Dermatology Practical & Conceptual

Comparison of the Efficacies of Topical Liposomal Amphotericin B and Topical Clotrimazole in the Treatment of Pityriasis Versicolor

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ABSTRACT

Introduction: Pityriasis versicolor (PV) often exhibits recurrence even despite treatment, and a standardized therapy with a complete cure rate remains elusive. Given the fungicidal property of amphotericin B, its potential for PV treatment warrants investigation.

Objectives: This study aimed to compare the efficacy of topical liposomal amphotericin B and clotrimazole cream in treating PV.

Methods: A randomized controlled trial was conducted with 44 PV patients, aged 15 to 70 years, who were equally assigned to either the amphotericin or clotrimazole group. The trial was registered at the Iranian Registry of Clinical Trials on March 7th, 2022. PV diagnosis was confirmed in all patients through positive microscopic results. The amphotericin group received topical gel containing liposomal amphotericin B 0.4%, while the other group received topical cream containing clotrimazole 1%. Both treatments were applied twice daily to the affected skin lesions for 14 days. The primary outcomes assessed were mycologic cure, clinical cure, and complete cure at day 14 post-treatment.

Results: Both drugs demonstrated successful treatment outcomes, with comparable rates of mycologic cure (77.3%), clinical cure (63.6%), and complete combined cure (63.6%). There was no significant difference between the groups in terms of the degree of cure (P=0.75). Adjustments for age, sex, lesion extent, and lesion site yielded insignificant risk ratio and risk difference estimates for the complete cure rate (P>0.05).

Conclusions: The topical application of liposomal amphotericin B 0.4% is equally effective as topical clotrimazole 1% in treating pityriasis versicolor. These findings suggest that liposomal amphotericin B could be considered as a viable alternative treatment for PV. Further research is warranted to explore its long-term consequences and safety profile.

Introduction

Pityriasis versicolor (PV), also known as tinea versicolor, is a prevalent superficial fungal infection of the skin that is benign and noncontagious [1]. The treatment of PV can be effectively achieved through the use of topical and/or systemic agents [1,2]. Topical medications are generally considered the first-line therapy for PV [1]. Among the various topical antifungal agents available, several azole compounds that disrupt ergosterol biosynthesis have been extensively studied for their efficacy in treating PV [3]. These studies have primarily focused on comparing the effectiveness of newer topical and oral antifungal agents with well-established clotrimazole, which has been widely recognized for its therapeutic benefits [1].

However, there is a noticeable dearth of research exploring the use of amphotericin B in the treatment of PV, despite its lipophilic properties and ability to bind to ergosterol, a crucial sterol in the fungal cell wall. This binding action leads to the leakage of intracellular components, while also stimulating free radical production and enhancing the body's phagocytic system for fungi elimination [3,4]. As a fungicidal agent, amphotericin B is effective against a broad range of organisms, such as yeast, protozoa (leishmania), flat worms, molds, and algae [5-7]. However, considering the unique characteristics and pharmacologic features of amphotericin B, its potential as a therapeutic option for treating PV warrants investigation. Therefore, we hypothesized that liposomal amphotericin B could exhibit favorable therapeutic effects and demonstrate comparable efficacy to clotrimazole. Additionally, we sought to explore whether factors such as patients' age, gender, and site of lesion would influence treatment success.

Objectives

In a clinical context, finding a medication with improved efficacy and minimal side effects for the treatment of PV is of significant value. This is particularly crucial due to the common recurrence of the disease, which can adversely affect a patient's quality of life. The primary outcomes assessed in this study were mycologic cure and clinical cure at the end of the treatment course. Accordingly, the aim of this study is to compare the efficacy of topical liposomal amphotericin B with clotrimazole cream in the treatment of tinea versicolor, with a focus on determining the most effective therapeutic approach for PV management.

Methods

Study Design and Ethical Considerations

This study was conducted as a single-blind clinical trial from March 7 to July 22, 2022. The trial utilized systematic random sampling, and the blinding method is described in detail below. Ethical approval for the study was obtained from the Ethics Committee of Shiraz University of Medical Sciences in February 2021 (Ethical Committee Approval ID: IR.SUMS.MED.REC. 1399.543). The study was registered in the Iranian Registry of Clinical Trials on March 7, 2022, with trial registration number IRCT20220221054082N1. Written informed consent was obtained from all participants after explaining the study purpose, research procedures, and the protection of patients privacy. The publication of skin images included in the manuscript was done only with the patients' written informed consent. The study adhered to the applicable CONSORT guidelines and was conducted in accordance with the principles stated in the Declaration of Helsinki.

Participant Selection

Patients with pityriasis versicolor who visited Shahid Faghihi, Dermatology Clinic, Shiraz, Iran, were included in the study. The diagnosis of PV was based on clinical grounds and Wood's light examination. Microscopic confirmation of the skin infection was performed using two consecutive potassium hydroxide (KOH) smear examinations, with a 2-day interval between each examination. The study included patients aged between 15 to 70 years whose disease extent was less than 10%. Exclusion criteria for the study were as follows: patient dissatisfaction to participate, history of receiving topical or systemic antifungal agents in the past month, immunosuppressed conditions, sensitivity to antifungal drugs, negative result in either of the KOH smear examinations, non-adherence to medications, and pregnancy or breastfeeding. Initially, 80 patients were recruited, but some patients declined to participate in the second sampling for KOH smear examination. Ultimately, 44 patients were

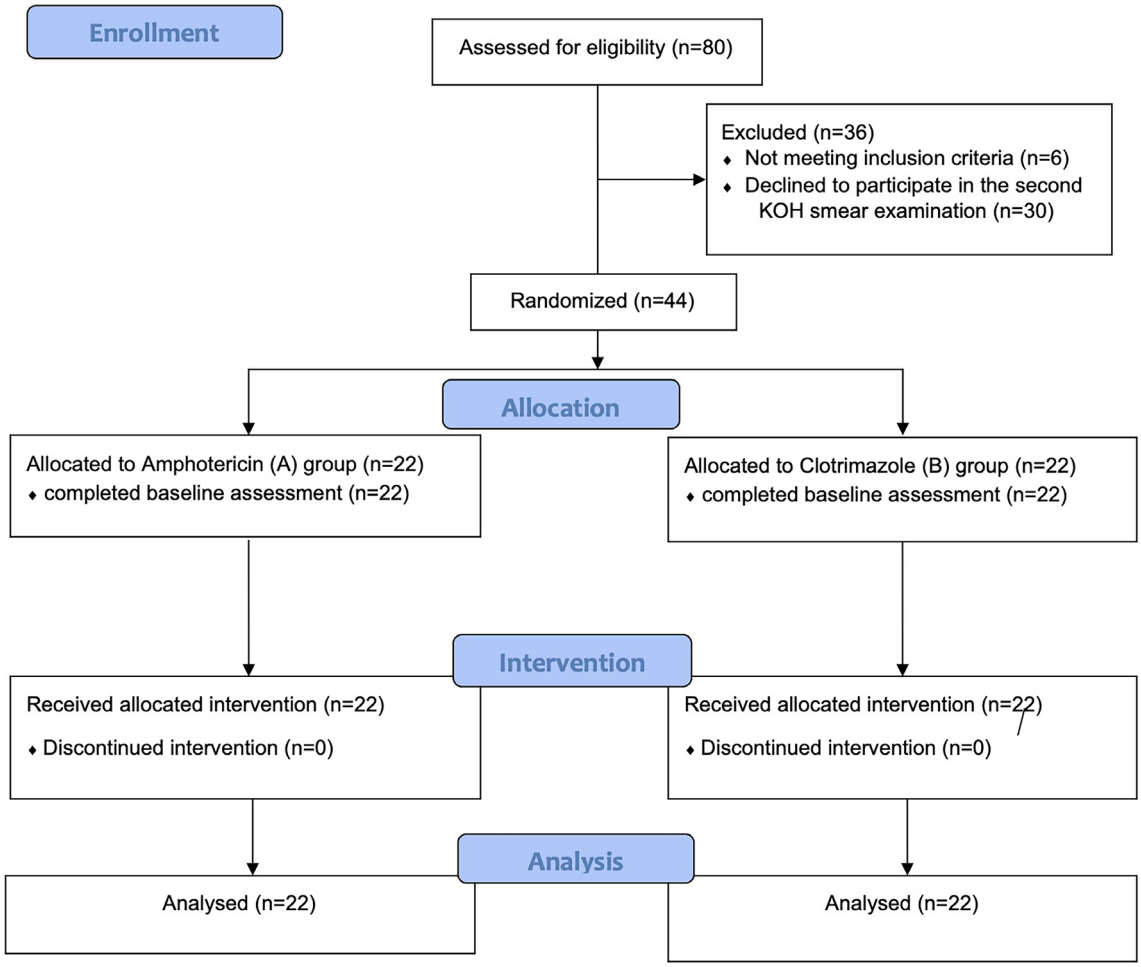

Figure 1. Changes in Sample Size at Different Stages.

randomly allocated to two groups: the Amphotericin group (A group) and the Clotrimazole group (B group). Figure 1 illustrates the patient allocation process.

Intervention

The diagnosis of PV was initially made based on clinical grounds and Wood's light examination. Mycologic confirmation was then performed through microscopic examination of scales soaked in 10% potassium hydroxide (KOH) during the first visit. For the subsequent KOH examination, patients were instructed not to bathe or use any antifungal agent for 2 days before the second sampling. Patients with two positive KOH smear results were randomly assigned to either the intervention group or the control group using a permuted block technique. To maintain blinding, the intervention medications were prepared by a researcher who was not involved in the study and were directly delivered to the patients. The intervention group applied liposomal amphotericin B topical gel (Sina Ampholish 0.4%, Exir Nano Sina Company), while the control group applied clotrimazole topical cream (Clotrimazole-Najo 1% cream, Najo Company) on their skin lesions twice a day for 14 days. Due to the different formulations of the antifungal agents (gel versus cream), the study was not blinded to the patients. Thus, blinding was maintained for the researchers. The patients' data was coded with the letter A indicating the amphotericin group and the letter B representing clotrimazole, followed by a consecutive numerical assignment (A/B1, A/B2, etc.) to conceal the patients categorization and the intervention drug used.

Data Collection and Clinical Assessment

During the first visit, a dermatologist obtained the patient medical history, performed a physical examination, evaluated the eligibility criteria, photographed the skin lesions, and assessed the extent of the disease. The dermatologist also recorded information related to the skin lesions, such as color, size, site of involvement, time of onset, and any previous treatments received. Demographic information, including age, sex, height, weight, and personal contact number, was collected using a new medical record for each patient. Microscopic examination of specimens in KOH were performed twice by another researcher, and the results were reported to the dermatologist. Patient who met the eligibility criteria were randomized to receive the intervention

medication. After 2 weeks, the patients returned to the clinic without bathing, and another dermatologist assessed the clinical improvement of their lesions compared to the initial visit.

Outcome Measures

The primary time point for measurement was 2 weeks after the start of treatment or when patients completed a 14-day course of treatment. The proportion of participants with mycological cure was determined based on a negative result in the KOH smear examination at 14 days post-treatment [1,8]. Another primary outcome was clinical cure after 2 weeks of treatment, which was subjectively assessed by a dermatologist based on the improvement of skin lesions (absence of scaling and skin lesion removal) compared to the initial visit. Clinical cure also included participant-reported cure based on cessation of symptoms, such as scaling, itching and disappearance of the lesion. Complete cure was defined as both 100% clinical cure and laboratory cure. Incomplete cure was referred to either clinical cure without laboratory cure or laboratory cure without full clinical cure. The adverse effects assessment included harms reported in the study at any time during treatment.

Statistical Analysis

According to the study conducted by Kausar et al [9] and using Cochrane formula, we reached a P value of 28% and P = 0.2 (D = 0.2P). The standard error obtained was 0.05. Finally, a sample size of 22 patients was obtained for each group. Data were analyzed using SPSS v.21 software. Descriptive statistics were used to summarize the demographic and clinical characteristics of the participants. Continuous variables were reported as standardized mean difference (SMD) ± standard deviations (SD) or medians with interquartile ranges, depending on their distribution. For descriptive analysis, we used T-test, ANOVA test, Mann-Whitney test, paired T-test, and independent tests. Using a binominal regression model, we assumed a log link function to produce risk ratios, when exponentiated, can be directly interpreted as risk ratios. To obtain risk difference, the method assumes an identity link function to obtain regression coefficients that are risk differences. A P value of less than 0.05 was considered statistically significant.

Results

A total of 44 patients participated in the study, comprising 24 female (54.5%) and 20 male (45.5%). The mean age of participants in amphotericin and clotrimazole was 31.18± 14.94 and 36.77± 14.74 years, respectively. There were no significant differences between the groups in terms of sex (P = 0.22) and age (P = 0.21). The most common form of fungal cutaneous infection in both study groups was observed on the head, neck, extremities, or trunk with regionally isolated lesions, without a significant difference (P = 0.24) (Table 1). Patients were also categorized based on the extent of skin involvement into <1%, 1-3%, and >3% groups (Table 1). More than 80% of patients treated with amphotericin had 1-3% involvement, while 50% of patients treated with clotrimazole had >3% involvement. The study groups differed significantly in terms of lesion extent (P = 0.02). The average duration of the disease was 4.27± 3.87 months for the amphotericin group and 6.77 ±6.80 months for the clotrimazole group, without a significant difference (P = 0.14). The most

Table 1. Baseline Demographic Information of the Study Population and Distribution of Patients across Variable Categories.

Variable	Category	Amphotericin Group	Clotrimazole Group	P-value
Gender	Female	10 (45.45%)	14 (63.64%)	0.226
	Male	12 (54.55%)	8 (36.36%)	
Age	Mean (years)	31.18± 14.94	36.77± 14.74	0.218
Lesion extent	Less than 1%	0 (0%)	1 (4.55%)	0.027
	1-3%	18 (81.83%)	10 (45.45%)	
	More than 3%	4 (18.18%)	11 (50.00%)	
Disease duration	Mean (months)	4.27± 3.87	6.77 ±6.80	0.141
Lesion color	Brown	14 (81.82%)	18 (63.64%)	0.16
	White	7 (31.82%)	2 (9.09%)	
	Red	0 (0%)	1 (4.55%)	
	Reddish brown	1 (4.55%)	1 (4.55%)	
Site of lesion	Head, neck, or extremities	12 (54.55%)	7 (31.82%)	0.244
	Trunk	8 (36.36%)	10 (45.45%)	
	Multiple sites	2 (9.09%)	5 (22.73%)	

Table 2. Distribution of Patients across Mycologic, Clinical Cure, and Degree of Cure Modules.

Cure definition	Category	Amphotericin group	Clotrimazole group	P-value	RR (95% CI)
Microscopic cure	Effective	17 (77.3%)	17 (77.3%)	1	1 (0.73 to 1.38)
	Ineffective	5 (22.7%)	5 (22.7%)		
Clinical cure	< 50%	3 (13.6%)	2 (9.1%)	0.752	Reference
	50-99%	5 (22.7%)	7 (31.8%)		0.69 (0.26 to 1.85)
	100%	14 (63.6%)	13 (59.1%)		0.86 (0.39 to 1.93)
Degree of cure	Complete	14 (63.6%)	13 (59.1%)	0.757	1.08 (0.67 to 1.72)
	Partial	8 (36.4%)	9 (40.9%)		

CI = confidence interval.

Table 3. Impact of Age, Gender, Lesion Site, and Size on Drug Efficacy for Complete Cure (Log-Binomial Logistic Regression).

Complete cure	Risk ratio (95% CI)	P-value	Risk difference (95% CI)
Interventions (crude)	1.07 (0.67 to 1.72)	0.757	0.04 (-0.24 to 0.33)
Interventions (adjusted by age)	1.05 (0.65 to 1.69)	0.833	0.04 (-0.24 to 0.34)
Interventions (adjusted by gender)	1.30 (0.87 to 1.93)	0.199	0.13 (-0.13 to 0.40)
Interventions (adjusted by the size of the lesion)[b]	1.08 (0.68 to 1.74)	0.729	-0.001 (-0.30 to 0.29)
Interventions (adjusted by the site of the lesion)[c]	1.02 (0.65 to 1.68)	0.922	0.04 (-0.24 to 0.34)

[a]Men in comparison with women; [b]>3% in comparison with ≤3%; [c]in comparison with head, neck, or extremities.
CI = confidence interval.

common lesion color was brownish discoloration, observed in 81.82% and 63.64% of the patients in each group, respectively. There was no significant difference in lesion color between the groups (P = 0.16). One patient in the topical amphotericin B group experienced (irritation and dryness), which was tolerable, and the intervention was continued. No adverse effects were reported by the patients who received clotrimazole.

The results of the primary outcome measures are summarized in Table 2 using the chi-square test. Both liposomal amphotericin B and clotrimazole successfully treated most patients (77.3%) based on microscopic examination. There was no significant difference in microscopic cure between the two antifungal agents (P= 1, RR=1, 95%CI: 0.73-1.38). Regarding clinical cure, 14 (63.6%) and 13 (59.1%) of the patients who received amphotericin B and clotrimazole, respectively, achieved full recovery. The analysis also showed similar clinical effectiveness of both medications (P > 0.05). When assessing mycologic and clinical treatments combined, 14 (63.6%) and 13 (59.1%) of patients in amphotericin and clotrimazole groups, respectively, showed complete cure. No significant difference was found between the groups regarding the degree of cure (P = 0.75, RR=1.08, 95% CI: 0.67-1.72).

Table 3 presents the estimation of the interventions effect on complete cure as a clinical outcome. The risk ratio and risk difference for complete cure without any adjustments were estimated at 1.07 (95% CI: 0.67 to 1.72) and 0.04 (-0.24 to 0.33), respectively. In other words, the likelihood of complete cure in the amphotericin group increased by only 0.07 compared to the clotrimazole group, which was not statistically significant (P = 0.75). Binomial logistic regression was used to compute adjusted estimates of the risk ratio and risk difference. Adjustments for age, sex, lesion extent, and lesion site resulted in negligible relative and absolute changes in the clinical outcome. Therefore, regardless of their age, sex, lesion size, and site, patients in both groups showed almost equal response to amphotericin B and clotrimazole. None of these factors had a statistically significant effect on the efficacy of the drugs (P > 0.05).

Conclusions

PV is commonly treated with ketoconazole, a topical antifungal agent [10,11]. Previous studies have shown that ketoconazole cream is equally effective as 1% clotrimazole and 1% terbinafine cream [12,13]. Although clotrimazole is widely used and proven effective [3], there is ongoing research to identify alternative effective agents for PV treatment, beyond the commonly used azoles.

Several studies have explored the efficacy of different treatment options for PV. For example, the effectiveness

of oral griseoflovin [14], 1% diclophenac gel [15], a single 400 mg dose of itraconazole [16], and fluconazole [17] were found to be lower than that of topical clotrimazole [18]. Other antifungal agents, such as mycoderm lotion [19], topical terbinafine [20,21], and sertaconazole cream [22], have demonstrated even better efficacy compared to topical clotrimazole. In a study by Khosravi et al [19], the therapeutic effects of a new antifungal lotion (mycoderm) were compared to clotrimazole lotion in 68 patients. The patients applied the lotions twice a day for two weeks. The cure rates reported by patients in the clotrimazole and mycoderm groups were 71% and 91.9%, respectively, with a statistically significant difference ($P < 0.05$). The rate of full clinical cure was observed in 51.6% and 70.3% of the clotrimazole and mycoderm groups, respectively.

Amphotericin B, a polyene antifungal agent, exhibits broad-spectrum activity against various fungal organisms. It binds to ergosterol, disrupting the fungal cell wall and causing leakage of intracellular contents [4]. Additionally, amphotericin B stimulates the body immune response against fungi by inducing the production of free radicals [3]. While amphotericin B is commonly used for systemic fungal infections [4], its topical formulation, specifically liposomal amphotericin B, has been primarily investigated for the treatment of other fungal conditions such as cutaneous leishmaniosis, cutaneous candidiasis, vaginal mucormycosis, and onychomycosis [5-7]. The potential of liposomal amphotericin B in the topical treatment of PV remains largely unexplored.

To address this gap in the literature, we conducted a study to investigate the therapeutic effects of liposomal amphotericin B in treating PV. Based on its pharmacological characteristics and potential advantages, we hypothesized that amphotericin B would demonstrate comparable efficacy to clotrimazole in terms of clinical and microscopic cure rates. Microscopic cure refers to a negative result of KOH smear examination of the lesion after the treatment course. In our study, topical liposomal amphotericin B achieved microscopic cure in 77.3% of cases after two weeks of treatment, which was comparable to the therapeutic success rate as patients treated with topical clotrimazole cream. In terms of clinical cure, 14 (63.6%) of the patients who received amphotericin B and 13 (59.1%) of those who received clotrimazole were fully treated ($P > 0.05$). These findings suggest that topical liposomal amphotericin B is an effective antifungal agent for both mycological and clinical treatments of patients with PV. Figures 2 and 3 depict the before and after treatment images of a male and a female with PV who were treated with amphotericin B.

In a similar study conducted by Sepaskhah et al in 2017 [18], topical tacrolimus was compared to topical clotrimazole in 50 patients. Clinical and microscopic assessments were performed at the beginning of the study, as well as at the end of 3rd and 5th weeks of treatment. The results showed no significant differences were observed in laboratory and clinical cure rates between the two groups. However, the 5-week treatment with tacrolimus did not significantly affect the hypopigmentation of the lesions.

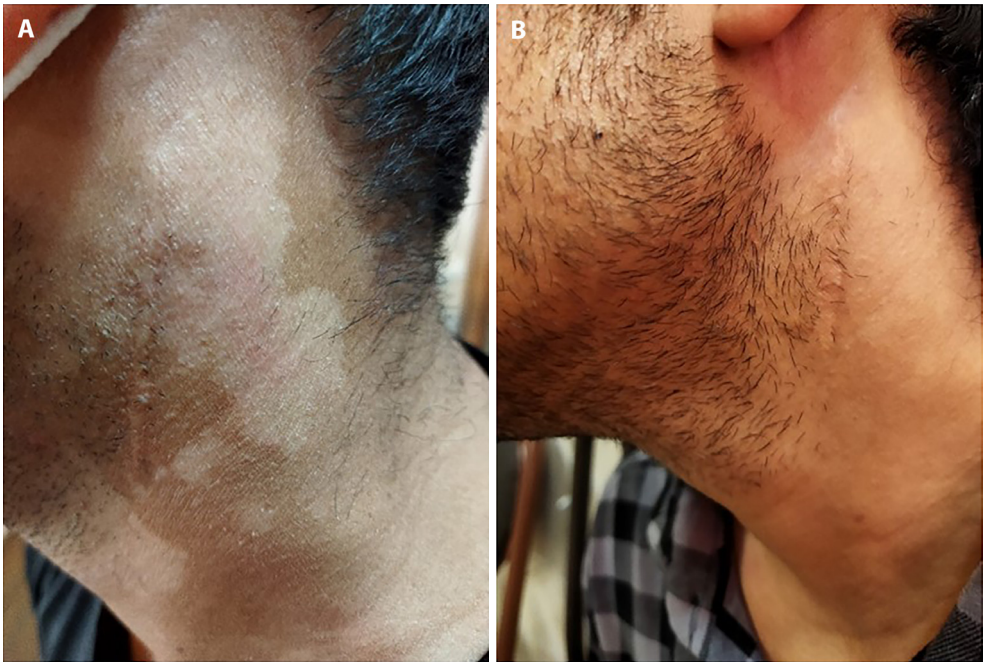

Figure 2. (A) A 37-Year-Old Man from Shiraz with a Whitish Neck Lesion for 5 Months, with <1% Skin Involvement. (B) Complete Clinical and Mycological Cure of the Same Patient after 14 Days of Topical Amphotericin B Treatment.

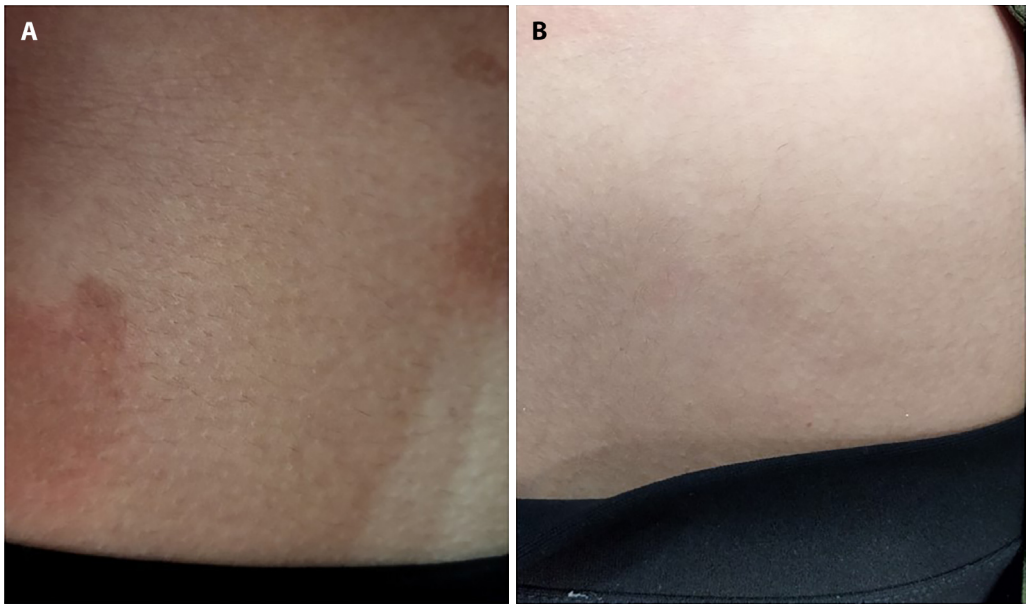

Figure 3. (A) A 17-Year-Old Girl from Shiraz with Lesions on the Lower Abdominal Area for 3 Weeks, with <1% Skin Involvement. She Was Advised to Apply Amphotericin Gel Twice Daily for 2 Weeks. (B) Complete Cure Observed Two Weeks after Treatment.

The hypopigmentation observed in pityriasis versicolor may be attributed to the inhibitory effect of azelaic acid, produced by Malassezia species, on tyrosinase, an enzyme involved in melanogenesis [23]. Additionally, the production of free radicals by lipoperoxidase can lead to skin damage and impaired pigmentation [23]. It is important to note that pigmentary changes may take weeks to months to resolve, even after successful eradication of the fungus [1].

In our study, when considering both mycologic and clinical treatments combined, 14 (63.6%) and 13 (59.1%) of patients in the amphotericin and clotrimazole groups, respectively, achieved complete cure. Although there was no statistically significant difference in the complete cure rates between the two groups, liposomal amphotericin B showed a slight numerical advantage (RR = 1.07; 95% CI: 0.67-1.72). However, this difference was not statistically significant (P > 0.7). Azoles are known to possess anti-inflammatory properties and have fungistatic effects [24]. In contrast, topical liposomal amphotericin B has fungicidal properties and may theoretically lead to better treatment outcomes. The lack of a significant difference in complete cure rates observed between the two groups may be attributed to the limited statistical power of the study, raising the possibility that the benefits of amphotericin B may have been underestimated. Further studies with larger sample sizes should be conducted to confirm these findings. Nevertheless, it is worth noting that all patients who achieved full clinical cure were also found to be microscopically free of PV at the end of the study, irrespective of the treatment received.

In the present study, we found that topical clotrimazole was well-tolerated, and none of the patients treated with clotrimazole reported any side effects. However, it is possible for some individuals to experience local side effects such as skin irritation, dryness, and allergic reactions [25]. Serious systemic side effects with topical clotrimazole are extremely rare. Topical amphotericin B is generally considered safe, although there is a potential for dose-dependent adverse reactions, particularly with higher concentrations or prolonged use [26]. One case in our study experienced tolerable skin sensitivity while receiving topical liposomal amphotericin B. The appropriate concentrations for topical amphotericin B range from 0.1% to 0.4%, and treatment typically lasts 2 to 4 weeks, depending on the formulation and severity of the condition [27]. Prolonged use, however, is not recommended. It is worth noting that liposomal formulations of amphotericin B improve drug delivery and enhance efficacy and safety [26]. On the other hand, the intravenous use of liposomal amphotericin B is associated with side effects such as hyperpyrexia, hypotension, renal damage, and hypokalemia [4]. For severe or recurrent cases, oral medications such as itraconazole and fluconazole are considered second-line treatments [28]. While polyene antifungals like amphotericin B provide broad-spectrum coverage against most pathogenic fungi, they are generally less effective against dermatophytes [4]. As a result, azoles, which primarily target superficial infections caused by dermatophytes, are recommended as the first-line treatment, while polyene antifungals should be reserved for severe fungal infections.

We also hypothesized that the therapeutic efficacy of our intervention would not be influenced by patients' demographic and baseline characteristics. The statistical analysis

of relative risk and risk difference estimates, adjusted to account for potential confounding effects of age, sex, lesion extent, and lesion site, did not yield significant results in our study. Thus, it appears that the therapeutic efficacy of these antifungal agents is independent of patients age, gender, and the location of skin lesions.

There are several limitations to our study that should be considered. First, there are various diseases that share similar manifestations to pityriasis versicolor and must be differentiated, including seborrheic dermatitis, secondary syphilis, pityriasis rosea, pityriasis alba, vitiligo, erythrasma, and Malassezia furfur [29]. While we relied on the standard KOH examination for confirmation of mycologic cure, the lack of color contrast in the KOH mount may have affected the visualization and accuracy of the results. The use of additional staining techniques, such as methylene blue stain, ink blue stain, or Swartz-Medrik stain, could have improved the diagnostic accuracy. Another limitation is the absence of long-term follow-up care in our study. Pityriasis versicolor is known for its tendency to recur, and longer-term assessments would have provided valuable insights into the durability of treatment outcomes. Additionally, our study design only included patients with limited skin involvement, which may limit the generalizability of our findings to cases with more extensive or severe disease. Further studies involving a broader range of patients, including those with more severe or widespread pityriasis versicolor, are needed to evaluate the potential dose-dependent adverse reactions associated with topical amphotericin B and to assess its efficacy in diverse populations.

In conclusion, our study demonstrates that the topical application of liposomal amphotericin B 0.4% is comparable in efficacy to topical clotrimazole 1% for the treatment of pityriasis versicolor. These findings suggest that topical liposomal amphotericin B can serve as a viable alternative treatment option for pityriasis versicolor. However, it is important to note that based on our current findings, we do not recommend topical liposomal amphotericin B as the primary treatment choice for PV. Further research is needed to better understand the potential consequences and safety profile of using liposomal amphotericin B in the long term, as well as its comparative effectiveness and cost-effectiveness compared to other treatment options.

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