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COMPARATIVE STUDY OF EFFICACY OF COMBINED TREATMENT WITH KETOCONAZOLE 2% CREAM AND ADAPALENE 0.1% GEL VS. KETOCONAZOLE 2% CREAM MONOTHERAPY IN PITYRIASIS VERSICOLOR

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COMPARATIVE STUDY OF EFFICACY OF COMBINED TREATMENT WITH KETOCONAZOLE 2% CREAM AND ADAPALENE 0.1% GEL VS. KETOCONAZOLE 2% CREAM MONOTHERAPY IN PITYRIASIS VERSICOLOR

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ABSTRACT

Background: Pityriasis Versicolor (PV) is an infection of the superficial layers of skin caused by *Malassezia* yeasts. It is a non-contagious disease characterized by hypo and hyperpigmented macules on the body. Up to 40% of people face itching, decreased quality of life, social stigmatization, and embarrassment due to the lesions. Adapalene with Ketoconazole provides an efficient option for PV patients due to better toxicity profile and rapid action on the lesions.

Objective: Comparison of efficacy of combined therapy with Ketoconazole 2% cream and adapalene 1% gel against Ketoconazole 2% cream monotherapy in Pityriasis Versicolor.

Methods: Total 90 patients (45 in each group) were included in the study. Group-A was treated with combination of Ketoconazole 2% cream & adapalene 1% gel while group-B was given Ketoconazole 2% cream monotherapy. Study design was randomized controlled trial and SPSS version 26 was used for data analysis.

Results: Mean age of the patients was 24.3 ± 4.3 and 23.3 ± 3.9 years in group-A and B, respectively. There were 30 males (66.7%) & 15 females (33.3%) in group-A while 35 males (77.8%) and 10 females (22.2%) in group-B. Mean duration of disease was 2.0 ± 0.9 months in group-A & 2.3 ± 1.2 months in group-B. The efficacy of combined therapy with Ketoconazole 2% cream & adapalene 1% gel was found to be better when compared with Ketoconazole 2% cream monotherapy in Pityriasis Versicolor. Difference between two groups ($p=0.011$) was statistically significant.

Conclusion: It was concluded that adapalene 0.1% gel & ketoconazole 2% cream in combination is more effective than ketoconazole 2% cream monotherapy in the treatment of PV.

Recommendation: It is recommended to use a combination of adapalene 0.1% gel & ketoconazole 2% cream than ketoconazole 2% cream monotherapy in the treatment of PV.

Keywords: Ketoconazole 2%, Adapalene, Efficacy, *Malassezia* spp., Pityriasis versicolor.

INTRODUCTION

Pityriasis Versicolor (PV) is an infection of the superficial layers of skin caused by *Malassezia* yeasts. It is a dimorphic fungus, occurring mostly in Hot and humid environments. The predominant species involved in causing the disease are *M. globosa*, *M. furfur*, and *M. sympodialis*. These species are prevalent in the subcontinent [1]. There is a prominent role of climate, occupation, and socioeconomic conditions discovered in the literature. Males and females equally suffer from the disease. The fungus is present in healthy skin but in favorable conditions, can transform into its pathological mycelial form and lead to skin infections [2]. A study from Lahore reported that the frequency of fungal infections was 12.5%, focusing on the considerable fungal disease burden in Pakistan due to its hot and humid climate. PV is a disease more common in tropical and sub-tropical regions [2]. It is reported more in people with low immunity, e.g., Cushing disease, malnourishment, hyperhidrosis, poor general health but not in pregnancy and diabetes mellitus. Other than environmental factors, it is postulated that 20% of cases show a familial predisposition to the disease [2,3].

PV is a non-contagious disease characterized by lesions described as multiple hypo and hyperpigmented macules, which may merge into large patches and have well developed scales. These may become prominent by stretching the skin (Zeliri's sign) or 'evoked scale sign.' It may present in variable colors hence called versicolor. It is an asymptomatic condition but may present with itching or disfiguring skin condition leading to embarrassment and restriction of clothing choice. Pityriasis versicolor (PV) is a common disorder of pigmentation reported from tropical and subtropical regions [3,4]. The Areas mostly affected by the disease include the face, trunk, upper limbs, buttock, sub mammary area, axilla, and groin [5]. They are present in sites rich in sebaceous glands and produce lipases that release fatty acids from TG's present in sebum [5].

Malassezia is lipophilic yeasts and constitutes 75%-98% of the normal skin of healthy adults. It may be associated with other skin conditions as seborrheic/ atopic dermatitis, dandruff, and complicated systemic fungal infections, especially in immunocompromised individuals [6]. It is imperative to distinguish PV from other similar conditions: vitiligo, pityriasis alba, chloasma, erythrasma, secondary syphilis, confluent and reticulated papillomatosis, pityriasis rotunda for better prognosis [1]. It is diagnosed clinically and microscopically with the help of KOH (potassium hydroxide). It has a characteristic "spaghetti and meatball appearance," representing hyphae and spores of the fungus [1].

The first-line PV treatment is topical antifungal therapy and systemic antifungals, while other treatment options such as selenium sulfide, zinc pyrithione and Whitfield's ointment are also known to be effective and widely used. Current treatment options of Pityriasis Versicolor include synthetic antifungals, e.g., Ketoconazole. However, due to resistant strains that are emerging, it is becoming difficult to treat [7]. Other treatment options for PV include topical and oral route treatments [4].

Hence, due to strains that are resistant, combined treatment may prove a better option in reducing the stress in treatment. Literature proves that the combination of Ketoconazole 2% cream & 0.1% adapalene gel compared to ketoconazole cream alone shows clinical improvements that are efficient and faster [2]. It is mainly an asymptomatic ailment, yet up to 40% of people suffer discomfort and emotional distress due to pigmentary changes, which may persist for months to years after the fungus is cleared from the lesion. Adding on to the agony are frequent relapses, which aggravate the failure of treatment. The literature search

shows inadequacy over the topic, and the need for more research for this easy, well- tolerated, efficient, and less harmful option for the treatment of PV patients is warranted.

Rationale of this study was to see the efficacy of combined versus monotherapy of topical treatment options to provide insight into topical treatment efficacy regarding symptom resolution. Emotional distress, self-consciousness, and socialstigmatization highlight the need for treatment, which offers fewer side effects and is more effective [4]. Objective of the study was to see the efficacy of Ketoconazole 2% cream and Adapalene 0.1% gel versus Ketoconazole 2% cream monotherapy in pityriasis versicolor. As Ketoconazole used alone has caused the emergence of resistant strains and is associated with higher chances of relapse, combination therapy improves drug efficacy, achieves a faster cure rate, and prevents the development of resistant strains.

MATERIAL AND METHODS

This Randomized controlled trial was conducted in Dermatology Department of Lady Reading Hospital, Peshawar from 18-06-2020 to 17-12-2020 over a period of six months. Data was collected by non-probability consecutive sampling technique from 90 patients (45 in each group). WHO sample size calculation formula was used to calculate the sample size. Patients of either gender, age range of 18 to 50 years, clinically suggestive of pityriasis versicolor and diagnosis confirmed on KOH examination of skin scrapings with disease limited to the upper trunk, not involving more than 12% of the total trunk area were included in the study. Patients with known hypersensitivity/allergy to Ketoconazole or Adapalene, patients with concurrent severe diseases (Cardiac, Renal, or hepatic diseases) and pregnant/ lactating mothers were excluded from the study.

The study was conducted after formal approval from the Hospital Ethical and Research Committee. The 90 patients fulfilling the inclusion criteria were subjected to history taking and clinical examination to demonstrate the size and extent of lesions. The study's purpose was explained to the patients, informed written consent from those who agreed to participate in the study, demographic data like age, sex, and address was obtained. Eligible patients were randomly assigned to two groups by lottery method.

Group-A included those who received Ketoconazole 2% cream (morning application) & adapalene 0.1% gel (night application). In group B Ketoconazole 2 % cream was applied twice daily. To compare the efficacy of combined and monotherapy, participants were asked to return four weeks after initiating treatment for clinical and microscopic evaluation. A more than 50% improvement in clinical signs, negative fluorescence on Wood's lamp examination, and a negative result on KOH examination of skin scrapings after four weeks of treatment initiation was considered effective. All patients received topical medications for four weeks.

The evaluation included clinical assessment, Wood's light examination, KOH test and photography of lesions. The clinical assessment involved scaling & pigmentation (hyper or hypopigmentation). Improvement in clinical signs was classified into 5 grades: significant improvement ($\leq 75\%$ improvement), improved ($\geq 50\%$ - $>75\%$ improvement), slight improvement ($\geq 0\%$ - $>50\%$ improvement), unchanged (0% improvement). At the end of the study, the efficacy of the treatment was assessed.

DATA ANALYSIS PROCEDURE

SPSS was used for data analysis. Mean SD was computed for scale variables like the age of the patient and the duration of disease. Frequencies & percentages were calculated for the

categorical variable like gender and efficacy. Chi square test was applied to compare efficacy in two groups & p-value of ≤ 0.05 as taken as significant. Efficacy in the two groups were stratified among the age, gender and duration of disease to see the effect modification.

RESULTS

A total of 90 patients (45 in each group) were included in the study. Group-A was treated with combined therapy with Ketoconazole 2% cream and adapalene 1% gel while group-B was given Ketoconazole 2% cream monotherapy. Mean age of the patients was 24.3 ± 4.3 and 23.3 ± 3.9 years in group-A and B, respectively. There were 30 males (66.7%) & 15 females (33.3%) in group-A while 35 males (77.8%) and 10 females (22.2%) in group-B. Mean duration of disease was 2.0 ± 0.9 months in group-A & 2.3 ± 1.2 months in group-B. The efficacy of combined therapy with Ketoconazole 2% cream & adapalene 1% gel was found to be better when compared with Ketoconazole 2% cream monotherapy in Pityriasis Versicolor. Difference between two groups was statistically significant ($p=0.011$). Stratification with regard to age, gender and duration of disease was also carried out.

Table 1: Distribution of patients by age

Age (Year)	Group-A (Combination)		Group-B (Ketoconazole)	
	No.	%	No.	%
18-25	26	57.8	32	71.2
≥ 26	19	42.2	13	28.8
Total	45	100.0	45	100.0
Mean \pm SD	24.3 ± 4.3		23.3 ± 3.9	

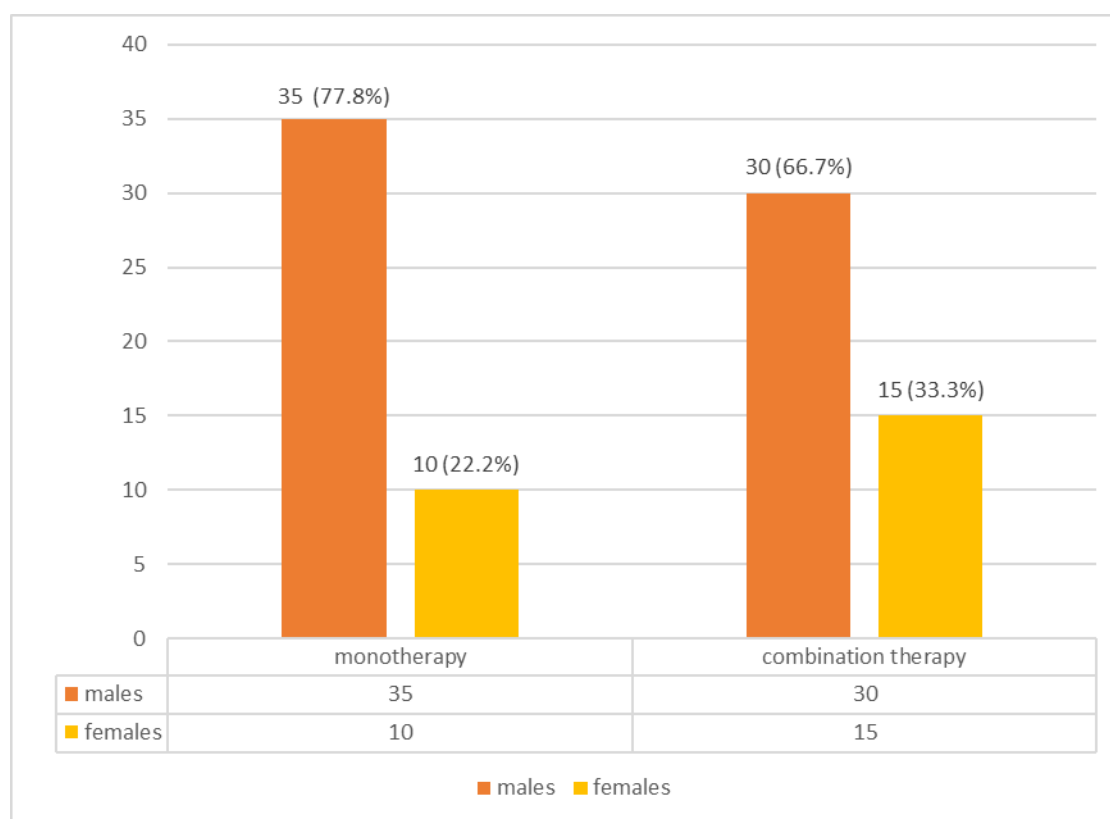


Figure 1: Frequency of gender

Table 2: Distribution of patients by duration of disease

Duration of disease (months)	Group-A (Combination)		Group-B (Ketoconazole)	
	No.	%	No.	%
≤ 3	43	95.5	38	84.4
≥ 3	2	04.5	7	15.6
Total	45	100.0	45	100.0
Mean±SD	2.0±0.9		2.3±1.2	

Table 3: Distribution of patients by efficacy

Efficacy	Group-A (Combination)		Group-B (Ketoconazole)	
	No.	%	No.	%
Yes	42	93.3	33	73.3
No	3	6.7	12	26.7
Total	45	100.0	45	100.0
Chi square	= 6.480			
P value	= 0.011			

Table 4: Stratification of efficacy in two groups among age

Age (Year)	Group	Efficacy		Total	P value
		Yes	No		
18-25	Group-A	23	3	26	0.121
	Group-B	23	9	32	
Total		46	12	58	
≥ 26	Group-A	19	0	19	0.028
	Group-B	10	3	13	
Total		29	3	32	

Table 5: Stratification of efficacy in two groups between genders

Gender	Group	Efficacy		Total	P value
		Yes	No		
Male	Group-A	27	3	30	0.021
	Group-B	23	12	35	
Total		50	15	65	
Female	Group-A	15	-	15	*
	Group-B	10	-	10	
Total		25	-	25	

*No statistics are computed because Efficacy is a constant.

Table 6: Stratification of efficacy in two groups for duration of disease

Duration of disease	Group	Efficacy		Total	P value
		Yes	No		
≤ 3 months	Group-A	41	2	43	0.006
	Group-B	28	10	38	
Total		69	12	81	
> 3 months	Group-A	1	1	2	0.571
	Group-B	5	2	7	
Total		6	3	9	

DISCUSSION

Pityriasis Versicolor (PV) is an infection of the skin caused by *Malassezia* yeasts. It is a non-contagious disease characterized by hypo or hyperpigmented macules that commonly involve face, upper arms & trunk [1]. Pityriasis Versicolor affects males and females equally. In this study, out of 90 patients, 65(72.2%) were males while 25(27.7%) were females, this is consistent with the results of the study conducted by Naeem et al. in which 71% of the patients were males and 29% were females [8], the possible reason suggested is high amounts of outdoor activities in males, which results in sweating leading to *Malassezia* infection.

Pityriasis Versicolor affects young adults. In the study 52(57.7%) out of 90 patients fell in 21 to 30 years age group with mean age of 24.56 ± 4.736 . In a study by Munir et al. the mean age of patients was about 21 years with 90% of the study population were <30 years of age [2]. The reason is attributed to high levels of androgens, leading to increased sebum production associated with PV development.

The study results showed that pityriasis versicoloris effectively treated with both monotherapy or combination therapy. However, the efficacy improves further with a drug like Adapalene to the standard ketoconazole topical treatment option. The reason maybe suggested due to the biological effects and the mechanisms through which Adapalene works. Adapalene can be safely used topically because its absorption into the skin is scarce. The ADP is metabolized by O- demethylation, hydroxylation, and conjugation, while the excretion is mainly biliary. Through topical administration, Adapalene is concentrated in the corneum layer due to its lipophilic properties. A small amount reaches the epidermis and hence the systemic circulation and makes it less toxic [9]. Rusu A et al. showed that Adapalene possesses anti-inflammatory, keratolytic, immunomodulatory, antiproliferative, neuroprotective, and antibacterial activities. Hence, they make it a suitable add-on to the traditional treatment approach for skin disorders, especially PV. It is well-tolerated, with the least side effects option that shows positive skin disorders literature efficacy [9].

The results were like Essam Bakr et al., who compared the clinical outcomes of 0.1% adapalene gel vs 2% ketoconazole cream & their combination in PV in an RCT. Their results showed higher rates improvement & higher rates of well-satisfied patients in combination groups than monotherapy. Supporting the suggestion of Adapalene's efficacy to expedite healing in PV patients [10]. The results supported the literature results, where Shi TW et al. compared the efficacy of combination therapy with Adapalene 0.1% gel & ketoconazole 2% cream versus monotherapy with ketoconazole 2% cream in Pityriasis versicolor and found the improvement rate to be 92% in the combination group while 72% in the monotherapy group [11].

CONCLUSION

This study concludes that a combined therapy with adapalene 0.1% gel and ketoconazole 2% cream is more effective than ketoconazole 2% cream monotherapy in the treatment of PV.

RECOMMENDATION

It is recommended to use a combination of adapalene 0.1% gel & ketoconazole 2% cream than ketoconazole 2% cream monotherapy in the treatment of PV.

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