Gel In The Treatment Of Facial Acne Vulgaris - a Randomised Control Trial, Int J Drug Deliv Technol. 2026;16(71s): 1114-1118. DOI: 10.25258/ijddt.16.71s.130

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Acne vulgaris is a prevalent chronic inflammatory disorder of the pilosebaceous unit, affecting approximately 85% of adolescents and a considerable number of adults worldwide.[1] The pathogenesis of acne is multifactorial, primarily involving abnormal follicular keratinization, increased sebum production, colonization by Cutibacterium acnes, and a subsequent inflammatory cascade.[2] Recent evidence has expanded this understanding by highlighting the role of Malassezia species, which contribute to acne exacerbation through their lipase activity, hydrolyzing sebum triglycerides into irritating free fatty acids that aggravate follicular inflammation and acneiform eruptions.[3] This highlights the influence of the broader skin microbiome, including yeasts, in acne pathophysiology. Adapalene, a third-generation synthetic retinoid, is widely recognized as a first-line topical treatment for mild-to-moderate acne.[4] It functions by selectively binding to retinoic acid receptors RAR-β and RAR-γ, thereby normalizing keratinocyte differentiation, preventing microcomedone formation, and reducing inflammation.[5]

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Despite its proven efficacy and tolerability, adapalene monotherapy may have a delayed onset of action and may not adequately address all inflammatory acne lesions in some patients.[6] Ketoconazole, an imidazole antifungal agent, inhibits ergosterol synthesis, reducing Malassezia colonization on the skin.[7] Beyond its antifungal properties, ketoconazole exhibits anti-inflammatory effects by inhibiting leukotriene and cytokine pathways, as well as anti-androgenic actions on sebaceous glands that decrease sebum production.[8] Controlled clinical studies have demonstrated the potential of topical ketoconazole 2% cream to reduce inflammatory acne lesions, suggesting its therapeutic value.[9,10] The combination of adapalene and ketoconazole offers a complementary dual mechanism of action: adapalene primarily targets comedogenesis and inflammation, while ketoconazole addresses seborrhea, Malassezia colonization, and associated inflammatory mediators.[11] This combination may be particularly advantageous for patients with oily skin types, seborrheic dermatitis overlap, or Malassezia-driven acneiform flares. However, randomized controlled trials directly comparing adapalene alone with the combination of adapalene and ketoconazole remain limited, with gaps in evidence regarding efficacy, safety, and optimal patient selection. This study aimed to address these gaps by evaluating the efficacy and safety of topical ketoconazole 2% cream combined with adapalene 0.1% gel versus adapalene 0.1% gel alone in the treatment of mild-to-moderate facial acne vulgaris through a randomized controlled trial.

METHODOLOGY

This randomized controlled trial was conducted at the outpatient clinic of Dermatology, Venereology, and Leprosy in R L Jalappa Hospital and Research Centre, Sri Devaraj Urs Medical College, Tamaka, Kolar, from September 2025 to February 2026. Patients aged 12 years and above, of any gender, presenting with mild-to-moderate facial acne vulgaris (Grade1 and Grade 2) and having an inflammatory lesion count between 10 and 50 were included. Exclusion criteria comprised severe acne (Grade 3 and Grade 4), acne fulminans, recent use (within 8 weeks) of systemic antibiotics, isotretinoin, antifungals, topical retinoids, antibiotics or antifungals, pregnancy or lactation, known allergies to ketoconazole or adapalene, active facial infections requiring systemic therapy, and use of systemic steroids or immunosuppressants. Eligible participants were randomized into two groups using computer-generated block randomization. Group A (Combination group) received topical adapalene 0.1% gel applied once nightly and ketoconazole 2% cream applied once daily in the morning. Group B (Control group) received adapalene 0.1% gel alone once nightly, with a matching emollient cream or placebo applied in the morning. Participants were counseled on sun protection and moisturizer use. The treatment duration was 8 weeks, with follow-up visits scheduled at baseline, weeks 2, 4, 6, and 8. A final safety follow-up was conducted via phone at week 10. Acne severity and treatment response were assessed using standardized tools, including the Global Acne Grading System (GAGS) and Investigator Global Assessment (IGA). Serial standardized photographs were taken at each visit under consistent lighting and positioning and evaluated by a blinded third observer using the Global Photograph Assessment (GPA) scale. Subjective side effects such as irritation, erythema, and burning sensation were recorded using a visual discomfort scale ranging from 0 to 10 at every visit. Data were collected and entered into Microsoft Excel and analyzed using SPSS software version 22 or 27. Normality of data distribution was evaluated using the Shapiro-Wilk test. Categorical variables were expressed as frequencies and proportions and analyzed with Chi-square or Fisher's exact tests. Continuous variables were presented as means with standard deviations or medians with interquartile ranges and compared between groups using independent t-tests or Mann-Whitney U tests, as appropriate. Statistical significance was set at $p < 0.05$. Sample size calculation was based on detecting a clinically meaningful difference of 6 inflammatory lesions between groups, assuming a standard deviation of 8 lesions, with 80% power and a two-sided alpha of 0.05. This resulted in a requirement of 28 participants per group, adjusted to 33 per group (66 total) to account for an anticipated 10–15% dropout rate. Ethical approval was obtained from the Institutional Ethics Committee, and informed consent was obtained from all participants or guardians prior to enrollment. The principal investigator bore the study costs. Safety monitoring was conducted throughout the study period to evaluate tolerability and adverse events associated with the interventions.

RESULTS

The mean age of participants was comparable between Group A (Adapalene + Ketoconazole) and Group B (Adapalene alone) (21.8 ± 4.2 years vs. 22.3 ± 4.5 years; p = 0.642). The gender distribution was also similar, with males constituting 54.5% of Group A and 51.5% of Group B (p = 0.803). The mean duration of acne did not differ significantly between the groups (13.2 ± 6.1 months in Group A vs. 12.7 ± 5.8 months in Group B; p = 0.731). Likewise, baseline acne severity assessed using the Global Acne Grading System (GAGS) showed comparable scores in both groups (23.6 ± 4.5 vs. 24.1 ± 4.8; p = 0.668). The Investigator's Global Assessment (IGA) scores at baseline were also similar (3.1 ± 0.5 in Group A and 3.0 ± 0.6 in Group B; p = 0.492). Since all p-values were greater than 0.05, there were no statistically significant differences between the two groups at baseline. This indicates that the study groups were well matched with respect to demographic characteristics, disease duration, and acne severity, ensuring comparability before initiation of treatment (Table 1).

Table 1: Baseline demographic and clinical characteristics of study participants.

Variable	Group A (Adapalene + Ketoconazole) n=33	Group B (Adapalene) n=33	p-value
Age (years), Mean ± SD	21.8 ± 4.2	22.3 ± 4.5	0.642
Male, n (%)	18 (54.5)	17 (51.5)	0.803
Female, n (%)	15 (45.5)	16 (48.5)	
Duration of acne (months), Mean ± SD	13.2 ± 6.1	12.7 ± 5.8	0.731
Baseline GAGS score, Mean ± SD	23.6 ± 4.5	24.1 ± 4.8	0.668
Baseline IGA	3.1 ± 0.5	3.0 ± 0.6	0.492

score, Mean ± SD			

At baseline, the mean GAGS scores were comparable between Group A (Adapalene + Ketoconazole) and Group B (Adapalene alone) (23.6 ± 4.5 vs. 24.1 ± 4.8; p = 0.668), indicating similar initial disease severity. After 8 weeks of treatment, Group A demonstrated a significantly lower mean GAGS score compared to Group B (8.4 ± 3.2 vs. 12.7 ± 4.1; p < 0.001). The mean reduction in GAGS score was also significantly greater in Group A (15.2 ± 4.1) than in Group B (11.4 ± 4.3; p < 0.001). The percentage reduction in GAGS score was markedly higher in Group A, achieving a mean reduction of 64.4 ± 12.1%, compared with 47.3 ± 13.4% in Group B (p < 0.001). These findings indicate that the combination of adapalene and ketoconazole was significantly more effective in reducing acne severity than adapalene monotherapy over the 8-week treatment period. The superior reduction in both absolute and percentage GAGS scores suggests enhanced therapeutic efficacy of the combination regimen (Table 2).

Table 2: **Comparison of treatment efficacy based on GAGS score reduction at Week 8.**

Outcome	Group A (n=33)	Group B (n=33)	p-value
Baseline GAGS score (Mean ± SD)	23.6 ± 4.5	24.1 ± 4.8	0.668
Week 8 GAGS score (Mean ± SD)	8.4 ± 3.2	12.7 ± 4.1	<0.001
Mean reduction in GAGS score	15.2 ± 4.1	11.4 ± 4.3	<0.001
Percentage reduction (%)	64.4 ± 12.1	47.3 ± 13.4	<0.001

A greater proportion of participants in Group A (Adapalene + Ketoconazole) achieved favorable clinical outcomes compared to Group B (Adapalene alone). In Group A, 24.2% of participants achieved complete clearance of acne (IGA 0) compared to 9.1% in Group B, while 36.4% were rated as almost clear (IGA 1) compared to 21.2% in Group B. Conversely, higher proportions of participants in Group B remained in the mild (42.4%) and moderate (27.3%) disease categories compared with Group A (30.3% and 9.1%, respectively). This indicates that acne severity was reduced more effectively in the combination therapy group. Treatment success, defined as achieving an IGA score of 0 or 1, was observed in 60.6% of patients in Group A compared with 30.3% of patients in Group B. This difference was statistically significant (p = 0.014), demonstrating that the addition of ketoconazole to adapalene significantly improved the likelihood of achieving successful treatment outcomes. Overall, the findings suggest superior clinical efficacy of the combination regimen in achieving greater acne clearance and improving global acne severity (Table 3).

Table 3: **Comparison of Investigator Global Assessment (IGA) response at Week 8.**

IGA Outcome	Group A (n=33)	Group B (n=33)	p-value
Clear (IGA 0), n (%)	8 (24.2)	3 (9.1)	
Almost Clear (IGA 1), n (%)	12 (36.4)	7 (21.2)	
Mild (IGA 2), n (%)	10 (30.3)	14 (42.4)	
Moderate (IGA 3), n (%)	3 (9.1)	9 (27.3)	
Treatment success* n (%)	20 (60.6)	10 (30.3)	0.014

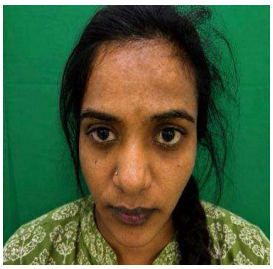
*Treatment success = ≥2-grade reduction from baseline and final IGA score 0 or 1.

The incidence of treatment-related adverse effects was low and comparable between Group A (Adapalene + Ketoconazole) and Group B (Adapalene alone). Mild erythema was reported in 18.2% of participants in Group A and 15.2% in Group B (p = 0.744), while burning sensation occurred in 15.2% and 12.1% of participants, respectively (p = 0.721). Similarly, dryness or scaling was observed in 21.2% of participants receiving combination therapy compared to 18.2% of those receiving adapalene alone (p = 0.759). Pruritus was infrequent in both groups, affecting 9.1% of participants in Group A and 6.1% in Group B (p = 0.641). Treatment discontinuation due to adverse effects was rare, occurring in only one participant in each group (3.0%), with no significant difference between the groups (p = 1.000). The mean Visual Discomfort Score was slightly higher in Group A than in Group B (2.3 ± 1.1 vs. 2.0 ± 1.0), but this difference was not statistically significant (p = 0.286). Overall, all p-values were greater than 0.05, indicating no significant differences in adverse effect frequency or treatment tolerability between the two groups. These findings suggest that the addition of ketoconazole to adapalene did not increase treatment-related adverse effects and was generally well tolerated by patients (Table 4).

Table 4: **Comparison of adverse effects and tolerability between study groups.**

Adverse Effect	Group A (n=33) n (%)	Group B (n=33) n (%)	p-value
Mild erythema	6 (18.2)	5 (15.2)	0.744
Burning sensation	5 (15.2)	4 (12.1)	0.721
Dryness/Scaling	7 (21.2)	6 (18.2)	0.759
Pruritus	3 (9.1)	2 (6.1)	0.641
Treatment discontinuation	1 (3.0)	1 (3.0)	1.000
Mean Visual Discomfort Score (0–10)	2.3 ± 1.1	2.0 ± 1.0	0.286

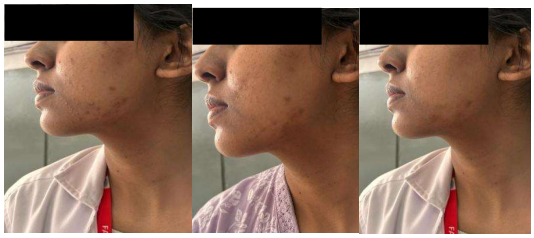
GROUP A: TOPICAL KETOCONAZOLE 2% CREAM ONCE IN THE MORNING PLUS ADAPALENE 0.1% GEL ONCE AT NIGHT.



BASELINE **2ND WEEK** **4TH WEEK**

6TH WEEK **8TH WEEK**

GROUP B: VERSUS ADAPALENE 0.1% GEL ONCE AT NIGHT.



BASELINE **2ND WEEK** **4TH WEEK**

6TH WEEK **8TH WEEK**

DISCUSSION

The current study evaluated the efficacy and safety of combining topical ketoconazole 2% cream with adapalene 0.1% gel versus adapalene 0.1% gel alone in mild-to-moderate facial acne vulgaris. It demonstrated a significant improvement in acne severity with combination therapy, showing greater reduction in GAGS scores and higher treatment success rates compared to adapalene monotherapy, while maintaining comparable tolerability. Comparing these findings to studies on pityriasis versicolor (PV) treatment, a consistent pattern emerges supporting the enhanced efficacy of combination therapy involving ketoconazole and adapalene. Ahmad et al. reported significantly higher improvement rates (86.7%) with ketoconazole plus adapalene 1% gel compared to ketoconazole monotherapy (46.7%) in PV patients, although the combination was associated with increased mild irritation.[12] Similarly, Bakr et al. found that the combination of adapalene 0.1% gel and ketoconazole 2% cream yielded better clinical improvement and patient satisfaction than either agent alone, with mild or no side effects, reinforcing the synergistic potential of this regimen.[13] Munir et al. also demonstrated superior efficacy of the ketoconazole 2% cream and adapalene 0.1% gel combination (91.11% efficacy) over ketoconazole alone (75.56%) in PV treatment, with statistical significance and consistent results across demographic subgroups.[14] Shi et al. observed that the combination therapy provided faster and greater clinical improvement compared to ketoconazole monotherapy, particularly at earlier time points (Weeks 1 and 2), with statistically significant superiority maintained at Week 4. While the Shi et al. study focused on a superficial fungal infection and the current study addressed acne vulgaris, both conditions share involvement of Malassezia species and inflammation, providing a plausible mechanistic rationale for the combination's effectiveness in both contexts. [15] While these PV studies focus on fungal skin infection rather than acne, the shared mechanism of combining antifungal and anti-inflammatory/keratolytic effects parallels the acne study's rationale. Both contexts highlight adapalene's role in normalizing keratinization and reducing inflammation, complementing ketoconazole's antifungal and anti-inflammatory actions, thereby enhancing overall therapeutic outcomes. In contrast, Rad et al., compared terbinafine 1% cream with ketoconazole 2% cream monotherapies for PV and found no statistically significant difference in cure rates, though terbinafine showed a trend toward higher efficacy.[16] This study did not involve adapalene, highlighting that the addition of adapalene, as seen in the other PV studies and the current acne study, may be a key factor in improving treatment success beyond antifungal monotherapy. Regarding safety, all these studies report mild, localized adverse effects such as erythema, dryness, and burning sensation, with no significant differences between combination and monotherapy groups. This consistency supports the tolerability of the combination regimen across different dermatological conditions and patient populations. Notably, the current study's longer treatment duration (8 weeks vs. 2 weeks in Shi et al.) and focus on acne severity scoring systems provide a more detailed assessment of efficacy over time in acne management The current study's findings align with the broader literature indicating that combining adapalene with ketoconazole enhances clinical efficacy and patient outcomes compared to single-agent therapy. The combination's dual action on microbial colonization and inflammatory/keratinization pathways appears to provide a more comprehensive approach, applicable across related dermatological conditions such as acne vulgaris and pityriasis versicolor.

CONCLUSION

The combination of topical ketoconazole 2% cream with adapalene 0.1% gel demonstrated superior efficacy in reducing

acne severity compared to adapalene monotherapy in patients with mild-to-moderate facial acne vulgaris. This was evidenced by significantly greater reductions in GAGS scores, higher treatment success rates based on Investigator Global Assessment, and improved clinical clearance without an increase in adverse effects. The dual mechanism targeting both comedogenesis and Malassezia colonization offers a comprehensive therapeutic approach, particularly beneficial for patients with oily skin or Malassezia-associated acneiform flares. The combination regimen was well tolerated, with comparable safety profiles to adapalene alone. These findings support the use of ketoconazole as an effective adjunct to adapalene in acne management, addressing both microbial and inflammatory components to enhance treatment outcomes.

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