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# Comparative Study of Efficacy of Combined Treatment with Ketoconazole 2% Cream and Adapalene 0.1% Gel Versus Ketoconazole 2% Cream Monotherapy in Pityriasis Versicolor

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## ABSTRACT

**Background and Aim:** Pityriasis versicolor is a frequent cutaneous superficial mycotic infection of Malassezia species manifesting as hypopigmented or hyperpigmented scaly macules. Although topical antifungals such as ketoconazole are often employed, relapse and partial resolution of skin color changes are common. Recent observations suggest that the concurrent use of antifungals with agents such as adapalene (a topical retinoid) might have the potential to improve the treatment effectiveness by stimulating epidermal turnover and antifungal penetration. The present study aimed to compare the ketoconazole 2% cream and adapalene 0.1% gel combined treatment efficacy with ketoconazole 2% cream monotherapy in patients with pityriasis versicolor. **Patients and Methods:** This comparative study investigated fifty patients with pityriasis versicolor in the Department of Dermatology JPMC Karachi from December 05, 2024 to March 04, 2025. Patients were randomly allocated to two groups of 25 each. Patients in whereas Group-A were administered with ketoconazole 2% cream once daily and Group-B a combined therapy based on ketoconazole 2% cream (once daily) and adapalene 0.1% gel (applied nightly). Clinical score and mycological (KOH examination) findings were recorded at baseline and at the end of treatment. Efficacy was assessed based on lesion clearance, symptom resolution, and mycological cure rates. SPSS version 20 used for data analysis. **Results:** At the end of 4 weeks, Group A (combined therapy) showed significantly higher clinical improvements and high mycological treatment rates than Group B (monotherapy). Group A ($P < 0.05$) complete clearance seen in 84% of patients in Group B vs 60%. The adverse effects were limited to minimum and mild local irritation in the adapalene group, which was spontaneously resolved. **Conclusion:** The combination of ketoconazole 2% cream and adapalene 0.1% gel proved to be more effective than ketoconazole monotherapy in pityriasis versicolor treatment, with a better clinical and micological reaction. This combination can represent a more efficient timely approach, especially in cases with resistant or recurrent lesions.

## INTRODUCTION

Pityriasis versicolor (PV) caused by malassezia species is a superficial fungus infection of the skin, a dimorphic yeast that thrives in warm and humid climate. Clinically, PV often covered with fine, well-defined scales presents as multiple hypo- or hyper-pigmented macules that may coalesce into larger patches. The lesions can appear in a variety of colors, hence the term "versicolor." Although typically asymptomatic, some patients may experience mild itching or cosmetic concerns, which can lead to psychological distress and limitations in clothing choices [1]. Despite its benign nature, PV can significantly affect the quality of life of patients due to its chronicity, persistent recurrence and cosmetic concerns, especially in adolescents and young adults [2]. Current therapeutic strategies aimed at eradicating fungal loads and preventing relapses. Topical antifungal agents, especially azoles such as ketoconazole, clotrimazole, and selenium sulfide, considered the first row treatment in most simple cases. Of these, ketoconazole 2% cream is a well - established option that is due to its fungicidal and fungal activity against Malassezia species [3].

However, monotherapy with topical antifungal cannot always give satisfactory outcomes, especially in cases associated with extensive lesions, recurrence, or altered host immunity. As a result, auxiliary treatment that target related pathological factors such as follicular occlusion, inflammation, or changed skin barrier can provide increased efficacy. Such a potentially auxiliary adapalene is a third-generation topical retinoid known for

comedolytic, anti-inflammatory and keratolytic properties. Although it indicated mainly for acne vulgaris, adapalene has shown advantage in other dermatoses characterized by hyperkeratosis and microbial colonization [4]. Several studies have established ketoconazole as a foundation stone in PV's topical management [5-7]. A randomized trial displayed that ketoconazole 2% cream achieved a high clinical treatment rate within four weeks of application with minimal side effects [8]. Subsequent studies have validated these findings and referred to the comprehensive spectrum antifungal activity and favorable tolerance profile of ketoconazole. Despite its efficacy, recurrence remains a frequent problem, with rates ranging from 60% to 80% within a year [9].

Adapalene, although traditionally used in acne management, has been studied for its synergistic role in treating superficial cutaneous infections and disorders involving keratinization [10]. Its ability to modify differentiation and promote desquamation may be beneficial in the facility of removing embedded fungus elements within the stratum corneum. Additionally, neutrophil can help reduce the anti-inflammatory action of the adapalene, erythema and irritation through the prohibition of chemotaxis and cytokine production, which often seen in the inflammatory variants of the PV [11]. The difference in literature underlines the need for well - designed clinical trials to evaluate the therapeutic superiority of adapalene and ketoconazole therapy on monotherapy. Such evidence can guide physicians more effective for PV and towards relapse-preventable treatments, especially in patients with recurrent or resistant forms of the disease. The rationale for combining ketoconazole with adapalene lies in their complementary mechanism. While ketoconazole targets fungal pathogen, adaplane can improve skin trade, increase the entry of the drug, and aid in the extraction of residual lesions. This joint approach can provide better efficacy in terms of wound withdrawal and relay prevention compared to monotherapy with ketoconazole alone. However, strong clinical data on such combinations is limited, requiring further discovery.

## METHODOLOGY

### Study Design and Setting

This comparative study investigated fifty patients with pityriasis versicolor in the Department of Dermatology JPMC Karachi from December 05, 2024 to March 04, 2025.

### Inclusion and Exclusion Criteria

Patient's age ≥ 12 years (either gender), clinically diagnosed PV confirmed by positive Wood's lamp fluorescence and KOH microscopy (lesions covering ≤ 20 % body surface area) enrolled. Systemic or topical antifungals/retinoid in the preceding 4 weeks, Immunosuppression, pregnancy, lactation Known allergy to azoles or retinoid, and concomitant dermatologic disorders that could confound assessment excluded.

Patients were randomly allocated into two Groups; Group-A (Morning: Ketoconazole 2 % cream applied thinly to all lesions and 2 cm beyond margins, Night: Adapalene 0.1 % gel applied similarly), and Group-B (Ketoconazole 2 % cream twice daily (morning and night) to identical areas). The Outcome measures were Primary Outcome (Composite clinical and mycologic cure defined as ≥ 50 % reduction in composite clinical score (erythema, scaling, lesion size; each graded 0–3), negative Wood's lamp fluorescence, and negative 10 % KOH microscopy of skin scrapings). Time to onset of visible improvement (first follow-up, Day 14), patient-reported pruritus reduction on a 10-point VAS, and incidence of adverse events (local irritation, erythema, dryness) were secondary outcomes. Baseline and at the end of treatment data collection recorded demographics (age, gender, residence), disease duration, wound distribution and baseline clinical score.

SPSS version 20 utilized for data analysis. Quantitative variables such as age and duration of disease calculated as a mean and standard deviations. The frequencies and percentage for qualitative variables including gender, residence, wound site, socio-economic status, business status and efficacy were calculated. Treatment efficacy of both groups compared using Chi-Square test. The effect modifier controlled through stratification based on age, gender, habitat, and site of wound, socio -economic status, professional status and duration. P-value ≤ 0.05 was considered statistically significant.

## RESULTS

50 patients with a clinically diagnostic pityriasis versicolor were nominated and equally divided into two treatment groups: Group A (N = 25), who received a combination therapy of ketoconzole 2% cream (morning) and Adapalene 0.1% gel (night), and Group B (N = 25), who applied 2% Cream Monotherapy daily. The mean age of participants in both groups was comparable, and the majority were males (Group A: 60%; Group B: 48%). Urban residents comprised a higher proportion in both groups (Group A: 72%; Group B: 80%). Mean reduction in pruritus (VAS score 0–10); Group A: 6.5 ± 1.2 and Group B: 4.2 ± 1.5. This indicates better symptom relief in Group A by Day 14 of treatment. Adverse events included mild erythema, dryness, and local irritation. No serious adverse reactions reported in either group. Treatment efficacy compared in Figure-1. Adverse events in treatment groups shown in Figure-2. Primary Outcome: Treatment Efficacy as presented in Table 1. Table 2 shows the adverse event of treatment groups.

**Table 1**

*Primary Outcomes; Treatment Efficacy (N=50)*

| Group | Effective | Not Effective | Total |
|---|---|---|---|
| Group A | 21 (84%) | 4 (16%) | 25 |
| Group B | 15 (60%) | 10 (40%) | 25 |
| Total | 36 | 14 | 50 |

**Table 2**

*Adverse Events*

| Group | Adverse Events Reported | No Adverse Events | Total |
|---|---|---|---|
| Group A | 3 (12%) | 22 (88%) | 25 |
| Group B | 5 (20%) | 20 (80%) | 25 |
| Total | 8 (16%) | 42 (84%) | 50 |

**Figure 1**
*Treatment Efficacy*

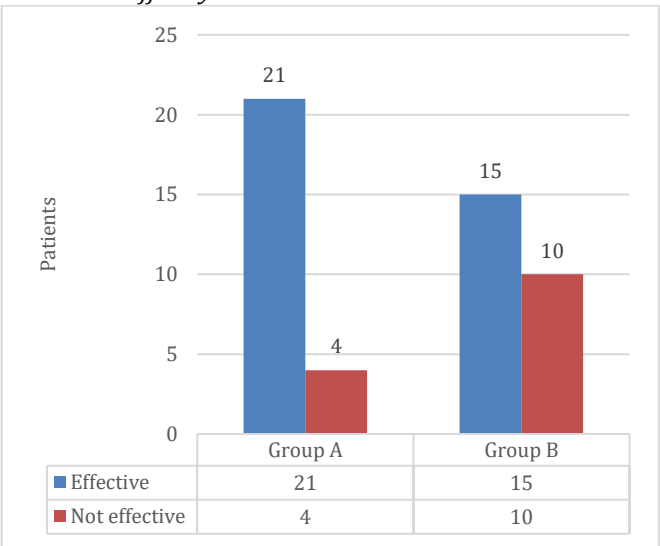
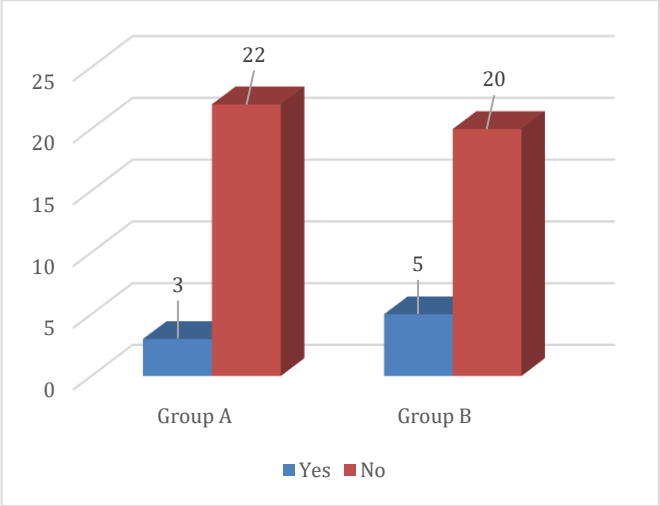



**Figure 2**
Adverse Events




## DISCUSSION

The current study mainly focused on the comparison of efficacy and safety of a combination therapy (ketoconazole (ketoconazole 2% cream + adapalene 0.1% gel) vs. ketoconazole 2% Cream Monotherapy. The results demonstrated that the combination therapy was more effective than the monotherapy, in which a high-ratio of patients receiving clinical and mycological cure and experiencing greater symptomatic relief. The combination therapy of Ketoconazole and Adapalene significantly improved clinical and mycologic outcomes in PV patients with an acceptable safety profile. Early pruritus relief and a lower rate of non-response were observed in Group A, supporting its recommendation for first-line treatment.

The findings of this study align with the pathophysiological understanding of PV, a superficial fungus infection with an inflammatory component. While ketoconazole, an imidazole antifungal, is effective in innovating the development of Malassezia species, adapalene in addition to a synthetic retinoid – enhance outcomes by promoting epidermal turnover, reducing inflammation and improving the parentage of the antifungal agent. This can explain the better efficacy seen in Group A, where 84% of patients obtained clinical treatment compared to 60% in the monotherapy group. Similar findings reported in earlier studies [12, 13].

Previous studies reported that combined therapy offered pruritus score than monotherapy [14, 15]. Similarly, in addition, the average decrease in the pruritus score was evaluated using a 10-point visual analogue scale (VAS), much higher in-group A (6.5 ± 1.2) than group B (4.2 ± 1.5). This suggests that the combination therapy not only achieved better mycological clearance, but also offered better symptomatic relief in addressing a common complaint in PV.

In terms of safety, both the treatment modalities were well tolerated. Both groups reported adverse events such as mild erythema, dryness and local irritation, but they were self-limited and did not require dissection of treatment. Importantly, no serious adverse phenomena observed, indicating that addition of adaplane did not increase the overall risk of treatment -related complications. These findings resemble earlier study results [16].

Demographic features of the study population, including age and gender distribution, relatively balanced among groups. Group A (60%) was noted a slightly higher ratio of male participants, and most patients in both groups were inhabited in urban areas JPMC Karachi has significant reflections for healthcare-chewing population. These demographic trends did not appear to significantly affect the results of treatment. Previous randomized controlled trials reported similar findings that age and gender had no association with treatment outcomes [17, 18].

The better efficacy of the combination therapy seen in this study corresponds to the findings of previous studies, which have detected auxiliary treatment in PV [19, 20]. However, literature is limited on specific use of adapalene in fungi infections. Therefore, this study contributes to the novel insight into the possible utility of retinoid as an auxiliary in antifungal therapy. However, certain limitations must be acknowledged. The sample size was relatively small (n = 50), and the duration of the follow -up was limited to four weeks. Long -term results, including recurrence rate, were not evaluated. Additionally, while randomization employed, blinds not mentioned and supervisor bias can be introduced during clinical evaluation.

## CONCLUSION

The combination of ketoconazole 2% cream and adapalene 0.1% gel appears to be a more effective treatment option for Pityriasis versicolor compared to ketoconazole monotherapy, which provides better clinical reaction and symptomatic relief without compromising safety.

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