ORIGINAL ARTICLE

Efficacy of Azoles Antifungals in Treatment of Pityriasis Versicolor

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ABSTRACT

Introduction: Pityriasis versicolor is superficial fungal infection. Topical drugs are often effective in treatment of limited disease while systemic drugs are more suitable in extensive cases The systemic triazole drugs, itraconazole and fluconazole have shown promising results at different doses. **Aims**: To assess the efficacy and safety of oral fluconazole combined with ketoconazole shampoo and oral itraconazole in the treatment of Pityriasis versicolor. **Methods**: The study was conducted at department of Dermatology at Nepalgunj Medical College from March 2019 to February 2020. Total 100 patients of both genders with Pityriasis versicolor were randomly allocated into two groups with 50 patients in each group. Patients in Group I received oral fluconazole 300mg a week for two consecutive weeks along with ketoconazole 2% shampoo twice weekly for two weeks while those in Group II received itraconazole 200mg daily for one week. Efficacy was assessed in terms of negative fungal hyphae. The drug is considered safe if no patients were withdrawn for clinical adverse effects or laboratory abnormalities. **Results:** In this study age ranged from 18 to 50 years with mean age of 31.1 years in Group I and 31.92 years in Group II. Efficacy was seen in 78% of Group I patients as compared to 54% in Group II patients at two weeks and 94% in Group I and 90% in Group II at four weeks. No significant adverse effects were reported in any of the group. **Conclusion**: Fluconazole along with ketoconazole shampoo is more effective than itraconazole in treatment of pityriasis versicolor with minimal side effects, at lesser cost.

Keywords: Efficacy, Fluconazole, Itraconazole, Ketoconazole, Pityriasis versicolor

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INTRODUCTION

Pityriasis versicolor(PV) is common fungal infection of the stratum corneum caused by lipophilic yeast of Malassezia species.[1] It is more common in warm and humid conditions. The genus Malassezia is part of the normal skin microflora. It needs predisposing factors for multiplication and subsequent conversion from the commensal yeast form to the mycelial phase. Factors associated with increased risk of acquiring PV are increased environmental humidity, application of oily preparation and creams, corticosteroid overuse, genetic predisposition, malnutrition and hyperhidrosis.[2] It is clinically characterized by discrete, round to oval, hyperpigmented or hypopigmented slightly scaly macules, on the trunk, upper arms and face.[3] History and clinical examination are enough to diagnose PV. The clinical diagnosis can be confirmed by direct microscopic examination of infected skin scraping treated with 10% potassium hydroxide (KOH). Microscopic visualization of the fungi appears as short, thick hyphae with a large number of variously sized spores.[4] PV is generally asymptomatic, the greatest concern for patients leading to sought treatment is the unpleasant cosmetic appearance of the skin. Topical antifungals such as ketoconazole, miconazole or terbinafine are currently the first line of treatment for PV and systemic antifungals are recommended for severe or recalcitrant cases.[5] Azole antifungal agents, causes inhibition of cytochrome P450 dependent lanosterol 14-α-demethylase, resulting in impaired sterol synthesis in fungal cell membranes to limit cell function and growth.[6,7] This study is conducted to assess the efficacy and safety of oral fluconazole combined with ketoconazole shampoo and oral itraconazole in the treatment of PV.

METHODS

A hospital based comparative prospective study was conducted at department of Dermatology at Nepalgunj Medical College from March 2019 to February 2020. Patient of both genders, aged 18 to 50 years who had a clinical diagnosis of PV confirmed by mycological examination (10% KOH) were included in the study. Patient with known sensitivity to itraconazole or fluconazole, who received any topical or systemic antifungal therapy during last one month, other superficial or systemic fungal infection, any history of renal or hepatic disease or malignancy, history of alcoholism, pregnant or lactating women and patients with other chronic illness (diabetes, hypertension) were excluded from the study. Data regarding the demographic parameters like age, gender and duration of complaints were recorded.

Eligible patients were randomly divided into two equal groups. Group I patients were asked to take oral fluconazole 300mg a week for two consecutive weeks along with ketoconazole 2% shampoo biweekly for two weeks, Group II patients were asked to take itraconazole 200mg daily for one week. Detailed

history of every patient was taken, clinical and Wood's lamp examination was done, at first visit. Wood's lamp examination usually showed yellowish fluorescence of the involved skin. Patient were asked to follow up after two weeks and four weeks to assess the clinical and mycological improvement. At each visit, patients were examined regarding scaling, hyperpigmentation, hypopigmentation and pruritus.

Clinical evaluation was done by the naked eye appearance of the lesions, presence of re-pigmentation and disappearance of the lesions. The following criteria was adopted for this.

No improvement: Persistence of lesions and presence of scaling.

Moderate improvement: Lesions were less prominent and/or moderate decrease in scaling.

Marked improvement: Lesions appeared pale with presence/ or absence of mild scaling and disappearance of some of the lesions

Complete clinical cure: Complete disappearance of lesions.

Mycological evaluations which included direct KOH preparation from the most prominent lesion and Wood's lamp examination were also performed. Efficacy was defined in terms of mycological cures when the KOH examination was negative that is absence of fungal hyphae and spores.

The quantitative variables like age and duration of complain were calculated in means. The qualitative variables like gender, clinical improvement were calculated taking frequency and percentage. All the data were analyzed using SPSS version 25.Comparision of efficacy in two groups was done by chi-square test. A p-value of less than 0.05 ($p<0.05$) was considered as significant.

Safety assessment was carried out in the two study groups at the end of second week and further re-assessed at the end of fourth week follow-up. Laboratory investigations such as complete blood count, liver and renal function tests were done at baseline and at the end of two weeks and subsequently repeated at the end of four weeks. Possible signs of side effects were recorded. Drug is considered to be unsafe if the laboratory parameters were deranged (not within normal range) or if the patient developed severe nausea , vomiting, headache or skin lesion other than that of PV which lead to disturbance in daily activities and needed medical intervention.

RESULTS

Total 101 patients aged 18 to 50 years were enrolled in our study. Patients of Group I (n=50) received 300 mg fluconazole as a single dose and repeated weekly for two weeks along ketoconazole 2% shampoo biweekly for 2weeks, Group II(n=50) patients received itraconazole 200mg daily for one week. One patient in Group I lost follow-up thus was excluded from study.

Mean age was 31.1±9.22 years in Group I and 31.92±8.98 years in Group II. Average duration of complaint was 12.84 months in Group I and 12.44 months in Group II, with a range of two months to 36months in both groups. Among total study population 61(61%) were male and 39(39%) were female. Male to female ratio was 1.5:1.There were 31(62%) males and 19(38%) females in Group I while 30(60%) male and 20(40%) females in Group II. There were no statistically significant ($p>0.05$) differences regarding age, sex and duration of complaints between the two groups as shown in Table I.

	Group I	Group II	P value
Gender			
Male	31	30	>0.05
Female	19	20	
Mean Age(years)	31.1	31.9	>0.05
Mean duration of complain(months)	12.84	12.44	>0.05

Table I: Characteristics of Patients

At four weeks 21(21%) of total patients showed complete clinical cure, 12(24%) in Group I and 9(18%) in Group II with no statistical significance ($p>0.05$). Eight(8%) patients: 3(6%)in Group I and 5(10%) in Group II had no clinical improvement as shown in Table II.

Clinical improvement	Group I	GroupII	Total
Complete cure	12 (24%)	9 (18%)	21 (21%)
Marked improvement	21 (42%)	14 (28%)	35 (35%)
Moderate improvement	14 (28%)	22 (44%)	36 (36%)
No improvement	3 (6%)	5 (10%)	8 (8%)
Total	**50**	**50**	**100**

Table II: Clinical evaluation at 4 weeks

Mycological cure was seen in 39(78%) patients in Group I as compared to 27(54%) in Group II ($p=0.01$) at two weeks. Efficacy was seen in 47(94%) patients in Group I as compared to 45(90%) in Group II ($p=0.46$) at four weeks as shown in Figure 1.

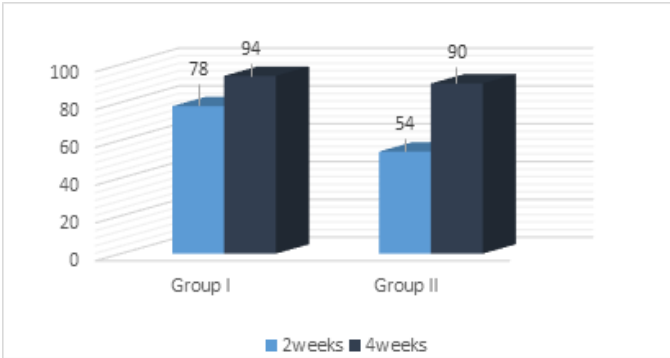

Figure 1: Mycological cure in Group I and Group II(%)

The laboratory parameters for all the patients were within normal limits in both groups before and after the treatment. There was no major side effect of the drugs except tolerable headache (three Patients) and gastrointestinal disturbances (10 patients) in few patients as shown in Table III. That resolved without any intervention and did not lead to discontinuation of the treatment. No patient developed any new skin rashes. No adverse effects were reported after completion of treatments.

Adverse effects	Group I (Num %)	GroupII (Num %)
Abdominal discomfort	1 (2%)	3 (6%)
Diarrhea	3 (6%)	1 (2%)
Nausea	2 (4%)	
Headache		3 (6%)

Table III: Adverse effects in patients of Group I and Group II

DISCUSSION

PV is the fungal infection of superficial layer of skin commonly caused by M.sympodialis, M.furfur and M.globosa.[8] PV is common in the post-pubertal age where sebaceous glands are active and in the individuals who sweat more.[9] As Malassezia species are endogenous to the skin flora, it is difficult to eradicate. Systemic therapy such as fluconazole and itraconazole can be used successfully in extensive and recurrent PV.[10] In a study by Farschian et al has shown 93.33% mycological cure rate after completing two weeks treatment with 300mg fluconazole as single dose repeated weekly for two weeks.[11] In another study by Bhogal et al mycological cure after four weeks of treatment was observed 82.2% and 64.4% with fluconazole 400mg single dose and 150mg per week dose for four weeks respectively.[12] On the basis of these studies 300mg fluconazole as single dose repeated weekly for two weeks is observed to be the best.

There were several studies in which ketoconazole 2% shampoo was applied as treatment. In a study, by Tran cam V et al in 240 pityriasis versicolor patients were classified into three groups: Fluconazole 300 mg a week and 2% ketoconazole foam twice a week for two weeks (Category I), Itraconazole 200 mg daily for one week (category II); Ketoconazole 2% foam daily for two weeks (Category III). After four weeks of treatment, the highest cure rate was observed in Category I (81.2%), followed by Category II (66.3%) andcategory III (60.0%). It was reported in the study that the most effective regimen for PV patients is fluconazole 300 mg per week combined with ketoconazole 2% twice a week for two weeks.[13] Similarly in this study fluconazole 300 mg per week combined with ketoconazole 2% twice weekly for two weeks is observed to be more effective.

In comparative study done by Badri et al, patients receiving fluconazole two doses 300mg given one week apart with patients taken an association of fluconazole (two doses 300mg given one week apart) and ketoconazole shampoo the first day. At the end of the study, there was no significant difference in clinical presentation and in improvement rate PV between fluconazole and association of fluconazole and ketoconazole shampoo.[14]

Studies have evaluated the efficacy of 400 mg itraconazole administered once and for three days as compared to 200 mg itraconazole for 5 or 7 days.[15, 16] While Kose et al demonstrated that a single 400 mg dose was equivalent to 200 mg for 7 days,[16] Kokturk et al found a single 400 mg dose to be ineffective, with itraconazole regimens of 400 mg for three days and 200 mg for 5 days both producing significantly greater mycological and complete cure (p = 0·001).[15] Though in this study we opted to recommend 200mg itraconazole capsule for 7 days over 400mg itraconazole capsule for three days , as the patients had to take only one capsule a day which was more convienent with better compliance.

In the present study, the prevalence of disease was more among males (61%) when compared to females (39%) , Ghosh et al[8] ,Rao et al[17] and Krishnan et al[18] have also observed almost similar results with more prevalence of cases in males. This could be attributed to their profession and outdoor activities and easy accessibility of the health care services. In our research, fluconazole 300mg a week along with 2% ketoconazole shampoo twice a week for two weeks has proved to be significantly better than itraconazole 200mg daily for one weeks at two weeks regarding the mycological cure in the treated patients. This might be due to the combined antifungal action of oral fluconazole and ketoconazole shampoo. But at four weeks, there was not much difference demonstrated between mycological cure in both the treatment groups. The findings in our study is similar to other studies that shows mycological cure in patients treated for two weeks with oral fluconazole.[11, 12] The both regimen are safe. Itraconazole and fluconazole are well tolerated by most patients, the common side effects being gastrointestinal disturbances, which are mild and transient in nature.[19, 20,21,22] Therapy with fluconazole along with ketoconazole shampoo is preferable in view of single dose administration and lesser cost as compared to itraconazole with better results in short term. However studies have different results on short-term and long term effectiveness of both regimen. Residual dyschromia even after the successful treatment is problematic.[10] Normalization of pigment following successful therapy is variable and may take months, depending on individual skin type and coincidental skin exposure. In this study also complete normalization of color was observed in some patients (21%) only, as it mostly resolve within few months of treatment.

LIMITATIONS

The study was based on single center outpatient sample, the follow up of the patients was of short duration. So the findings of this comparative study may not reflect the exact scenario of general population. Further study is needed to assess the

long term response to the treatments and to calculate relapse rate. We included only those cases who were confirmed by KOH examination; however, KOH examination is not 100% sensitive for PV.[23] This could result in the exclusion of KOH-negative cases. Dermoscopy evaluation of lesions might help in proper assessment of the disease severity in pretreatment, treatment and post treatment phase.

CONCLUSION

Although in our study we found significant superiority of fluconazole 300mg along with 2% ketoconazole shampoo twice weekly at initial two weeks but both treatment were similar at four weeks. Both fluconazole along with 2% ketoconazole shampoo and itraconazole were well tolerated and no serious drug-related events were reported in our study.

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