Efficacy and Safety in 1% Clotrimazole Powder, Adjuvant Therapy in Patients with Superficial Fungal Cutaneous Infection in Intertriginous Areas

Rasthawathana Desomchoke MD*, Sumanas Bunyaratavej MD*, Charussri Leeyaphan MD*, Nuntida Prasertworonun MD*, Chuda Rujitharanawong MD*, Lalita Matthapan BSc*, Penvadee Pattanaprichakul MD*

** Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University Bangkok, Thailand*

Background: *Superficial fungal cutaneous infection is commonly found in intertriginous area.*
Objective: *To assess 1% clotrimazole powder (1% CP) efficacy for adjuvant treatment of superficial fungal cutaneous infection in intertriginous areas.*
Material and Method: *The study performed as an open-label, randomized, comparative study for evaluating the effects of 1% clotrimazole cream (1% CC) with 1% CP in patients infected with dermatophytes (DMPs) or Candida spp. in intertriginous area, comparing to patients treated with 1% CC as control by demonstrating complete cure rate at 4, 8, and 12 weeks as well as relapse rates during a 24-week period including patient satisfaction.*
Results: *Sixty-seven patients with mean age of 54.6 years were included in this study. Of those, 61.2% were males. Thirty-five patients were infected with DMPs and 32 with Candida spp. The complete cure rates of experimental group were significantly higher than the control group, as observed within four weeks ($p = 0.01$), especially for dermatophyte infection ($p = 0.039$). Two cases had recurrent candidiasis in the control group. In both groups, relapse up to 24 weeks were not statistically different. Additionally, there was no difference in patients' satisfaction towards convenience of drug application.*
Conclusion: *Using of the 1% CP could be suggested as an adjuvant therapy and possibly preventive agent for superficial fungal cutaneous infection in intertriginous areas.*

Keywords: *1% clotrimazole powder, Dermatophytes, Candidiasis, Intertrigenious areas, Superficial fungal cutaneous infection*

J Med Assoc Thai 2016; 99 (12): 1355-9
Full text. e-Journal: *http://www.jmatonline.com*

Dermatophytes and *Candida* spp. are common pathogens that caused superficial fungal cutaneous infection in humans[1,2]. Intertriginous areas are the most frequent affected parts due to a warm and humid environment for fungal growth[3]. Topical antifungal medications are frequently prescribed for localized superficial fungal infection. Among those medications, imidazole derivatives such as clotrimazole cream is the main therapeutic options[5-8]. Imidazoles powder preparation were commonly used in many conditions including tinea pedis interdigitalis prophylaxis[9-11]. Nevertheless, clotrimazole powder has not been clearly stated in the treatment or prevention in intertriginous fungal skin infection.

Clotrimazole powder has been introduced into dermatologic practices. Powder formulation is believed to suitable for the treatment of dermatophytes and *Candida* spp. infection in intertriginous areas as its advantages of convenient usage and lack of sticky feeling. However, there is a limited data on efficacy and safety on this medication formula. The present study presented the results of open-label, randomized, comparative study of 1% clotrimazole cream and 1% clotrimazole cream plus 1% clotrimazole powder in patients with superficial fungal cutaneous infection in intertriginous areas.

Correspondence to:
Bunyaratavej S, Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand.
Phone: +66-2-4194333, Fax: +66-2-4115031
E-mail: consultskin@yahoo.com

Material and Method

Study design

The present trial was performed in accordance with the Declaration of Helsinki and had been approved by the Ethics Committee of Faculty of Medicine Siriraj Hospital, Mahidol University, and regulatory authorities approved the study protocol. The present trial was a preliminary, prospective, open-label, comparative study to evaluate the efficacy and safety of 1% clotrimazole powder. Patients' proven infection either dermatophyte or *Candida* spp. infection were randomized by blocked randomization to receiving 1% clotrimazole cream

(control group) or 1% clotrimazole cream and 1% clotrimazole powder formulation (experimental group). All patients were instructed to apply the topical medication on affected area twice daily for four continuous weeks. Patients' adjuvant systemic medications for their comorbid diseases such as diabetes, dyslipidemia, and hypertension were allowed to continuously use in the present study. The certificate approval number was 635/2554 (EC3).

Patients

All patients were enrolled from the outpatient service, Department of Dermatology, Faculty of Medicine Siriraj hospital, Mahidol University. Patients older than 18 years of age suspected with intertriginous fungal skin infection were recruited and comprehensively examined by assigned two dermatologists. After examination, the potassium hydroxide (KOH) preparation and fungal culture were performed to confirm the diagnosis. The presence of pseudohyphae and budding yeast cells under direct microscopic examination indicated *Candida* infection, and the presence of branching septate hyphae with or without arthroconidia determined dermatophyte infection. The fungal culture was the gold standard for the definite diagnosis. Informed consent was achieved from all participants before enrolled to the study. The exclusion criteria included all of the followings: pregnant and breast feeding patients, patients with tinea pedis and fungal infection on the facial area and condition which indicated to use oral antifungal agents such as widespread infection or immunocompromised host. Patients who had been using systemic antifungal treatment within six months or topical therapy for two weeks before enrolled in the study were also excluded. There were no other topical treatments allowed to apply on the treated areas.

Assessment

The patients were scheduled to evaluate the response at 4 weeks after starting the treatments, and at 8, 12, and 24 weeks. Repeating skin examination and mycology laboratory were performed in every visit up to 24 weeks if the affected areas did not achieve either clinical or mycological cure. After complete cure accomplished, the patients in the experimental group were asked for continuously use 1% clotrimazole powder to complete 24 weeks. The final follow-up visit at 24 weeks after started the treatment was using telephone interview asking patients for their disease signs and symptoms and satisfaction of the treatment.

Evaluation of drug effectiveness

The assessment of efficacy was placed on physical and mycological examination. Complete cure was considered as both clinical and mycological cure. The clinical cure was no residual signs and symptoms of fungal infection whereas mycological cure was negative KOH preparation and fungal culture. Relapse was specified as the appearance of clinical signs and symptoms of fungal infection and proven mycological examination.

Statistical analysis

Statistical Package for the Social Sciences (SPSS version 18) was used for analysis. Demographic data were illustrated as mean ± SD and median and range where appropriate. The complete cure rates in control and experimental groups were compared at baseline using the Student's t test, the Mann-Whitney U-test, and the Chi-square test. The Chi-square test or the Fisher's exact test were used to assessed the complete cure rate per group. ANOVA (Scheffe analysis) was used to evaluate patients' satisfaction score of applying both medication formulas at the end of the study.

Results

There were 67 patients, 41 males (61.2%) and 26 females (38.8%) who participated in this study. The mean age was 54.6±18.1 years (range 18 to 86 years). Demographic data of patients were shown in Table 1.

The complete cure rates of all patients with fungal intertriginous skin infection caused by dermatophyte or *Candida* spp. in experimental group were significantly higher than the control group observed within 4 weeks ($p = 0.01$).

Thirty-five patients were classified into dermatophytosis group. The mean age was 51.2±19 years, 65.7% and 34.4% were males and females, respectively. The complete cure rates at four therapeutic assessment visits demonstrated in Fig. 1. There was a statistically significant difference in number of patients who achieved complete cure between control and experimental group in 4 weeks after treatment in dermatophytosis group ($p = 0.039$). No statistically significant difference in number of patients who achieved complete cure rate between both groups in 8, 12, and 24 weeks after starting the study. There were two patients had disease relapsed at 8 and 12 weeks, respectively.

Thirty-two patients were classified into candidiasis group. The mean age was 58.3±16.5years, 56.3% and 43.7% were males and females, respectively.

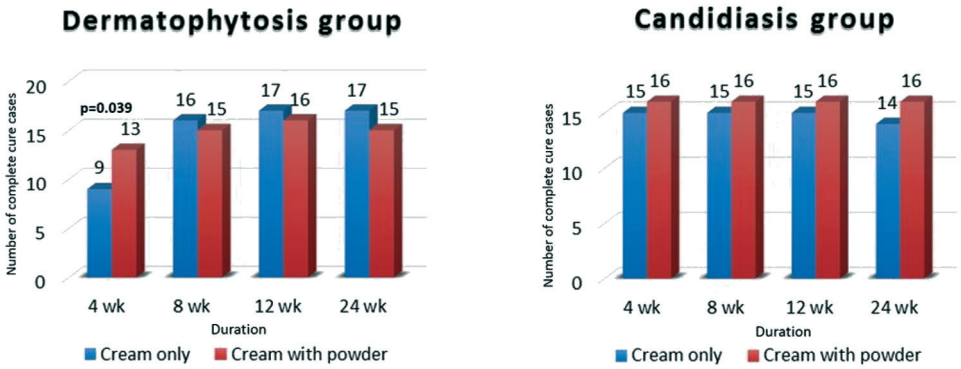

Fig. 1 The result of effect 1% clotrimazole cream and 1% clotrimazole cream plus powder in dermatophytosis and candidiasis groups.

The complete cure rates at four therapeutic assessment visits demonstrated in Fig. 1. Although there were more patients who reached complete cure in the experimental group during the study period, no statistically significant in number of patients. Remarkably, there were two patients in the control group having recurrent candidiasis at the same lesion at 8 and 24 weeks after achieved complete cure.

Patients' satisfaction assessment

We performed patients' satisfaction assessment questionnaire by telephone interview at the end of the study. All patients were asked for their convenience to apply either topical cream or powder formula as assigned in the treatment scheme. Both dermatophytosis and candidiasis group had no statistical significance in preference on medical application of cream over powder (Table 2).

Mycology

In dermatophytosis group, the most common isolate was *Trichophyton rubrum*, followed by *Trichophyton mentagrophytes* which accounted for 51.4% and 28.6%, respectively. *Candida tropicalis*

Table 1. Demographic data and predisposing factors of dermatophytosis and candidiasis groups

Factors	Total (n = 67)	Dermatophytosis (n = 35)	Candidiasis (n = 32)
Sex: male	41 (61.2%)	23 (65.7%)	18 (56.3%)
Age (year), mean (SD)	54.6 (18.1)	51.2 (19.0)	58.3 (16.5)
Site of infection			
Axilla	12 (17.9%)	4 (11.4%)	8 (25%)
Groin	34 (50.7%)	17 (48.6%)	17 (53.1%)
Toe web	12 (17.9%)	11 (31.4%)	1 (3.1%)
Submammary fold	1 (1.5%)	0 (0%)	1 (3.1%)
Gluteal cleft	8 (11.9%)	3 (8.6%)	5 (15.6%)
Risk factors			
Hyperhidrosis	38 (56.7%)	21 (60.0%)	17 (53.1%)
Diabetes mellitus	17 (25.4%)	7 (20.0%)	10 (31.3%)
Use corticosteroid	23 (34.3%)	9 (25.7%)	14 (43.8%)

Data were presented as n (%) unless otherwise specified

Table 2. Number of patients towards medical application of cream and powder formulas

Antifungal regimen	Dermatophytosis (n = 35)		Candidiasis (n = 32)	
	Convenient	Not convenient	Convenient	Not convenient
1% clotrimazole cream	17 (89.5%)	2 (10.5%)	7 (43.75%)	9 (56.25%)
1% clotrimazole cream with powder	16 (100%)	0 (0%)	7 (43.75%)	9 (56.25%)

Data were presented as n (%)

(43.8%) and *Candida albicans* (31.3%) were frequent isolated in candidiasis group.

Side effects

There was no report of any side effects in both control and experimental groups in the present study.

Discussion

Superficial fungal cutaneous infection especially in intertriginous areas such as the groin, submammary folds, gluteal clefts are commonly seen and increasing in clinical practice. Both dermatophytes and *Candida* spp. are the most common pathogens in general population. There are 20% of populations affected by fungal infection worldwide[4]. Recognition and proper treatment of superficial fungal infection are essential to reduce to burden of the disease in both physical, psychological, and social aspects.

Clotrimazole is an imidazole derivative which mainly used in the treatment of localized superficial fungal infection caused by *Candida* spp. and dermatophytes[5]. Clotrimazole are formulated in many forms such as cream, lotion, and powder. This was the first open-label, randomized study to evaluate the efficacy, and safety of 1% clotrimazole powder in patients who experienced superficial fungal infection in the intertriginous areas.

The complete cure rate in all patients infected with both fungal infections in the intertriginous areas was good especially in patient infected with dermatophyte. There was statistically significant increased in the complete cure rates in the dermatophytes-infected groups treated with 1% clotrimazole cream and powder at the 4 weeks of the treatment. In contrary, the complete cure rates in the candidiasis group treated with both 1% clotrimazole cream and 1% clotrimazole cream and powder was not statistically significant, however, the experimental group had trend towards favorable results. This may explain that the treatment in candidiasis is less troublesome than the treatment in dermatophytosis patients probably due to fungicidal activity against *Candida* spp. Furthermore, the properties of 1% clotrimazole powder with enhancing dryness and uncomplicated to apply to affected areas may boost the efficacy of 1% clotrimazole cream for treating dermatophytes infection. Recurrent infection after completely cure had found only in candidiasis patient who received clotrimazole cream alone. It was possible from unchanged environment such as moist area and *Candida* spp. was found as normal flora in the gastrointestinal and genitourinary areas[3].

There was no difference in adverse effects and relapse rates in both control and experimental groups. The patients' satisfaction scores towards medication convenience in the present study were similar in both groups. This means the additional application of 1% clotrimazole powder does not cause difficulty for the patients.

A limitation of the present study is small number for each group and the shorter follow-up period; therefore, relapse or recurrence rates may not be well presented. Thus, an extended long-term follow-up study of our survivors should be performed.

In conclusion, 1% clotrimazole powder with conventional cream therapy was convenient and safety to use. It was an effective treatment option in dermatophytes superficial cutaneous infection to achieve more complete cure within four weeks, and possible agent for preventing the superficial cutaneous fungal infection.

What is already known on this topic?

Dermatophytes and *Candida* spp. are common pathogens caused superficial fungal cutaneous infection in intertriginous areas.

Topical antifungal medications particularly clotrimazole cream is frequently prescribed for localized superficial fungal infection.

What this study adds?

Combination of 1% clotrimazole powder with conventional cream therapy was convenient and safe for treatment in superficial fungal intertriginous infection.

This combination therapy significantly achieved more complete cure within four weeks in dermatophyte infection.

Acknowledgements

The present study was funded by Kaspa Pharmaceutical (Thailand) company.

Potential conflicts of interest

None.

References

1. Sei Y. 2006 Epidemiological survey of dermatomycoses in Japan. Med Mycol J 2012; 53: 185-92.
2. Bassiri-Jahromi S, Khaksari AA. Epidemiological survey of dermatophytosis in Tehran, Iran, from 2000 to 2005. Indian J Dermatol Venereol Leprol

2009; 75: 142-7.
3. Yosipovitch G, Tur E, Cohen O, Rusecki Y. Skin surface pH in intertriginous areas in NIDDM patients. Possible correlation to candidal intertrigo. Diabetes Care 1993; 16: 560-3.
4. Marques SA, Robles AM, Tortorano AM, Tuculet MA, Negroni R, Mendes RP. Mycoses associated with AIDS in the Third World. Med Mycol 2000; 38 (Suppl 1): 269-79.
5. Sawyer PR, Brogden RN, Pinder RM, Speight TM, Avery. Clotrimazole: a review of its antifungal activity and therapeutic efficacy. Drugs 1975; 9: 424-47.
6. Rajan VS, Thirumoorthy T. Treatment of cutaneous candidiasis: a double blind, parallel comparison of sulconazole nitrate 1% cream and clotrimazole 1% cream. Australas J Dermatol 1983; 24: 33-6.
7. del Palacio A, Ortiz FJ, Perez A, Pazos C, Garau M, Font E. A double-blind randomized comparative trial: eberconazole 1% cream versus clotrimazole 1% cream twice daily in Candida and dermatophyte skin infections. Mycoses 2001; 44: 173-80.
8. Spiekermann PH, Young MD. Clinical evaluation of clotrimazole. A broad-spectrum antifungal agent. Arch Dermatol 1976; 112: 350-2.
9. Albanese G, Di Cintio R, Giorgetti P, Galbiati G, Ciampini M. Recurrent tinea pedis: a double blind study on the prophylactic use of fenticonazole powder. Mycoses 1992; 35: 157-9.
10. Galimberti RL, Belli L, Negroni R, Castro JM, Rohwedder R, Tuculet MA. Prophylaxis of tinea pedis interdigitalis with bifonazole, 1% powder. Dermatologica 1984; 169 (Suppl 1): 111-6.
11. Pereda J, Noguera X, Boncompte E, Alguero M, Izquierdo I. Efficacy of flutrimazole 1% powder in the treatment of tinea pedis. Mycoses 2003; 46: 126-31.

ประสิทธิภาพและความปลอดภัยในการใช้แป้งยา clotrimazole powder 1% ในการรักษาเสริมของผู้ป่วยที่มีการติดเชื้อรา ที่ผิวหนังชั้นตื้นบริเวณซอกพับ

รัศม์ฐวัฒน์ ดีสมโชค, สุมนัส บุณยะรัตเวช, จรัสศรี พียาพรรณ, นันทิดา ประเสริฐวรนันท์, ชุดา รุจิธารณวงศ์, ลลิตา มัฏฐาพันธ์, เพ็ญวดี พัฒนปรีชากุล

ภูมิหลัง: *ภาวะติดเชื้อราที่ผิวหนังชั้นตื้นพบได้บ่อยโดยเฉพาะบริเวณซอกพับของผิวหนัง*

วัตถุประสงค์: *เพื่อประเมินประสิทธิภาพของแป้งยา clotrimazole ในการรักษาเสริมของผู้ป่วยที่มีการติดเชื้อราที่ผิวหนังชั้นตื้นบริเวณซอกพับ*

วัสดุและวิธีการ: *เป็นการศึกษาเปรียบเทียบแบบเปิดและใช้การสุ่มเพื่อเปรียบเทียบผลของการใช้ยาครีม clotrimazole 1% กับแป้งยา clotrimazole 1% ในผู้ป่วยที่ติดเชื้อกลากแท้ หรือ Candida spp. ที่ซอกพับ เปรียบเทียบกับผู้ป่วยที่ใช้ยาครีม clotrimazole 1% เป็นกลุ่มควบคุม โดยประเมินจากอัตราการหายโดยสมบูรณ์ในระยะเวลาที่ 4, 8 และ 12 สัปดาห์ และอัตราการเกิดเป็นซ้ำในช่วงระยะเวลา 24 สัปดาห์ รวมถึงความพึงพอใจของผู้ป่วย*

ผลการศึกษา: *มีผู้ป่วยทั้งหมด 67 ราย อายุเฉลี่ย 54.6 ปี และ 61.2% เป็นผู้ชาย พบผู้ป่วย 35 ราย ติดเชื้อกลากแท้ และ 32 ราย ติดเชื้อ Candida spp. ที่ผิวหนัง อัตราการหายโดยสมบูรณ์ของกลุ่มทดลองสูงกว่ากลุ่มควบคุมอย่างมีนัยสำคัญในการประเมินช่วง 4 สัปดาห์แรก ($p = 0.01$) โดยเฉพาะสำหรับการติดเชื้อกลากแท้ ($p = 0.039$) ในกลุ่มควบคุมพบผู้ป่วย 2 ราย มีการกลับเป็นซ้ำของ Candida spp. ในทั้งสองกลุ่ม การกลับเป็นซ้ำในช่วง 24 สัปดาห์ ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ ร่วมกับไม่พบความแตกต่างของความพึงพอใจผู้ป่วยต่อความสะดวกสบายในการใช้ยา*

สรุป: *การใช้แป้ง clotrimazole 1% สามารถแนะนำใช้เป็นการรักษาเสริม และอาจช่วยป้องกันการติดเชื้อราที่ผิวหนังชั้นตื้นบริเวณซอกพับได้*
