COMPARISON OF EFFICACY OF COMBINATION OF 2% KETOCONAZOLE SOLUTION WASH AND TOPICAL 1% CLOTRIMAZOLE WITH TOPICAL 1% CLOTRIMAZOLE ALONE IN CASES OF PITYRIASIS VERSICOLOR

Ayesha Anwar, Naeem Raza, Najia Ahmed, Hyder Ali Awan*

Pak Emirates Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan, *King Abdul Aziz Naval Base, Jubail, Saudia Arabia

ABSTRACT

Objective: Comparison of efficacy of combination comprising 2% ketoconazole solution wash plus topical 1% clotrimazole versus topical 1% clotrimazole alone in management of patients with Pityriasis versicolor.

Study Design: Randomized controlled trial.

Place and Duration of Study: Dermatology department, Pak Emirates Military Hospital Rawalpindi, from Oct 2016 to Apr 2017.

Material and Methods: Sixty patients of Pityriasis versicolor, both male and female were included in study. Diagnosis of Pityriasis versicolor was made clinically and confirmed microscopically by examining skin scrapings for fungal hyphae. Patients with concomitant systemic illnesses or those who had received anti-fungal in last three months were excluded from study. Random number tables were used to allocate patients to the two treatment groups. Group A received 2% ketoconazole shampoo twice per week for four weeks plus topical 1% clotrimazole twice daily application for 2 weeks. Group B received only topical therapy with 1% clotrimazole cream applied twice daily for 2 weeks. Assessment of treatment efficacy was done by clinical examination of patient and microscopy of skin scrapping for fungal hyphaedone at baseline and at end of study (4 weeks of treatment). A negative clinical examination and negative skin scrapping for fungal hyphae was considered effective therapeutic response.

Results: In group A, the mean age of patients was 29.76 ± 8.89 years and in group B was 27.67 ± 10.46 years. Efficacy in group A was observed in 22 (73.33%) patients while in group B in 14 (46.67%) patients.

Conclusion: Combination of 2% ketoconazole solution wash plus topical 1% clotrimazole was found more effective in treatment of patients with Pityriasis versicolor as compared totopical 1% clotrimazole alone.

Keywords: Clotrimazole, Fungal hyphae, Ketoconazole, Pityriasis versicolor.

INTRODUCTION

Pityriasis versicolor (PV) is a chronic, superficial cutaneous fungal infection caused by fungus Malassezia (M). The condition is characterized by multiple, circular to oval, hypo or hyperpigmented macules or thin plaques with scaling occurring over the trunk, proximal arms and neck[1]. Malassezia, a lipophilic dimorphic fungus, is present as a part of normal micro-flora of human skin and that of other vertebrate hosts. Predisposing conditions such as alteration in skin condition due to increased sweating, poor hygiene and changes in host defenses can make it pathogenic. Commonly isolated species in patients of PV are Malasseziaglobosa (66%), M furfur (20%), M restricta (3%) and M sympodialis (3%)[2]. PV is common worldwide with prevalence of upto 50% in tropical countries due to the propensity of the fungus to grow in warm humid conditions. Adolescents and physically active adults are commonly affected due to increased sebum production as a result of hormonal changes that allows a lipid rich environment promoting fungal growth[3]. Diagnosis of PV is mainly clinical; based on characteristic skin lesions on clinical examination, Wood's light examination of the lesion showing yellow fluorescence and microscopy of skin scraping on KOH smear. KOH mount examination shows characteristic spaghetti and meatball appearance

Correspondence: Dr Ayesha Anwar, Coy Comd, Army Medical College Rawalpindi Pakistan
Email: ayesha.rana1@gmail.com
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of fungal hyphae under the microscope[4]. Currently the first line treatment of PV is topical antifungals; systemic antifungals being used only for severe and recalcitrant cases[5]. Topical agents for treatment include eclotrimazole, selenium sulfide (2.5% to 5%) shampoo, ketoconazole shampoo, zinc pyrithione, nystatin, 3% salicylic acid, topical terbinafine, tretinoin, 1% diclofenac gel and adapalene gel. 6-7 Systemic therapy includes fluconazole, itraconazole, and terbinafine[6]. Ketoconazole and clotrimazole belong to azole group of antifungals. They act on fungal cell wall synthesis by inhibiting cytochrome *p*-450 dependent 14-alpha lanosteroldemethylase. Majority of patients visiting a dermatology clinic prefer topical treatments. Moreover they have fewer side effects and higher concentrations of active drug in the skin[8]. In different studies, treatment with ketoconazole solution wash or ketoconazole soap as an adjunct to topical antifungal therapy in the management of Pityriasis versicolor was more effective in rates of cure as well as preventing recurrence[8-9]. Despite treatment, recurrence rate of PV is very high, being 60% in the first year and 80% in the second year[4]. This study was designed to compare the efficacy of combination of ketoconazole solution wash twice per week for four weeks plus 1% topical clotrimazole twice daily application for two weeks versus 1% topical clotrimazole twice daily application for two weeks in treatment of patients with Pityriasisversicolor. Comparison would help us make better decisions regarding effective treatment of PV.

MATERIAL AND METHODS

The study, a randomized controlled trial was done at Dermatology outpatient department of Pak Emirates Military Hospital Rawalpindi from October 2016 to April 2017. The sample size was calculated using WHO sample size calculator for two proportions with anticipated population proportion P1 of 96%[9] and anticipated population proportion P2 of 60%[9]. The calculated sample size was 60 with thirty patients each in both groups A and B. Non probability consecutive sampling technique was used. Sixty patients with a diagnosis of pityriasis versicolor, from dermatology outpatient department (OPD) at Pak Emirates Military Hospital Rawalpindi were selected after informed written consent. Formal approval of study from the hospital ethics committee was sought. Patients with a concomitant systemic illness, immunosuppression, extensive involvement (>20% body surface area) or known hyper-sensitivity to azole antifungals were excluded from the study. OPD registration number, age, gender and address with contact number were noted for every selected patient. Random number tables were used to allocate the patients to one of the two treatment groups. Help of other colleagues at the department was taken to control bias. A different doctor allocated the groups and treatment was given by another while a third doctor did the assessment at the end of treatment. Group A received ketoconazole shampoo twice per week for four weeks plus topical 1% clotrimazole twice daily application for 2 weeks. Group B received only topical therapy with 1% clotrimazole cream twice daily application for 2 weeks. The quantity of topical cream was calculated on the basis of a rough estimate of body surface area, that is 1g (2 finger tip units) for 4% body surface area. After taking appropriate history and physical examination of all the patients, diagnosis was confirmed by microscopic examination of skin scraping. Skin was scraped with a blade, scraping collected on a slide, followed by addition of 1-2 drops of 10% KOH, covered by cover slip and observed after 10 min under ×10 and ×40 of light microscope. Assessment of treatment efficacy was done with help of clinical examination of patient and skin scraping for microscopy at the baseline and after 4 weeks of treatment, at the end of study. For analysis of data, SPSS version 21.0 was used. Mean and standard deviation were used to calculate quantitative variables like age and duration of illness. Gender and efficacy which are qualitative variables were calculated by taking frequency and percentages. Efficacy was compared by application of chi-square test between the two groups. A *p*-value of <0.05 was

considered significant. Effect modifiers like age, gender and duration of illness were controlled by stratification. Post stratification chi-square test was applied to see effect on outcome.

RESULTS

The age of the patients in group A ranged from 15 to 50 years (mean ± SD= 29.76 ± 8.89) and in group B ranged from 14 to 48 years (mean ± SD=27.67 ± 10.46). Age distribution was such that majority of patients in both groups were found to be in the age group 12-30 years. There were 23 (76.67%) males and 7 (23.33%) females in group A while 24 (80%) males and 6 (20%) females in group B. Mycological cure was achieved in 22 (73.33%) patients in group A and 14 (46.67%) patients in group B (*p*-value 0.035). Comparison of efficacy between the two groups showed that 22 (73.33%) patients in group-A and 14 (46.67%) patients in group-B were treated effectively, (*p*-value 0.035). Results of effect modifiers such as age, sex and duration of illness are tabulated in tables-I, II & III.

Table-I: Stratification for efficacy with regards to age.

(Age: 12-30)

Group	Efficacy		*p*-value
	Yes	No	
A	13	5	0.16
B	10	10	

Age: 31-50

Group	Efficacy		*p*-value
	Yes	No	
A	9	3	0.09
B	4	6	

Table-II: Stratification for eficacy with regards to gender

Male

Group	Efficacy		*p*-value
	Yes	No	
A	16	7	0.17
B	12	12	

Female

Group	Efficacy		*p*-value
	Yes	No	
A	6	1	0.052
B	2	4	

Table-III: Stratification for eficacy with regards to duration of disease.

1-4 weeks

Group	Efficacy		*p*-value
	Yes	No	
A	13	4	0.19
B	7	6	

>4 weeks

Group	Efficacy		*p*-value
	Yes	No	
A	9	4	0.12
B	7	10	

DISCUSSION

Pityriasis versicolor (PV) is a superficial fungal infection of worldwide distribution with increased prevalence in hot and humid environment. A number of topical and oral antifungal agents are effective in treating clinical symptoms and producing mycological cure. Imidazoles, triazoles and allylamines are the group of

antifungal agents with specific antifungal activity that can be applied topically or taken orally. Ketoconazole and topical clotrimazole both belong to azole antifungal group which interferes with fungal cell wallergosterol synthesis by inhibiting cytochrome P450 enzyme. Topical therapy has always been recommended as the first line of treatment for pityriasis versicolor because of its efficacy, ease of application and fewer side effects[10,11]. Oral therapy is only recommended in extensive and recalcitrant cases not responding to initial topical therapy[12]. The oral azoles are notorious for a number of drug interactions due to their effect on cytochrome P450 and may also cause hepatic and renal impairment. Therefore topical therapy remains first line and search for an ideal topical agent for the treatment of pityriasis versicolor continues. The newer topical azoles still under trial include sertaconazole, dapaconazole and luliconazole with effectiveness against malassezia species in PV[13,14] Another option that requires further work is to combine more than one topical agents and see if there is an increased efficacy. A trial by Shi *et al*[15] showed that adding adapalene to 2% ketoconazole in the treatment of PV increased the efficacy to 92% as compared to 72% with 2% ketoconazole alone. Similarly the addition of solution washes (ketoconazole/clotrimazole) to topical therapy also improved cure rates according to a study done in Nepal[9]. However no such trial exists in our population. In a randomized trial conducted by Shrestha *et al*, addition of 2% ketoconazole solution wash to topical 1% clotrimazole twice dailytherapy was effective in 90% whereas 1% clotrimazole alone was effective in 60% of patients with pityriasis versicolor[9]. These result are similar to our study. The literature review regarding the efficacy of 2% ketoconazole shampoo in PV shows variableresults. A multicenter randomized double blind trial conducted to evaluate the efficacy and safety of a single application versus three once daily applications (3 days) of ketoconazole 2% shampoo versus placebo shampoo in the treatment of mycologically confirmed pityriasis versicolor showed both regimens of ketoconazole shampoo to have significantly more efficacy than placebo. The clinical response rates were 73%, 69%, and 5% for the 3-day ketoconazole, 1-day ketoconazole, and placebo groups, respectively. However, the difference in the efficacy of the two ketoconazole treatment regimens was not found to be significant in this study[16]. Aggarwal *et al*[17] compared the efficacy of 2% ketoconazole shampoo with 2.5% selenium shampoo in PV. Patients were treated with either 2% ketoconazole shampoo or 2.5% selenium sulphide shampoo, once a week for three weeks. On clinical assessment after one month of start of therapy, 19 (95%) out of 20 patients treated with ketoconazole shampoo were cured while one case had mild residual disease. In selenium sulphide shampoo group, 17 (85%) out of 20 patients were cured. There was no significant difference observed in the response rates in the two groups[17.] Another randomized double blind study compared flutrimazole shampoo with ketoconazole shampoo in treatment of PV and found both the drugs to have comparable efficacy (75.9% and 80.8% respectively)[18]. This efficacy is comparable to our results where 73.33% patients in the ketoconazole solution wash group were effectively treated. A number of studies have compared 1% topical clotrimazole with other topical and oral antifungals in treatment of PV. A double-blind, randomized controlled clinical trial conducted by Dehghan *et al*[19] compared the efficacy of a single dose of 400 mg fluconazole versus 1% clotrimazole cream twice daily application for 2 weeks in patients of Pityriasis versicolor. After completion of four weeks of treatment, the results showed a significantly higherclinical response in patients treated with clotrimazole cream as compared to those receiving oral fluconazole (complete response 94.9% vs. 81.2% respectively, p=0.044)[19]. Another study showed 60% efficacy of single dose oral fluconazole in patients of PV[20]. This emphasizes the fact that topical therapy remains the mainstay of treatment in PV with an additional benefit of fewer side effects. Balwada *et al*[21] conducted a comparative study on topical

2% ketoconazole cream and 1% clotrimazole-cream in patients of Pityriasis versicolor. Assessment after 14 days revealed that 18/20 (90%) patients treated with ketoconazole cream were cured while 2 cases had significant residual lesions. In clotrimazole treated group, 17/20 (85%) patients were cured. No side effects were reported in both the groups. In a study done by Kausar *et al*[22] efficacy of single dose 400mg oral itraconazole was compared with two weeks twice daily application of topical 1% clotrimazole. Mycological cure rate was 66% in patients given oral itraconazole while it was 86.7% in patients that received topical therapy. This study again highlights and emphasizes on the importance of topical therapy in patients of Pityriasis versicolor. A number of newer topical azole antifungals are currently under trial for treatment of PV. These include sertaconazole, luliconazole and dapaconazole. Clinical evaluation of the efficacy of sertaconazole 2% cream in the management of pityriasis versicolor and a comparison with that of clotrimazole 1% cream was done by Tatavarthi and Ramachandra[13]. Sertaconazole was found to be more efficacious and safer as compared to topical clotrimazole for curing pityriasis versicolor patients in this study. Another topical azole dapaconazole was also found effective in PV[23]. Considering the response to 1% clotrimazole in patients with pityriasisversicolor, the results of our study are different as compared to trials conducted by Dehghan *et al*[19] Balwada *et al*[21] and Kausar *et al*[22] as a lower efficacy (46.67%) with 1% topical clotrimazole was found in our study. However efficacy of 2% ketoconazole solution in combination with 1% clotrimazole was more than that of 1% clotrimazole alone (73.33% versus 46.67%), findings similar to Shreshta *et al*[9]. This emphasizes the fact that2% ketoconazole solution wash in combination with 1% clotrimazole has a synergistic effect in PV treatment. It is consistent with results of our study that "combination of 2% ketoconazole solution was plus 1% topical clotrimazole is more effective than 1% topical clotrimazole alone in the treatment of Pityriasis versicolor". It is recommended that topical antifungals be considered first line in treatment of pityriasis versicolor because of their adequate efficacy and fewer side effects[24]. Based on our findings, it is recommended that topical therapy in combination be tried before proceeding to the option of oral antifungalsas it leads to better clinical efficacy and lesser likelihood of adverse effects. Despite the presence of a large number of treatment options, the optimal approach to treatment of pityriasis versicolor still remains unclear as only limited high-quality comparative studies on the relative efficacy of specific treatments for pityriasis versicolor are present. Various suggestions for control of disease and greater cure rates include longer courses of treatment, higher concentrations of topical active ingredients and higher doses of oral antifungals; however additional research is necessary to confirm this conclusion. Till then topical therapy in combination is a plausible option. Limitations of the current study include small sample size and shorter duration. Hence large randomized multicenter trials involving follow up at a longer duration are needed to further confirm the results of this study. An effective treatment that prevents recurrence is very much needed for this common skin ailment and combination topical therapies are a promising option.

CONCLUSION

It is concluded on the basis of our study that combination of 2% ketoconazole solution wash plus 1% topical clotrimazole is more efficacious than 1% topical clotrimazole alone in the treatment of Pityriasis versicolor.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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