Special Article

Topical Antifungal Agents for Seborrheic Dermatitis: Systematic Review and Meta-Analysis

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Objective: *Assess the efficacy of topical antifungal agents for seborrheic dermatitis treatment.*
Material and Method: *A systematic review and meta-analysis of all relevant randomized vehicle-controlled trials of topical antifungal agents for seborrheic dermatitis treatment were searched. The quality of the enrolled studies was measured by criteria from Cochrane Collaboration, followed by data extraction. Two reviewers independently assessed the present study articles. When there was a disagreement between the two reviewers, a consensus was made by the third reviewer. Pooled relative risk (PRR) statistical analysis was used to determine the efficacy of treatment.*
Results: *One thousand ninety five studies were reviewed and nine studies were included. Four reports studied the efficacy of ketoconazole, two of metronidazole, two of ciclopirox, and one of bifonazole. Ketoconazole was more effective than vehicle [PRR is 5.78 (95% CI, 2.17-15.40)], as was metronidazole [PRR is 1.83 (95% CI: 1.05-3.17)] ciclopirox [PRR is 3.00 (95% CI, 1.86-4.84)], and bifonazole [PRR is 1.86 (95% CI: 0.96-3.59)].*
Conclusion: *The meta-analysis in the present study showed that the topical antifungal agents that demonstrated strong and moderate evidence of the efficacy for seborrheic dermatitis treatment were ketoconazole and ciclopirox, respectively. They could be used as an alternative treatment for seborrheic dermatitis.*

Keywords: *Topical antifungal agents, Systematic review, Meta-analysis*

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Seborrheic dermatitis is a common inflammatory dermatosis. The prevalence of the disease is 3-5% of population with a slight male predominance and two aged peaks, infant and adult. Clinical findings include erythematous patches with white to yellow greasy scales. The majority of patients present with mild severity. There is increasing prevalence in patients with neurologic disorders such as Parkinson's disease and immunocompromised hosts such as HIV infected patients. The etiology of this disease is still unknown. However, two major factors are concerned, seborrhea[1] and *Malassezia furfur*[2]. The role of *Malassezia furfur* in pathogenesis of this disease is controversial. One study demonstrated that this kind of yeast colonization was found more on the lesional skin than on unaffected skin[3] while the other did not[4]. However, there is a conflict of evidence concerning quantization microbiology of this organism. It possibly plays an important role in the inflammatory lesion of this disease. Therefore, topical antifungal agents are commonly used as the conventional treatment. There has never been statistically conclusion about the efficacy of this agent. Therefore, the systematic review and meta-analysis were conducted to assess the efficacy of topical antifungal agents comparing with vehicle for seborrheic dermatitis treatment in the present study.

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Material and Method

Search strategy and selection criteria

The authors searched Pubmed MEDLINE, the Cochrane Central Register of Controlled Trials (The Cochrane Library) between 1996 and 2008[5] and checked every reference of all relevant studies. Furthermore, the authors contacted related authors and manufacturers for more information.

The included studies are randomized vehicle-controlled trials (RCT) that evaluated the effectiveness

of topical antifungals for all seborrheic dermatitis lesions, with the exception of scalp involvement. The effective treatment was defined as clinical improvement of > 75%. There was no limitation regarding the language of publication.

Data extraction and quality assessment

Two reviewers independently applied inclusion criteria to identified and retrieved articles. Then they extracted data from the included studies onto data extraction forms. When disagreement of data occurred between the two reviewers, a consensus was made by the third reviewers. The authors used the methodological quality of randomized controlled trials criteria from the Cochrane Reviewers' Handbook to assess the studies. The components of the criteria were sequence generation, allocation concealment, blinding of participants and investigators, incomplete outcome data, selective outcome reporting and other sources of bias. Studies that were clearly reported of sequence generation, allocation concealment and blinding of participants and investigators were considered as high.

Statistical synthesis and analysis

The extracted data were entered into Cochrane Revman software (version 5.0). Funnel test was done for assessing publication bias. The comparison in the aspect of efficacy of antifungal agents versus vehicle was conducted and showed in relative risk. After that, fixed effect model and Mantel-Haenzel method were used to combine relative risk of each study into pooled relative risk with 95% confidence interval. The heterogeneity was assessed using I^2 statistics (considering $I^2 < 30\%$ indicate low heterogeneity, while $I^2 > 75\%$ means high heterogeneity), χ^2 (Q-statistics, considering $p < 0.1$ indicate high heterogeneity) and graph. If heterogeneity between studies was found, etiology would be identified and responsible causative study would be excluded. Then, the results of remaining studies were recombined with fixed effect models. Quality of the present study was used as a variable for sensitivity analysis. For multiple group comparisons, comparing pairs with the closest similarity in baseline data would be chosen. For studies that consisted of two phases, only the end of the first phase results was extracted. If scalp lesions were co-reported with other cutaneous lesions, that study would be included. On the other hand, studies with separately reported scalp lesions were excluded. Moreover, if the results were presented in percentage, they would be converted into number of patients.

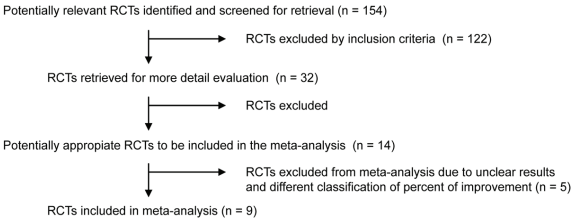


Fig. 1 Flow chart of identification of trials

Results

From 1,095 articles, 154 were the potentially relevant RCT screened for retrieval. Finally, nine studies were included. Fig. 1 shows stages of process of meta-analysis using QUOROM statement[6].

Four types of antifungal agents including ketoconazole, metronidazole, cicloporox, and bifonazole were used in the included studies of which formulations varied from cream, gel, and foam. The authors only evaluated each active ingredient without giving any regards to its formulation. The number of studies in each comparison is described in Table 1. The majority of studies found were ketoconazole (4 studies, 54%), followed by metronidazole (2 studies, 23%), ciclopirox (2 studies, 15%), and one study of bifonazole (8%). The funnel test showed that there was some degree of asymmetrical distribution of the study.

The characteristics of included studies are described in Table 2. Double-blind paralleled group comparison was conducted in all nine studies while no study demonstrated within-patient comparison. The duration of study broadly ranged from one week to five months, however, most of them were between three and eight weeks. The number of participants varied from 20 to 847 persons with the average of 40 to 60 persons. All included studies were conducted

Table 1. Number of studies of each drug

Medications	No. of studies
Ketoconazole versus vehicle	4
Metronidazole versus vehicle	2
Ciclopirox versus vehicle	2
Bifonazole versus vehicle	1
Total	9

Table 2. Characteristics of included studies

Study	No. of paticipants, duration of active phase (maintenance phase) randomized (dropouts), sites, severity	Interventions	Response rate	Quality
Antifungals versus vehicle				
Elewski BE 2007[7]	847, 4 weeks	Ketoconazole 2% foam vs. vehicle foam	239/427 (56%) vs. 176/420 (42%)	Very poor
Elewski BE 2007[7]	315, 4 weeks	ketoconazole 2% cream vs. vehicle cream	117/210 (56%) vs. 32/105 (31%)	Very poor
Green CA 1987[8]	20 (1), 4 weeks, face, (± scalp, chest, back)	Ketoconazole 2% cream (± 2% shampoo) vs. placebo	5/10 (50%) vs. 0/9 (0%)	Poor
Skinner RB 1985[9]	37, 1 month, 8 sites*	Ketoconazole 2% cream vs. vehicle	18/20 (90%) vs. 3/17 (17.6%)	Very poor
Koca R 2003[10]	84 (6), 8 weeks, face, mild-moderate	Metronidazole 0.75% gel vs. vehicle	18/48 (37.5%) vs. 10/30 (33%)	Very poor
Siadat A 2006[11]	56 (3), 8 weeks, face	Metronidazole 1% gel vs. placebo	12/26 (46%) vs. 2/27 (7.4%)	Very poor
Unholzer, A. 2002[12]	189 (0), 29 days, face, moderate-severe	Ciclopiroxolamine 1% cream vs. vehicle	24/92 (25%) vs. 8/97 (8.2%)	High
Dupuy P. 2000[13]	129, 28 days (28 days), face, mild-moderate	Ciclopiroxolamine 1% cream vs. vehicle	25/57 (44%) vs. 11/72 (15%)	High
Zienicke H. 1993[14]	100 (8), 4 weeks (2 weeks), face	Bifonazole 1% cream vs. vehicle	16/37 (43%) vs. 10/43 (23%)	Poor

in adolescent to adult patients (ranged from age 15-78 years). All lesions located on face and trunk with or without scalp involvement. The authors contacted four authors and manufacturers for further information. However, none of them responded to any requests.

Five out of nine studies (55.56%) were reported with very poor quality, two (22.22%) with poor quality, and two (22.22%) with high quality. Elewski B study was conducted in multiple comparisons, 2% ketoconazole foam, vehicle foam, 2% ketoconazole cream, and vehicle cream. The authors divided the present study into two comparison groups for analysis, 2% ketoconazole foam versus vehicle foam and 2% ketoconazole cream versus vehicle cream.

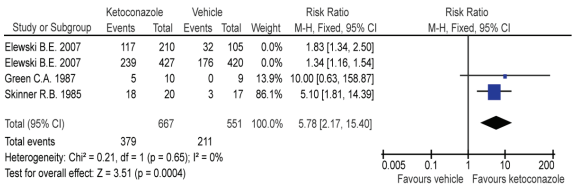
The results of effectiveness of each agent are described below.

Ketoconazole and vehicle[7-9]

The four studies were included (1,218 patients) with pooled relative risk of 1.50 (95% CI: 1.32-1.71), but the pooled results showed significant heterogeneity (I^2 74%, $\chi^2 = 11.36$, df = 3, p = 0.010). With that, the authors excluded two studies (both from Elewski B 2007) that evaluated the response of treatment differently from the others (IGA score or one as treatment success). Therefore, heterogeneity was removed. The relative risk pooled from the two studies with 56 patients was 5.78 (95% CI: 2.17-15.40) as described in Fig. 2.

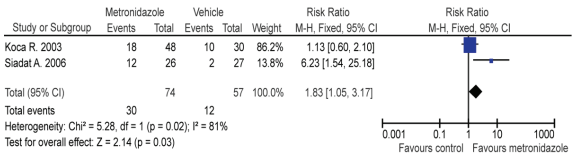
Metronidazole and vehicle[10,11]

The two studies were pooled (131 patients). The pooled relative risk was 1.83 (95% CI: 1.05-3.17), and it showed significant heterogeneity (I2 81%, $\chi^2 = 5.28$; df = 1, p = 0.02) as described in Fig. 3. This may have occurred from the formulation of metronidazole used in Koca R. study was 0.75% metronidazole gel



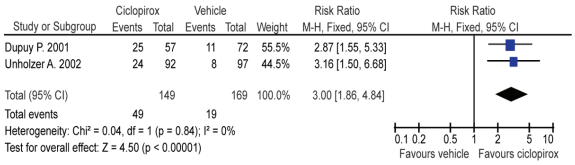
M-H = Mantel-Haenzel method

Fig. 2 Forest plot comparison between ketoconazole and vehicle



M-H = Mantel-Haenzel method

Fig. 3 Forest plot comparison between metronidazole and vehicle



M-H = Mantel-Haenzel method

Fig. 4 Forest plot comparison between ciclopirox and vehicle

while Siadat A study was 1% metronidazole gel. Therefore, the results of efficacy should be considered separately.

Ciclopirox and vehicle[12,13]

Two studies were included (318 patients). The pooled relative risk of two studies was 3.00 (95% CI: 1.86-4.84) as described in Fig. 4.

Bifonazole and vehicle[14]

Only one study was included (92 patients) of which the number of responsive patients was 16/37 (43%) in the bifonazole group and 10/43 (23%) in the vehicle group. Relative risk was 1.86 (95% CI: 0.96-3.59).

Discussion

More than half of the included studies were reported with very poor quality. They were variously different in methodology such as seasons, frequency of application, severity assessment, and outcome measurement. The overall result from meta-analysis showed that all topical groups of antifungal agents were more effective than the vehicle. Ketoconazole was the main agent of topical antifungal drug that was chosen to be studied. It provided strong evidence of its efficacy and the more effective outcome than the vehicle. Ciclopirox showed moderately strong evidence of its efficacy. Metronidazole and bifonazole showed weak evidence of their efficacy. This effective finding from the meta-analysis of the data supported that *Malassezia furfur* is one of the major pathological factors[2]. Antifungal agents work directly against yeast cells. Ketoconazole has more research evidence of its efficacy than others. This may be due to the support of studies by manufacturers or physician's preference. Some antifungal agents such as ketoconazole possess anti-inflammatory activity[15]. As a result, they exhibit more efficacy than other antifungal agents. The preference of therapeutic agent selection depends on medical evidence, physician experience, and patient satisfaction. The limitation of the present study was the criteria for classified quality level that was based on methodological bias. In a future study, more topical medication should be included. In addition, other aspects should be considered, for example, cost-effectiveness, patient satisfaction, or alternative medicine.

In conclusion, the meta-analysis in the present study shows that the topical antifungal agents that demonstrated the strong and moderate evidence of the efficacy for seborrheic dermatitis treatment are ketoconazole and ciclopirox, respectively. They could be used as an alternative treatment for seborrheic dermatitis. However, some unknown etiologic factors of this disease may have an effect on the successful response rate of its topical antifungal therapy.

Potential conflicts of interest

None.

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ยาต้านเชื้อราชนิดทาภายนอกสำหรับการรักษา seborrheic dermatitis: การทบทวนวรรณกรรมอย่างเป็นระบบ และการวิเคราะห์อภิมาน

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ผู้นิพนธ์ได้ศึกษาประสิทธิภาพของยาต้านเชื้อราในการรักษาโรค seborrheic dermatitis ชนิดทา โดยใช้การทบทวนวรรณกรรมอย่างเป็นระบบ และการวิเคราะห์อภิมานซึ่งสืบค้นงานวิจัยที่เกี่ยวข้องทั้งหมด ซึ่งเป็นการศึกษาเปรียบเทียบกลุ่มควบคุมแบบสุ่มของยาทาต้านเชื้อราชนิดต่าง ๆ ได้คัดกรองเข้าสู่การศึกษา โดยอาศัยเกณฑ์ของ Cochrane Collaboration ตามด้วยการสกัดข้อมูล การศึกษานี้มีแพทย์เป็นผู้ประเมินสองท่าน ถ้าเกิดข้อโต้แย้งจะขอความเห็นจากแพทย์ท่านที่สาม นำข้อมูลมาวิเคราะห์ผลด้วยวิธีทางสถิติได้แก่การหาค่า pooled relative risk (PRR) ของประสิทธิภาพในการรักษาของยา ผลการศึกษาจากงานวิจัย 1,095 ฉบับ มีงานวิจัยที่เข้าเกณฑ์ 9 ฉบับ (เป็นยา ketoconazole, metronidazole, ciclopirox และ bifonazole เท่ากับ 4, 2, 2 และ 1 ตามลำดับ) ketoconazole มีประสิทธิภาพสูงกว่ายาหลอก [PRR เท่ากับ 5.78 (95% CI, 2.17-15.40)], metronidazole [PRR เท่ากับ 1.83 (95% CI: 1.05-3.17)], ciclopirox [PRR เท่ากับ 3.00 (95% CI, 1.86-4.84)] และ bifonazole [PRR เท่ากับ 1.86 (95% CI: 0.96-3.59)] สรุปยาทา ketoconazole และ ciclopirox มีหลักฐานที่น่าเชื่อถือในระดับสูงและปานกลางถึงประสิทธิภาพในการรักษา ยาทั้งสองสามารถใช้เป็นทางเลือกในการรักษาโรคนี้ และคงมีปัจจัยอื่นที่ยังไม่ทราบเป็นสาเหตุของโรคนี้ จึงทำให้การตอบสนองของโรคต่อยาต้านเชื้อราไม่ดีเท่าที่ควร