Comparison of the efficacy of 2% ketoconazole shampoo vs. 2% climbazole shampoo in the treatment of pityriasis versicolor

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Background: Pityriasis versicolor is a recurrent non-inflammatory superficial fungal infection. Application of antifungal shampoo is a simple treatment modality for pityriasis versicolor that can be used on an extensive surface area. Currently, there is no study to evaluate the efficacy of climbazole shampoo. In this study, the efficacy of 2% ketoconazole shampoo was compared to 2% climbazole shampoo in the dermatologic clinic of Afzalipour Hospital, Kerman, Iran.

Methods: This triple-blind randomized clinical trial was performed on 60 patients diagnosed with pityriasis versicolor. Participants were categorized into groups A (ketoconazole shampoo) and B (climbazole shampoo) based on simple randomization. KOH smear was achieved from all participants at the baseline, four weeks after commencing treatment, and at three months follow–up. Participants were instructed to apply shampoo three times a week for three weeks on all body surfaces and scalp for 10 minutes before rinsing. Evaluation of treatment was based on clinical improvement and results of KOH smears. Complete cure was defined as negative KOH smear and complete clinical improvement.

Results: Seventy percent of the patients in the ketoconazole group and 43.3% of the patients in the climbazole group had negative smears four weeks after commencing treatment ($P = 0.037$). Complete clinical improvement at the three-month follow-up was 26.7% and 13.3% in the ketoconazole and climbazole groups, respectively ($P = 0.402$).

Conclusion: In the present study, 2% ketoconazole shampoo had significantly greater efficacy in terms of mycological cure than climbazole shampoo among pityriasis versicolor patients.

Keywords: ketoconazole, pityriasis versicolor, fungal infection

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INTRODUCTION

Pityriasis versicolor is a superficial non-inflammatory fungal infection that often becomes chronic and recurrent. It is most commonly observed in young adults, especially in tropical areas. The cause of the disease is lipophilic yeast of *Malassezia furfur*, *M. sympodialis*, and *M. globosa*, which are normal flora of the skin. Transformation of yeast form to the mycelial form leads to the development of skin lesions. Predisposing factors for pityriasis versicolor include pregnancy, immunosuppression,

hyperhidrosis, elevated humidity, high temperature, oily skin, and malnutrition, as well as long-term use of corticosteroids and antibiotics. The lesions occur as hypopigmented, hyperpigmented, or pink-colored macules and patches with fine scales. They are usually asymptomatic, but mild pruritus is occasionally present. The most common sites of involvement are seborrheic areas such as the neck, upper trunk, and proximal extremities [1-4].

Topical antifungal agents including polyenes, imidazoles (clotrimazole, ketoconazole, and miconazole), and allylamines (terbinafine) applied twice daily in the form of cream, lotion, or solution are the first line of treatment. Application of topical antifungal agents is often messy, laborious, and time-consuming; it can be accompanied by itching or stinging sensations, and irritant or allergic contact reactions may develop [3,5-7]. Systemic antifungal therapies such as azoles are prescribed in refractory, recurrent, and extensive cases. Systemic antifungals can have serious side effects such as gastrointestinal disturbance (nausea, vomiting, and diarrhea), interaction with other systemic drugs, hepatotoxicity, drug eruption, and cardiac arrhythmia (prolongation of QT interval) [3,8-10]. Shampoos such as selenium sulfide, ketoconazole, ciclopirox olamine, and zinc pyrithione are other treatment methods for pityriasis versicolor with easy application, short duration of treatment, and ability to use on extensive surface areas [11,12].

In this study, for the first time, the efficacy of 2% ketoconazole shampoo was compared against 2% climbazole shampoo among patients referring to the dermatologic clinic of Afzalipour Hospital, Kerman, Iran.

PARTICIPANTS AND METHODS

This triple-blind randomized clinical trial included 60 patients diagnosed with pityriasis versicolor from September 2019 to March 2020. Inclusion criteria were patients older than 12 years old who had positive KOH smear and Wood's lamp exam. Exclusion criteria were topical or systemic therapy with antifungal drugs, corticosteroids, or immunosuppressives within one month, pregnancy or lactation, and other dermatophytosis or any other serious illness. Diagnosis of pityriasis versicolor was based on positive KOH smear and Wood's lamp exam. Written informed consent was obtained from the participants. Then, participants were categorized into groups A (2% ketoconazole shampoo) and B (2% climbazole shampoo) based on simple randomization by Minitab 16 (Mini Tab Inc.). KOH smears were obtained from all participants at baseline and four weeks after commencing treatment. Furthermore, KOH smears were obtained three months after treatment to evaluate recurrence and persistent complete cure. Participants were instructed to apply the respective shampoos three times a week for three weeks on all body surfaces and scalp for 10 minutes before rinsing. The labels of the shampoos were changed to A and B, so the evaluators and patients were not aware of the type of treatment. Also, participants were asked to return the empty bottle of the shampoo after application for evaluation of compliance to the treatment.

Based on signs and symptoms including scaling, pruritus, and erythema, the participants were scored into four groups including 0 (lack of any signs or symptoms), 1 (mild signs or symptoms), 2 (marked signs or symptoms), 3 (severe signs or symptoms). Evaluation of treatment was based on clinical improvement and results of KOH smears. Complete clinical improvement was complete resolution of scaling, pruritus, and erythema. Marked clinical improvement was marked resolution of scaling, pruritus, and erythema (> 50%). Mild clinical improvement was a mild resolution of scaling, pruritus, and erythema (< 50%). Complete cure was defined as negative KOH smear and complete clinical improvement. The Ethics Committee of Kerman University of Medical Sciences approved the study proposal under ethics code IR.KMU.AH.REC.1397.107. The study was registered with the Iranian Registry of Clinical Trials, code IRCT20190811044510N1.

Data were analyzed blindly by a statistician who was unaware of treatment groups. SPSS 16 software (IBM, Armonk, NY, USA) was used for statistical analysis. Frequency, percentage, and mean ± standard deviation (SD) were used for descriptive analysis. The independent t-test and chi-squared test were used to compare quantitative and qualitative variables, respectively.

RESULTS

Sixty patients (30 patients in each group) completed the study. The patients' mean age

in the ketoconazole and climbazole groups was 34.92 ± 12.89 and 34.13 ± 10.57 years, respectively (P = 0.8). Most of the patients in both groups were male (56.7% in the ketoconazole group and 63.3% in the climbazole group; P = 0.598). Clinical features of the lesions in both groups at the baseline are demonstrated in Table 1. Seventy percent of the patients in the ketoconazole group and 43.3% of the patients in the climbazole group had negative smears four weeks after commencing treatment (P = 0.037) (Table 2; Figures 1 and 2). Complete cure at three months follow-up was 26.7% in the ketoconazole group and 13.3% in the climbazole group (P = 0.402). Recurrence rates in ketoconazole and climbazole groups at three months follow-up were 38.09% and 69.23%, respectively (P = 0.078) (Table 3). There was no significant correlation between clinical improvement and demographic features of the patients (age and sex) and site of the lesions in the ketoconazole group (P = 0.453, P = 0.364, P = 0.2) and climbazole group (P = 0.973, P = 0.705, P = 0.439), respectively. There were no side effects in either of the treatment groups.

Table 1. Clinical features of the lesions in both groups at baseline

Variables	Ketoconazole group N (%)	Climbazole group N (%)	*P*
Site			
Head & neck	16 (53.3)	15 (50)	
Trunk	9 (30)	14 (46.7)	0.253
Extremities	5 (16.7)	1 (3.3)	
Symptoms			
Scaling	23 (76.7)	16 (53.3)	0.058
Pruritous	16 (53.3)	18 (60)	0.602
Erythema	3 (10)	1 (3.3)	0.301
Severity of symptoms			
Mild	16 (53.4)	20 (66.7)	
Moderate	10 (33.3)	10 (33.3)	0.304
Severe	4 (13.3)	0 (0)	

Table 2. Mycological and clinical response one month after commencing treatment

Evaluation	Ketoconazole group	Climbazole group	*P*
Negative KOH smear	21 (70%)	13 (43.3%)	0.037
Complete clinical improvement	19 (63.3%)	15 (50%)	0.297
Marked clinical improvement	11 (36.7%)	15 (50%)	
Mild clinical improvement	0 (0%)	0 (0%)	
Complete cure	19 (63.3)	13 (43.3%)	

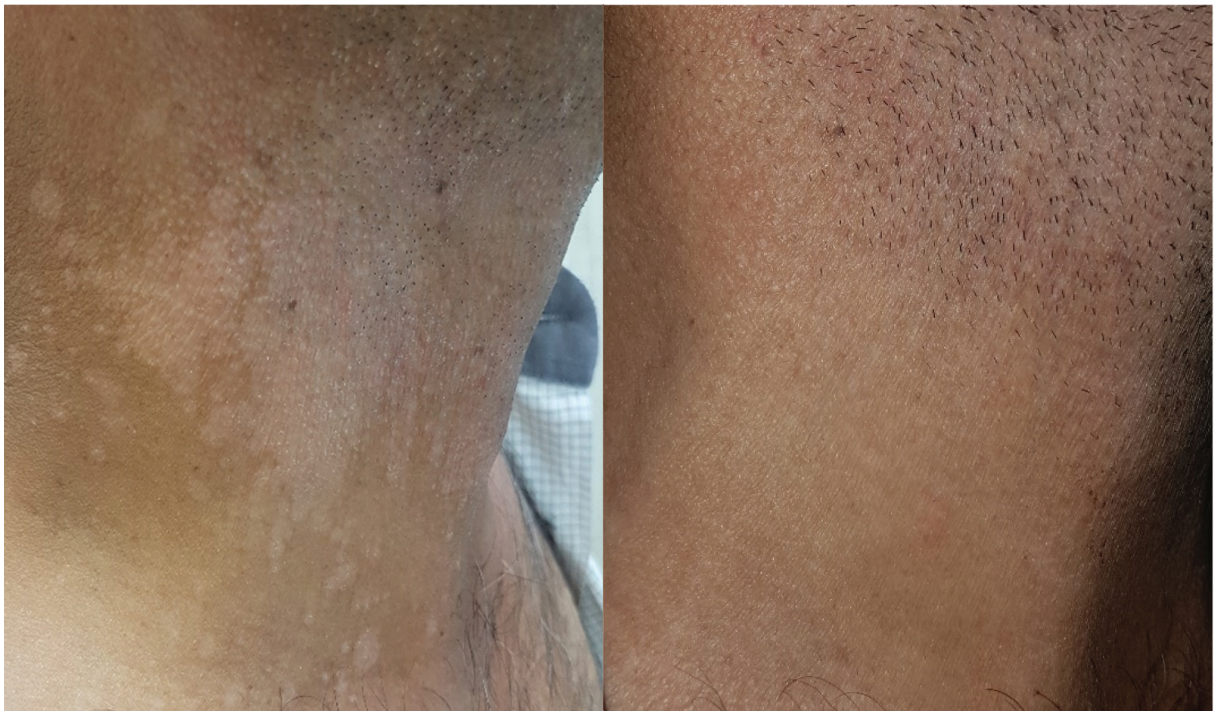

Figure 1. Pretreatment and post-treatment pictures of pityriasis versicolor lesions in the ketoconazole group

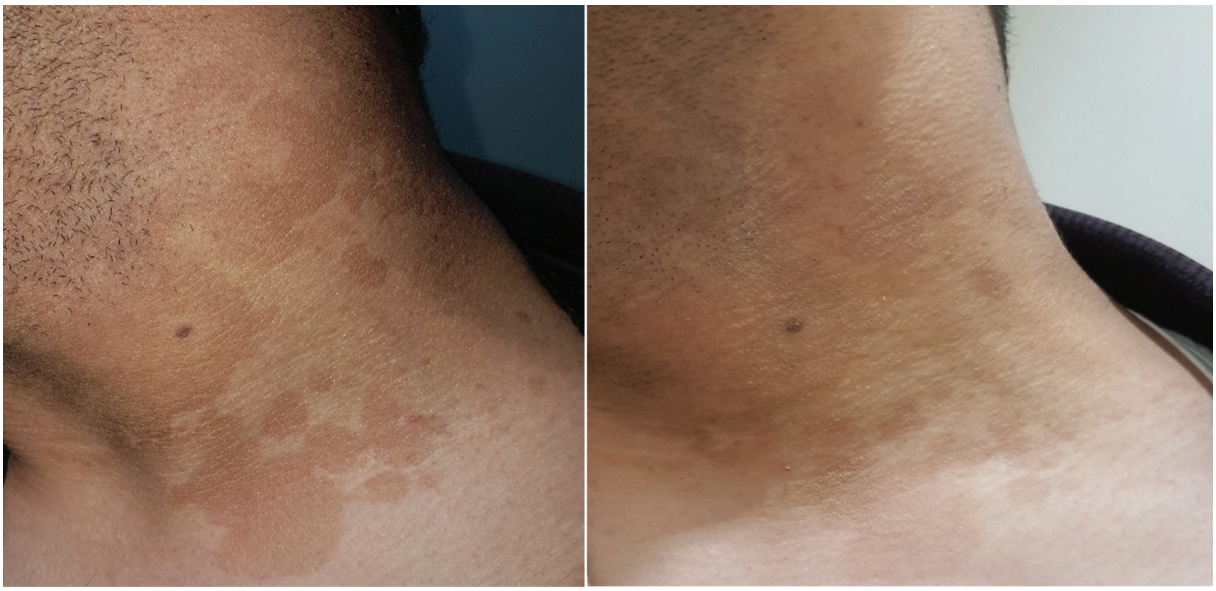

Figure 2. Pretreatment and post-treatment pictures of pityriasis versicolor lesions in climbazole group

Table 3. Mycological and clinical response at three months follow-up

Evaluation	Ketoconazole group	Climbazole group	*P*
Negative KOH smear	13/21 (61.90%)	4/13 (30.76%)	0.078
Recurrence	8/21 (38.09%)	9/13 (69.23%)	
Complete clinical improvement	8 (26.7%)	4 (13.3%)	0.402
Marked clinical improvement	16 (53.3%)	16 (53.3%)	
Mild clinical improvement	6 (20%)	10 (33.3%)	
Complete cure	8 (26.7%)	4 (13.3%)	

DISCUSSION

In this study, ketoconazole shampoo had significantly higher efficacy (70%) in terms of mycological cure than climbazole shampoo (43.3%) after four weeks of treatment ($P = 0.037$). Furthermore, the percentage of complete cure at three months follow-up in ketoconazole and climbazole groups was 26.7% and 13.3%, respectively, though the difference was not significant ($P = 0.402$).

Rigopoulos *et al.* in 2007 in Greece evaluated the efficacy of flutrimazole shampoo 1% versus ketoconazole shampoo 2% in the treatment of pityriasis versicolor. One month after commencing treatment, the rate of negative smears was 84.6% and 75.9% in the ketoconazole and flutrimazole groups, respectively (vs. 70% and 43.3% in the ketoconazole and climbazole groups of our study, respectively), and the difference was not significant. Also, the percentage of clinical cure one month after the treatment with ketoconazole and flutrimazole in the Rigopoulos *et al.* study was 80.8% and 75.9 %, respectively (vs. 63.3% and 43.3% in the ketoconazole and climbazole groups of our study, respectively). In the Rigopoulos *et al.* study, the shampoos were applied daily for two weeks, while we prescribed them thrice per week for three weeks. Thus, the higher percentage of negative smears in the Rigopoulos *et al.* study can be because of more shampoo usage among their patients [13].

Muzaffar *et al.* evaluated the efficacy of 2.5% selenium sulfide shampoo daily for 10 minutes for one week. They demonstrated negative smears in 60% of the patients one month after commencing treatment, lower than our study's ketoconazole group (70%) but higher than our climbazole group (43.3%). In the Muzaffar *et al.* study, selenium sulfide shampoo was used seven times (once per day for a week), but our patients used the shampoos a total of nine times across three-day intervals. Furthermore, Muzaffar *et al.* evaluated the application of 2% ketoconazole gel for 5 minutes every day for five days and found considerably higher efficacy (92%) than our results. Recurrence rates in the Muzaffar *et al.* study were 16.66% and 5%

in the selenium sulfide shampoo and ketoconazole gel groups, respectively. These were lower than the recurrence rates recorded in the current study (38.09% and 69.23% in the ketoconazole and climbazole groups, respectively) [14].

Fonzo *et al.* in Italy compared the efficacy of daily application of 2% ketoconazole cream vs. Ketomousse (1% ketoconazole, 0.5% zinc pyrithione, and 2% salicylic acid) for two weeks, resulting in complete clinical improvement in 47% and 29% of the patients after five weeks, respectively. The percentage of complete clinical cure after four weeks in our study was higher (63.3%) than the Fonzo *et al.* study. Application of shampoo on all the surface area of the body (instead of applying cream only on visible affected surface) can be the reason for the higher efficacy of 2% ketoconazole shampoo than 2% ketoconazole cream [15].

Yazdanpanah *et al.* evaluated the efficacy of a single dose of oral ketoconazole (400 mg), which led to complete clinical improvement in 87.9% of cases (vs. 63.3% of complete clinical improvement in 2% ketoconazole shampoo in our study). There was no adverse effect for the patients in both treatment groups in the present study, but in the Yazdanpanah *et al.* study, there were gastrointestinal and urinary adverse effects in 9.09% of the cases [16]. Currently, it is recommended to avoid prescribing systemic ketoconazole for the treatment of pityriasis versicolor because of the high risk of serious adverse effects such as hepatotoxicity and frequent interactions with other systemic drugs [9]. The mycological and clinical response rates recorded in the treatment of pityriasis versicolor in different studies are demonstrated in Table 4.

In the present study, there was no significant correlation between clinical improvement and demographic features of the patients (age and sex) and site of the lesions in both ketoconazole and climbazole shampoo groups, which is compatible with other studies [16,17].

CONCLUSION

In the present study, 2% ketoconazole shampoo had significantly greater efficacy in terms of mycological cure than climbazole shampoo among pityriasis versicolor patients. Although the recurrence rate was lower with 2% ketoconazole shampoo than 2% climbazole shampoo, the difference was insignificant.

Acknowledgments

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Conflict of interest: None declared.

REFERENCES

1. Sharma A, Rabha D, Choraria S, et al. Clinicomycological profile of pityriasis versicolor in Assam. Indian J Pathol

Table 4. Mycological and clinical response in the treatment of pityriasis versicolor in other studies

First author	At the end of treatment			At the follow-up session		
	Complete clinical improvement	Negative KOH smear	Complete cure	Complete clinical improvement	Negative KOH smear	Complete cure
Rigopoulos [13]						
1% flutrimazole shampoo	86.2%	75.9%	75.9%	NP	NP	NP
2% ketoconazole shampoo	88.5%	84.6%	80.8%	NP	NP	NP
Muzaffar [14]						
2.5% selenium sulphide shampoo	NP	60%	60%	NP	16.7%	16.7%
3% SA-10% sulphur soap	NP	50%	50%	NP	25%	25%
2% ketoconazole gel	NP	92%	92%	NP	95%	95%
Di Fonzo [15]						
1% ketoconazole foam	29%	100%	29%	82%	82%	82%
2% ketoconazole cream	47%	100%	47%	92%	92%	92%
Yazdanpanah [16]						
Oral fluconazole (300 mg, 2 doses)	NP	NP	NP	81.5%	NP	NP
Oral ketoconazole (400 mg, single dose)	NP	NP	NP	87.9%	NP	NP

NP, not performed; SA, salicylic acid

Microbiol. 2016;59(2):159.

2. Kazemi A, Ayatollahi-Mousavi SA, Jafari AA, et al. Study on pityriasis versicolor in patients referred to clinics in Tabriz. Jundishapur J Microbiol. 2013;6(8).
3. Hu SW, Bigby M. Pityriasis versicolor: a systematic review of interventions. Arch Dermatol. 2010;146(10):1132-40.
4. Gupta AK, Lane D, Paquet M. Systematic review of systemic treatments for tinea versicolor and evidence-based dosing regimen recommendations. J Cutan Med Surg. 2014;18(2):79-90.
5. Rad F, Nik-Khoo B, Yaghmaee R, et al. Terbinafin 1% cream and Ketoconazole 2% cream in the treatment of Pityriasis versicolor: a randomized comparative clinical trial. Pak J Med Sci. 2014;30(6):1273.
6. Shi TW, Zhang JA, Tang YB, et al. A randomized controlled trial of combination treatment with ketoconazole 2% cream and adapalene 0.1% gel in pityriasis versicolor. J Dermatolog Treat. 2015;26(2):143-6.
7. Cantrell WC, Elewksi BE. Can pityriasis versicolor be treated with 2% ketoconazole foam? J Drugs Dermatol. 2014;13(7):855-9.
8. Gupta AK, Daigle D, Foley KA. Drug safety assessment of oral formulations of ketoconazole. Expert Opin Drug Saf. 2015;14(2):325-34.
9. Yan JY, Nie XL, Tao QM, et al. Ketoconazole associated hepatotoxicity: a systematic review and meta-analysis. Biomed Environ. Sci. 2013;26(7):605-10.
10. Dehghan M, Akbari N, Alborzi N, et al. Single-dose oral fluconazole versus topical clotrimazole in patients with pityriasis versicolor: A double-blind randomized controlled trial. J Dermatol. 2010;37(8):699-702.
11. Hald M, Arendrup MC, Svejgaard EL, et al. Evidence-based Danish guidelines for the treatment of Malassezia-related skin diseases. Acta Derm Venereol. 2015;95(1):12-9.
12. Gupta AK, Foley KA. Antifungal treatment for pityriasis versicolor. J Fungi. 2015;1(1):13-29.
13. Rigopoulos D, Gregoriou S, Kontochristopoulos G, et al. Flutrimazole shampoo 1% versus ketoconazole shampoo 2% in the treatment of pityriasis versicolor. a randomised double-blind comparative trial. Mycoses. 2007;50(3):193-5.
14. Muzaffar F, Ejaz A, Mahmood K. Determination of cost effective topical therapy for pityriasis versicolor. J Pak Med Assoc. 2016;18(3):159-64.
15. Di Fonzo EM, Martini P, Mazzatenta C, et al. Comparative efficacy and tolerability of Ketomousse® (ketoconazole foam 1%) and ketoconazole cream 2% in the treatment of pityriasis versicolor: results of a prospective, multicentre, randomised study. Mycoses. 2008;51(6):532-5.
16. Yazdanpanah MJ, Azizi H, Suizi B. Comparison between fluconazole and ketoconazole effectivity in the treatment of pityriasis versicolor. Mycoses. 2007;50(4):311-3
17. Handjani F, Nasseri M. Comparison of a single oral dose of Fluconazole with Ketoconazole in the treatment of Tinea Versicolor. Iran J Dermatol. 2003;6(4):11-6.