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Comparison of Efficacy and Safety of Topical 1% Butenafine and Topical 1% Ciclopirox Olamine in the Treatment of Tinea Pedis and Evaluation of the Effects on the Quality of Life of These Treatmens: A Randomized Single-Blind Trial

Tinea Pedis Tedavisinde Topikal %1 Butenafin ve Topikal %1 Siklopiroks Olaminin Etkinlik, Güvenilirliğinin Karşılaştırılması ve Bu Tedavilerin Yaşam Kalitesi Üzerine Etkilerinin Değerlendirilmesi: Randomize Tek Kör Bir Çalışma

Abstract

Objective: The aim of the study is to compare efficacy and safety of topical 1% butenafine and topical 1% ciclopirox olamine in tinea pedis and to evaluate effects of these treatments on quality of life.

Methods: We conducted a randomized controlled trial on 80 patients with tinea pedis between May 2014 and May 2015. Of 80 patients, 40 were treated with 1% butenafine cream and 40 were treated with 1% ciclopirox olamine cream for one month. Clinical characteristics, Dermatology Life Quality Index (DLQI) scores, Physician's Global Assessment (PhGA), and Patient's Global Assessment were recorded.

Results: Forty patients (21 male, 19 female) on butenafine therapy and 40 patients (15 male, 25 female) on ciclopirox olamine therapy were enrolled in the study. Both treatments significantly improved the clinical signs and symptoms, but no significant difference was found between the groups (p>0.05). The DLQI scores decreased significantly after the treatments in both groups. The recurrence was observed only in two patients from ciclopirox olamine group.

Conclusion: Topical butenafine and ciclopirox olamine had similar high efficacy and safety in the treatment of tinea pedis. In addition, both two drugs had positive improvement on quality of life of the patients.

Keywords: Butenafine, ciclopirox olamine, efficacy, quality of life, safety, tinea pedis

Öz

Amaç: Tinea pedisli hastalarda topikal %1 butenafin ve topikal %1 siklopiroks olaminin etkinlik ve güvenilirliğinin karşılaştırılması ve bu tedavilerin yaşam kalitesi üzerine etkilerinin değerlendirilmesi amaçlandı.

Yöntemler: Mayıs 2014 ile Mayıs 2015 tarihleri arasında, tinea pedisli 80 hasta üzerinde randomize kontrollü bir araştırma yapıldı. Bu 80 hastanın 40'ı topikal %1 butenafin krem, diğer 40'ı topikal %1 siklopiroks olamin krem ile bir ay süre ile tedavi edildi. Klinik özellikler, Dermatoloji Yaşam Kalite İndeksi (DLQI) skorları, Doktorun Global Değerlendirmesi (PhGA) ve Hastanın Global Değerlendirmesi kaydedildi.

Bulgular: Butenafin tedavisi alan 40 hasta (21 erkek, 19 kadın) ve siklopiroks olamin tedavisi alan 40 hasta (15 erkek, 25 kadın) çalışmaya alındı. Her iki tedavi de klinik bulgu ve semptomları önemli derecede düzeltirken, gruplar arasında anlamlı farklılık saptanmadı (p>0,05). DLQI skorları her iki gruptaki tedavilerden sonra anlamlı olarak azaldı. Rekürrens sadece siklopiroks olamin grubundaki iki hastada gözlendi.

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Sonuç: Çalışmamızda tinea pedis tedavisinde topikal butenafin ve topikal siklopiroksolaminin benzer etkinlik, güvenilirliğe sahip olduğu saptanmıştır. Ayrıca yaşam kalitesi üzerine her iki ilaç benzer etkilere sahiptir.
Anahtar kelimeler: Butenafin, siklopiroks olamin, etkinlik, yaşam kalitesi, güvenlik, tinea pedis

Introduction

Tinea pedis is a dermatophyte infection particularly seen in soles and interdigital areas. The species of fungus causing tinea pedis are *Epidermophyton floccosum*, *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Trichophyton tonsurans* that especially in children. In the treatment of tinea pedis, imidazole, allylamine, and benzylamine groups and the other antimycotic agents such as ciclopirox olamine and nystatin are used (1).

Butenafine is an antimycotic agent with a known activity against bacteria from benzylamine group that prevents the synthesis of fungal cell walls by inhibiting squalene epoxidase. Ciclopirox olamine prevents respiration and transport of amino acids and alters the cell permeability by effecting fungal cytochrome, catalase, and peroxidase. Besides dermatophyte infections, ciclopirox olamine is also effective on *Candida*, gram-negative bacteria, and gram-positive bacteria infections (1).

Although topical butenafine and ciclopirox olamine are widely used agents in dermatophytoses, to our knowledge, there is only one *in vitro* study comparing the efficacy and safety of butenafine and ciclopirox olamine therapies in the literature (2). Further, there is no study investigating effects of these therapies on life quality of the patients with skin tinea infection.

We aimed to compare efficacy and safety of topical 1% butenafine and 1% ciclopirox olamine in tinea pedis and to evaluate effects of these therapies on life quality of the patients.

Materials and Methods

We conducted a randomized controlled trial on 80 patients with tinea pedis between May 2014 and May 2015 at the Dermatology Outpatient Clinic of Muğla Sıtkı Koçman University Training and Research Hospital. Ethic committee approval (Number 2014/01) was obtained prior to the study from the Muğla Sıtkı Koçman University Ethic Committee. The informed consent forms were also obtained before the examinations.

Of 80 patients, 40 were treated with 1% butenafine cream once a day and 40 were treated with 1% ciclopirox olamine cream twice a day for a month. Posology of the drugs was based on the previous studies and recommended frequency of use (3,4). The diagnosis of tinea pedis was based on the clinical findings and positive potassium hydroxide (KOH) examination. The three main findings, erythema, scaling, and pruritus, were rated on a score of 0 to 3 (0: none, 1: mild, 2: moderate, and 3: severe) and the patients with the score of ≥5 and above 18 years were selected in the study.

The exclusion criteria were as follows: presence of pregnancy or lactation, had been treated with systemic antifungals within 2 month or with itraconazole within 6 months, had been treated with systemic antibiotics within 2 weeks, had been treated with systemic corticosteroid or immunosuppressive agents within 6 weeks, and presence of other skin diseases that may affect results of the study (contact dermatitis, psoriasis etc.) (5).

Before the treatments, alanine aminotransferase, aspartate aminotransferase, complete blood count, serum urea, creatinine, total bilirubin, and total urine analysis of the patients were evaluated. Clinical examination was performed at the end of the treatment (4 weeks later) and at the 8th week to evaluate for recurrence. The efficacy and treatment response were assessed according to improvements in the scores of clinical signs and symptoms and negative KOH examination. Culture examinations were not performed.

In addition, Physician's Global Assessment (PhGA) and Patient's Global Assessment (PtGA) were evaluated at the end of the treatment. PtGA was performed according to the 5-point scale (5: greatly improvement, 4: somewhat improvement, 3: the same, 2: somewhat worse, and 1= much worse). PhGA was performed according to the following criteria; cleared (100% remission), excellent (90%-99% improvement), good (50%-89% improvement), fair (25%-49% improvement), poor (<25% improvement), and unchanged or worse (6). The Turkish version of Dermatology Life Quality Index (DLQI) scores of the patients were recorded before and after the treatments.

Results

Forty patients (21 male, 19 female, age range 21-62 years, mean 37.33±12.29) on 1% butenafine therapy and 40 patients (15 male, 25 female, age range 21-61 years, mean 42.15±11.68) on 1% ciclopirox olamine therapy were included in the study. The mean duration of tinea pedis were 2.68±3.18 years and 2.55±3.05 years in the patients on butenafine and ciclopirox olamine therapies, respectively (Table 1).

Dermatophytes were prominent in the KOH preparations in both two groups. Both two therapies significantly improved the clinical signs and symptoms (erythema, scaling, pruritus, maceration, and fissure) and there was no significant difference between butenafine and ciclopirox olamine groups for clinical efficacy ($p>0.05$) (Table 1).

According to PtGA, 35 patients (87.5%) in butenafine group and 31 patients (77.5%) in ciclopirox olamine group had excellent improvement (100% response). According to PhGA, 17 patients (42.5%) in butenafine group and 14 patients (35%) in ciclopirox olamine group had excellent improvement (100% response) (Table 2).

The DLQI scores were significantly decreased after the treatments in both two groups ($p<0.001$) and there was no significant difference for the improvement of life quality between two groups ($p>0.05$) (Table 2).

We did not observe any systemic or local side effects during the treatments. Four weeks after the end of the therapy, tinea

Table 1. Comparison of demographic and clinical characteristics of the patients in butenafine and ciclopirox olamine groups

	Butenafine group n=40 n (%) or mean ± SD	Ciclopirox olamine group n=40 n (%) or mean ± SD	p
Female **Male**	19 (47.5) 21 (52.5)	25 (62.5) 15 (37.5)	0.178
Age	37.33±12.29	42.15±11.68	0.076
Duration of the disease (year)	2.68±3.18	2.55±3.05	0.884
Erythema (BT) Mild-Moderate Severe	 39 (97.5) 1 (2.5)	 39 (97.5) 1 (2.5)	 1
Scaling (BT) Mild-Moderate Severe	 40 (100) 0 (0)	 39 (97.5) 1 (2.5)	 1
Pruritus (BT) Mild-Moderate Severe	 14 (35) 26 (65)	 17 (42.5) 23 (57.5)	 0.491
Maceration (BT) Mild-Moderate Severe	 39 (97.5) 1 (2.5)	 35 (87.5) 5 (12.5)	 0.201
Fissure (BT) Mild-Moderate Severe	 39 (97.5) 1 (2.5)	 39 (97.5) 1 (2.5)	 1
Erythema (AT) Absent Mild	 37 (92.5) 3 (7.5)	 37 (92.5) 3 (7.5)	 1
Scaling (AT) Absent Mild	 32 (80) 8 (20)	 36 (90) 4 (10)	 0.210
Pruritus (AT) Absent Mild	 40 (100) 0 (0)	 39 (97.5) 1 (2.5)	 1
Maceration (AT) Absent Mild	 39 (97.5) 1 (2.5)	 33 (82.5) 7 (17.5)	 0.057
Fissure (AT) Absent Mild	 36 (90) 4 (10)	 37 (92.5) 3 (7.5)	 1

Chi-square test, Independent t test, and Mann-Whitney U test, BT: Before treatment, AT: After treatment

pedis relapsed in two patients treated with ciclopirox olamine, whereas no relapse was observed in butenafine group.

Discussion

Topical butenafine and ciclopirox olamine are widely used agents in the treatment of dermatophytes (3,7). To our knowledge, there is only one *in vitro* study comparing the efficacy and safety of butenafine and ciclopirox olamine therapies. In this study, ciclopirox olamine had the broadest *in vitro* activity against dermatophytes, bacteria, and yeasts compared to butenafine and econazole. But, butenafine was 10-100 times more effective than azole group against dermatophytes (2). In the current study, although topical butenafine was slightly better than ciclopirox olamine, as the difference was not statistically significant, both two therapies had high efficacy and safety in the treatment of tinea pedis. In addition, the DLQI scores were significantly decreased after the treatments in two groups.

Thaker et al. (8) have compared topical sertaconazole and butenafine in the skin tinea infections and have found significant decrease in the scores of signs and symptoms. However, the higher improvement has been obtained with butenafine therapy according to Global Evaluation Response scores. Three patients had recurrence in sertaconazole group, whereas no patients had recurrence in butenafine group. In another study comparing topical butenafine and terbinafine, it has been noted that a faster response has been received with butenafine therapy (9).

Table 2. Comparison of butenafine and ciclopirox olamine groups for the efficacy and effect on life quality according to Physician's Global Assessment, Patient's Global Assessment, and the Dermatology Life Quality Index scales

	Butenafine group n=40 n (%) or mean ± SD	Ciclopirox olamine group n=40 n (%) or mean ± SD
Patient's Global Assessment		
Greatly improvement	35 (87.5)	31 (77.5)
Somewhat improvement	5 (12.5)	8 (20)
The same	0 (0)	1 (2.5)
Somewhat worse	0 (0)	0 (0)
Much worse	0 (0)	0 (0)
Physician's Global Assessment		
Cleared	17 (42.5)	14 (35)
Excellent	21 (52.5)	20 (50)
Good	2 (5)	5 (12.5)
Fair	0 (0)	1 (2.5)
Poor	0 (0)	0 (0)
Unchanged or worse	0 (0)	0 (0)
DLQI (BT)	9.45±4.30	9.90±4.74
DLQI (AT)	0.92±0.99	1.10±1.28

DLQI: Dermatology Life Quality Index, BT: Before treatment, AT: After treatment

Singal et al. (10) have evaluated the efficacy of topical butenafine and clotrimazole and have found significantly higher mycological cure rates in butenafine group at the first week of therapy. Mycological cure rates of butenafine have also been noticed higher at weeks 2, 4, and 8, but the difference was not significant. Lesher et al. (11) have reported that no relapse was seen in 37 patients with tinea cruris after the end of topical butenafine therapy. In another study performed by Thaker et al., (12) 98% of the patients with skin tinea infection were completely improved with topical butenafine at the end of 1 month. In our study, tinea pedis relapsed in two patients treated with ciclopirox olamine, whereas no relapse was seen in butenafine group.

Rotta et al. (13) have performed a meta-analysis including studies comparing topical antifungals with each other or placebo. Although there was no statistically significant difference between topical antifungals for mycological cure at the end of the treatment, they have stated that topical butenafine and terbinafine had higher efficacy than azole group and terbinafine also showed superiority compared to ciclopirox olamine. Since ciclopirox olamine is effective against also bacteria besides dermatophytes, Gupta et al. (7) have evaluated the efficacy of topical ciclopirox olamine in the treatment of tinea pedis with secondary bacterial infection, and have found ciclopirox olamine effective and safe. In another study, Aly et al. (4) also have reported that ciclopirox gel 0.77% twice in a day for a month was effective in the treatment of interdigital tinea pedis. Ciclopirox olamine has been reported to be effective in the treatment of diaper dermatitis due to *Candida albicans* (14).

Among side effects of topical butenafine and ciclopirox olamine, erythema, contact dermatitis, itching, and irritation have been reported previously (13,14). We did not observed any side effects during the study.

Study Limitations

The limitation of our study was that we did not perform culture examination.

Conclusion

Because the studies comparing efficacy of topical antifungals each other, particularly butenafine and ciclopirox olamine, and evaluating effect of these therapies on life quality are scarce, we conducted the current study. According to the PtGA and PhGA scales, butenafine was slightly better than ciclopirox olamine, as the difference was not statistically significant.

Consequently, topical butenafine and ciclopirox olamine had high efficacy and safety in the treatment of tinea pedis. In addition, both two drugs had positive improvement on life quality of the patients.

Ethics

Ethics Committee Approval: Ethic committee approval (Number 2014/01) was obtained prior to the study from the Muğla Sıtkı Koçman University Ethic Committee.

Informed Consent: The informed consent forms were also obtained before the examinations.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: A.K.P., Design: A.K.P., G.D., Data Collection or Processing: A.K.P., Analysis or Interpretation: A.K.P., A.A.B., E.T.A., G.D., Literature Search: A.K.P., A.A.B., E.T.A., Writing: A.K.P., A.A.B., E.T.A.

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