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Original Article

Efficacy of Combination of Topical Ketoconazole 2% Cream and Adapalene 0.1% Gel versus Topical Ketoconazole 2% Cream Alone in Treatment of Pityriasis Versicolor

Faiza Munir[1], Erfan Khattak[2], Wasiq Zafar Abbasi[3], Sabeen Shakir[4], Sameer Ahmed[5] and Amanat Ali[6]

[1]Department of Dermatology, Nishtar Hospital, Multan, Pakistan
[2]Department of Dermatology, Akhtar Saeed Medical College, Rawalpindi, Pakistan
[3]Department of Medicine, Abu-Amara Medical and Dental College, Lahore, Pakistan
[4]Department of Pharmacology, Akhtar Saeed Medical College, Rawalpindi, Pakistan
[5]Department of Pharmacology, Rawal Institute of Health Sciences, Rawalpindi, Pakistan
[6]Department of Pharmacology, HBS Medical and Dental College, Islamabad, Pakistan

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***Corresponding Author:**
Faiza Munir
Department of Dermatology, Nishtar Hospital, Multan, Pakistan
dr.faizamunir@gmail.com

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ABSTRACT

Pityriasis Versicolor (PV) is a superficial skin infection caused by *Malassezia* yeasts, resulting in hypo and hyperpigmented macules. It affects up to 40% of individuals, often leading to itching, decreased quality of life, and social stigma. **Objective:** To compare the efficacy of combination of topical ketoconazole 2% cream and adapalene 0.1% gel versus topical ketoconazole 2% cream alone in treatment of pityriasis versicolor. **Methods:** A comparative cross-sectional study was conducted at the Department of Dermatology, Nishtar Hospital, Multan, spanning from November 2020 to April 2021. Total 90 patients were divided equally into two groups: Group A received a combination of Ketoconazole 2% cream and adapalene 1% gel, while Group B received Ketoconazole 2% cream alone. The efficacy of both treatments was evaluated and compared. The study utilized SPSS version 26.0 for data analysis. **Results:** In terms of gender, 52.22% were male, and 47.78% were female across both groups. The mean duration of the disease was 5.84 ± 3.26 years in Group A and 6.04 ± 3.11 years in Group B, with an overall mean of 5.95 ± 3.17 years. The efficacy of Group A was 91.11%, with 41 participants showing positive results, while Group B had an efficacy of 75.56%, with 34 participants showing positive results. **Conclusions:** The study findings indicate that using a combination of adapalene 0.1% gel and ketoconazole 2% cream is more efficacious than using ketoconazole 2% cream alone in treating PV.

INTRODUCTION

Pityriasis versicolor, also known as tinea versicolor, is a common fungal infection of the skin characterized by the presence of hypo or hyperpigmented macules, most frequently observed on the trunk, neck, and proximal extremities. It is primarily caused by the overgrowth of *Malassezia* species, particularly *Malassezia* globosa and *Malassezia* furfurs, which are lipophilic yeasts normally residing on the skin [1, 2]. Factors contributing to the proliferation of Malassezia include warm and humid environments, increased sebum production, immunosuppression, hormonal fluctuations, and genetic predisposition. The transition of *Malassezia* from its yeast to its mycelial form is believed to play a pivotal role in the pathogenesis of pityriasis versicolor, leading to the disruption of normal skin pigmentation and the development of characteristic lesions [3]. Pityriasis versicolor is a ubiquitous dermatological condition, prevalent worldwide, with variations in incidence observed across different geographic regions and climatic conditions. In tropical regions, the prevalence of PV is as

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high as 50%, while in moderate and cold temperatures, it is estimated to be approximately 1-4% and 1% respectively [4]. The pathophysiology of pityriasis versicolor involves a complex interplay of factors contributing to the dysregulation of the cutaneous microbiome and the host immune response. *Malassezia* yeasts produce lipases and other enzymes that hydrolyze sebum triglycerides into fatty acids, creating an acidic environment that promotes fungal growth [5]. Furthermore, the presence of *Malassezia*-derived metabolites, such as azelaic acid, may induce alterations in melanocyte function, leading to the disruption of melanin production and subsequent pigmentary changes observed in pityriasis versicolor lesions. Dysfunctions in both innate and adaptive immune responses, as well as individual variations in host susceptibility, further contribute to the pathogenesis of the condition [6, 7]. Despite its benign nature, pityriasis versicolor often poses diagnostic and therapeutic challenges due to its chronic and recurrent course. Ketoconazole, a well-established antifungal agent, targets the fungal overgrowth responsible for the condition by inhibiting ergosterol synthesis in fungal cell membranes. Alone, it demonstrates significant efficacy in controlling the infection. However, the addition of adapalene, a third-generation retinoid, introduces an adjunctive therapy that addresses underlying inflammatory processes and abnormal keratinization associated with pityriasis versicolor[8, 9].

With limited research on combination therapy in Pakistan, this study underscored the need for investigation to enhance patient care. The rationale for this study lies in the therapeutic complexities of pityriasis versicolor, a condition known for its chronicity and recurrence. This study explored the efficacy of combining ketoconazole 2% cream with adapalene 0.1% gel for pityriasis versicolor, a condition known for its chronicity. By exploring this novel combination, it addressed the dual challenge of fungal overgrowth and inflammation, potentially improving treatment outcomes. This research filled a significant gap in the literature by comparing combination therapy to ketoconazole alone, offering valuable insights to optimize treatment approaches

METHODS

After approval from the hospital's ethical review board (vide letter #, REU/DER/14509, Date: 01/11/2020). The study design was comparative cross-sectional study. This study was conducted at Department of Dermatology Nishtar Hospital, Multan over a period of six months from November 2020 to April 2021 and included OPD patients. Written informed consent was obtained from all participants. A particular proforma was used to record each participant's medical history at the time of assessment. Sample size of 90 participants, with 45 individuals in each group, was calculated to keeping confidence interval of 95% and Power of test 80% taking anticipated efficacy of 90% in Group A (ketoconazole 2% cream plus adapalene 0.1% gel) and 72% in Group B (ketoconazole 2% cream alone) in patients diagnosed with pityriasis versicolor [17]. Patients of both genders diagnosed with pityriasis versicolor, aged 20 to 40 years having duration of disease ≤ 3 months with pityriasis versicolor which was diagnosed on presence of hyperpigmented macules discrete or confluent, slightly scaly macules showing yellow-green fluorescence under wood's lamp light. Patients with other dermatological conditions, pregnant or breastfeeding women, and those with contraindications to study medications were excluded. Participants were randomly assigned to one of two treatment groups: Group A: Combination therapy with topical ketoconazole 2% cream and adapalene 0.1% gel were applied once daily in morning to the affected areas for a duration of 4 weeks Group B: Topical ketoconazole 2% cream was given twice daily for 4 weeks. Administration of both topical medications ketoconazole 2% cream, both alone and in combination with adapalene 0.1% gel, was assessed using the fingertip unit method. This method involves applying 1 fingertip unit (equivalent to 0.5 gm of topical gel/cream) to cover 2% of the body surface area. Patients were instructed to cleanse the afflicted region with a gentle soap. Prior to each treatment application it was confirmed affected area dried then formulation was applied according to the extent of body surface area affected by pityriasis versicolor. The rule of 9 was utilized to calculate the body surface area. Patients were monitored at the second and fourth week. Compliance was evaluated on each subsequent appointment by inquiring about the patient's medicine usage, specifically if the cream or gel was applied correctly, at the appropriate time, and in the correct amount to the affected area. The patient's adherence to the physician's advice was considered as an indicator of compliance. After 4 weeks, both groups were assessed for the effectiveness of the treatment by a dermatologist with at least 5 years of experience after completing their fellowship. Efficacy of treatment was labeled upon disappearance of lesions at the end of 4 weeks. SPSS version 25.0 (IBM) was used to analyze the data. Results were presented as mean and standard deviation for quantitative variables i.e., age, weight, height, BMI and duration of disease. Frequency and percentage was calculated for qualitative variables like gender, body surface area involved, educational status, socioeconomic status and efficacy of drugs in both groups. Chi square was applied to compare the efficacy in both groups and p-value <0.05 was taken as significant. Effect modifiers like age, gender, BMI, education status, duration of disease and

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socioeconomic status were stratified and post-stratification chi-square was applied to see their effect on outcome. P-value <0.05 was taken as significant.

RESULTS

The mean age in Group A was 30.02 ± 6.05 years, while in Group B it was 29.98 ± 6.34 years, with an overall mean age of 29.87 ± 6.85 years. Most participants in both groups were aged 20-30 years, accounting for 55.56% in Group A and 60.0% in Group B, totaling 57.78% of the total participants. In our study there were 47 (52.22%) males and 43(47.78%) females. Among them, 24 males (51.06%) and 19 females (44.18%) were in Group A, while 23 males (48.93%) and 24 females (55.81%) were in Group B. The mean duration of the disease was 5.84 ± 3.26 years in Group A and 6.04 ± 3.11 years in Group B, with an overall mean of 5.95 ± 3.17 years. The mean duration of disease was 5.84 ± 3.26 years in Group A and 6.04 ± 3.11 years in Group B. Overall, the mean duration of disease was 5.95 ± 3.17 years. The mean BMI was 27.47 ± 4.50 in Group A and 27.62 ± 4.19 in Group B, with an overall mean of 27.39 ± 4.30. Regarding socioeconomic status, 42.22% of participants were classified as poor, 30.0% as middle, and 27.78% as upper. The majority of participants had ≤50% body surface area involved, accounting for 72.22% of the total participants as given in table 1.

Table 1: Details of Demographic Variables of Patients Included in Study

Variable	Characteristics	Group A	Group B	Total
Age	Mean ± SD	30.02 ± 6.05	29.98 ± 6.34	29.87 ± 6.85
	20-30	25 (55.56%)	27 (60.0%)	52 (57.78%)
	31-40	20 (44.44%)	18 (40.0%)	38 (42.22%)
Gender	Male	24 (51.06%)	23 (48.93%)	47 (52.22%)
	Female	19 (44.18%)	24 (55.81%)	43 (47.78%)
Duration of Disease	Mean ± SD	5.84 ± 3.26	6.04 ± 3.11	5.95 ± 3.17
	0-7 weeks	29 (64.44%)	28 (62.22%)	57 (63.33%)
	8-14 weeks	16 (35.56%)	17 (37.78%)	33 (36.67%)
BMI	Mean ± SD	27.47 ± 4.50	27.62 ± 4.19	27.39 ± 4.30
	Non-obese ≤ 30 kg/m^2	24 (53.33%)	25 (55.56%)	49 (54.44%)
	Obese > 30 kg/m^2	21 (46.67%)	20 (44.44%)	41 (45.56%)
Socioeconomic Status (income per day)	Poor (< 300 PKR)	18 (40.0%)	20 (44.44%)	38 (42.22%)
	Middle (300-1500 PKR)	14 (31.11%)	13 (28.89%)	27 (30.0%)
	Upper (>1500 PKR)	13 (28.89%)	12 (26.67%)	25 (27.78%)
Body Surface Area Involved	≤50%	33 (73.33%)	32 (71.11%)	65 (72.22%)
	≥50%	12 (26.67%)	13 (28.89%)	25 (27.78%)

The efficacy of Group A was 91.11%, with 41 participants showing positive results, while Group B had an efficacy of 75.56%, with 34 participants showing positive results. The p-value for the comparison between the two groups was 0.048 given in table 2.

Table 2: Comparison of Efficacy of Both Groups

Variables	Characteristics	Group A	Group B	p-Value
Efficacy	Yes	41 (91.11%)	34 (75.56%)	0.048
	No	4 (8.89%)	11 (24.44%)	

Table 3 presents the stratification of effectiveness for both drugs concerning gender, age, duration of disease, and BMI. For Gender in Group A, among males, 23 (92.0%) showed efficacy, while 18 (81.82%) did so in Group B, with p-values of 0.297 and 0.100, respectively. Among females, 18 (90.0%) in Group A and 16 (69.57%) in Group B showed efficacy, with p-values of 0.100 and 0.297, respectively. For Age in the age group of 20-30 years, 23 (92.0%) in Group A and 19 (70.37%) in Group B showed efficacy, with a significant p-value of 0.048. Among participants aged 31-40 years, 18 (90.0%) in Group A and 15 (83.33%) in Group B showed efficacy, with a p-value of 0.544. For duration of disease For participants with a duration of disease between 0-7 weeks, 26 (89.66%) in Group A and 22 (78.57%) in Group B showed efficacy, with a p-value of 0.251. Among those with a duration of disease between 8-14 weeks, 15 (93.75%) in Group A and 12 (70.59%) in Group B showed efficacy, with a p-value of 0.085. For BMI, among participants with BMI ≤ 30 kg/m2, 21(87.50%) in Group A and 18 (72.0%) in Group B showed efficacy, with a p-value of 0.178. For participants with BMI > 30 kg/m2, 20 (95.24%) in Group A and 16 (80.0%) in Group B showed efficacy, with a p-value of 0.136.

Table 3: Stratification of effectiveness of both drugs with gender, age, duration of disease & BMI

Variables	Category	Efficacy in Group A		Efficacy in Group B		p-value
		Yes	No	Yes	No	
Gender	Male	23 (92.0%)	02 (8.0%)	18 (81.82%)	04 (18.18%)	0.297
	Female	18 (90.0%)	02 (10.0%)	16 (69.57%)	07 (30.43%)	0.100
Age	20-30 years	23 (92.0%)	02 (8.0%)	19 (70.37%)	08 (29.63%)	0.048
	31-40 years	18 (90.0%)	02 (10.0%)	15 (83.33%)	03 (16.67%)	0.544
Duration of Disease	0-7 weeks	26 (89.66%)	03 (10.34%)	22 (78.57%)	06 (21.43%)	0.251
	8-14 weeks	15 (93.75%)	01 (6.25%)	12 (70.59%)	05 (29.41%)	0.085
BMI	≤30 kg/m^2	21 (87.50%)	03 (12.50%)	18 (72.0%)	07 (28.0%)	0.178
	>30 kg/m^2	20 (95.24%)	01 (4.76%)	16 (80.0%)	04 (20.0%)	0.136

Chi-square test observed difference was statistically insignificant

DISCUSSION

Topical therapy options for PV encompass lotions, shampoos and creams that are proven to be effective. These are administered on a daily basis or twice daily for different durations, rapidly enhancing clinical symptoms. Patient adherence may be influenced by the need for frequent and time-consuming applications, as well as by slight skin discomfort. Generalized topical therapies for PV do not particularly target Malassezia species. Instead, they

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employ physical or chemical methods to eliminate deceased contaminated tissue. Effective therapies for PV include selenium sulphide (in the form of lotion, shampoo or cream), propylene glycol, Whitfield's ointment, and zine pyrithione. These treatments have been found to be successful in addressing PV [10, 11]. In terms of age, our study found a mean age of 29.87 years, with a majority aged between 20 to 30 years. This aligns closely with the findings of Hameed *et al.*, who reported a slightly lower mean age of 28.42 years [12]. In our study, the combination therapy yielded an effectiveness rate of 91.11%, while ketoconazole 2% cream alone showed an effectiveness rate of 75.56%, with a statistically significant p-value of 0.048. Similarly, Hameed *et al.*, observed a higher frequency of improvement at 2 weeks with combination therapy compared to monotherapy (93.3% vs. 73.3%, p=0.000)[12]. Ashraf also reported a significantly higher frequency of improvement at 2 weeks with combination therapy compared to monotherapy (87.5% vs. 47.5%, p=0.000). These consistent findings across multiple studies underscore the efficacy of combination therapy in the treatment of pityriasis versicolor [13]. While Khan *et al.*, reported a notably younger mean age of 25.34 years. This contrasts with the male predominance reported by Khan *et al.*, with ratios of 2.1:1 [14]. These variations may be influenced by factors such as geographic location, genetic predisposition, environmental conditions, and study methodologies. In contrast, Wahid *et al.*, reported a significantly higher mean age of 51.3 years [15]. Our study findings align with those of Tawfik *et al.*, reported a significantly higher frequency of improvement with combination therapy compared to ketoconazole alone, with 96% of participants showing improvement in the combination therapy group compared to 74% in the ketoconazole alone group (P=0.023)[16]. The results of our study align with the findings of Shi *et al.*, who previously reported that the inclusion of adapalene 0.1% gel in 2% ketoconazole cream led to a significant increase in the proportion of patients (92% vs. 72%; P=0.0009) [17]. The results of our study are in line with previous research conducted by Anwar *et al.*, and Gobbato *et al* [18, 19]. Furthermore, our findings are consistent with those reported by Bakr *et al.*, who observed that a significant proportion of patients in both the combination therapy group and the monotherapy group experienced substantial improvement. Specifically, Bakr *et al.*, noted that 28 out of 30 patients (93.3%) in the combination group demonstrated marked improvement, while 25 out of 30 patients (83.3%) in the monotherapy group also showed significant improvement. These results provide additional support for the efficacy of both the combination therapy and monotherapy approaches in the treatment of the condition under investigation[20].

CONCLUSIONS

The study findings indicate that using a combination of adapalene 0.1% gel and ketoconazole 2% cream is more efficacious than using ketoconazole 2% cream alone in treating PV.

Authors Contribution

Conceptualization: FM
Methodology: FM, EK, WZA
Formal analysis: SS, SA
Writing-review and editing: AA

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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