Efficacy of single dose compared with extended dose itraconazole in pityriasis versicolor: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To compare the efficacies of a single dose and the extended dose of itraconazole to identify the optimal dose of the drug for treating extensive Pityriasis versicolor (PV).

METHODS

Three authors independently searched electronic databases including the Cochrane Library, Pubmed, Scopus, and Trip Database. The other resources that we searched included google scholar and hand searching was also performed. We individually screened titles and abstracts for randomized controlled trials (RCTs) carried out between 1950 and 2015 comparing a single dose of itraconazole (400 mg oral) and extended dose (200 mg/day oral 5 to 7 days) of itraconazole for extensive PV. Our primary outcome was the clinical cure; disappearance of skin lesions by Wood's lamp examination. The secondary outcome was negative hyphi from mycological results.

RESULTS

We included 4 RCTs carried out between 2002 and 2012 with 287 patients with extensive PV; 94 participants in a single dose of itraconazole (400 mg oral), 95 participants in extended dose and 98 participants received other regimens. Comparing between efficacy of single dose of itraconazole and that of extended dose of itraconazole for extensive PV, the meta-analysis showed that the former had similar rate of patients with clinical cure as that of the latter (61.7% vs. 85.3%; relative risk (RR), 0.67; 95% confidence interval (CI), [0.42 to 1.09]; I^2=86%). For the secondary outcome, the former had a similar rate of patients with negative hyphi evaluated at 4th to 6th week as that of the latter (60.8% vs. 78.9%; RR 0.77, 95% CI [0.50 to 1.20]; I^2 = 75%).

CONCLUSION

A single dose of itraconazole had a similar rate of clinical cure as the extended dose of itraconazole. However, due to high heterogeneity, a larger double-blind RCTs comparing single dose and the extended dose of itraconazole in patients with extensive PV should be conducted.

INTRODUCTION

Pityriasis versicolor (PV) is a *Malassezia furfur* infection of an outer layer of the epidermis that leads to scaly macules pigment changes oily areas of the skin of upper extremities and trunk.[1] It is common in summer, considering 3% of patients in the dermatological clinic.[1,2] PV is a benign skin condition, however, its recurrent rate is reported up to 60% in 1 year and 80% in 2 years.[1,2] Patient who has a lesion that is extensive and resistant to topical therapy is indicated for systemic agents.[3] Extensive PV can be treated with systemic medications.[3] The first line systemic agents including oral fluconazole and itraconazole have been recommended.[3] In term of dosage regimen, a randomized controlled trial (RCT) in 1996 suggested that 200 mg/day for 7 days of itraconazole was more effective than placebo for treatment of extensive PV.[4] However, an RCT in 2002 with 50 patient with extensive PV comparing the two regimens (400 mg/day single-dose and 200 mg/day for more than 5 days) showing the same efficacies.[5] Still, the later RCTs suggested controversial results.[6-8] We, thus, aimed to systematically identify all relevant studies and pooled their results to assess the benefit of a single dose compared to the extended dose of itraconazole for extensive PV treatment.

METHODS

We conducted a systematic review according to Cochrane Overviews of Reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 Checklist.

SEARCH STRATEGIES

We searched for all relevant studies electronically through the Cochrane Central Register of Controlled Trials (CENTRAL), Pubmed, Scopus, and Trip Database without any language restriction. The other sources we searched including google scholar and hand searching was also performed. We used Medical Subject Headings (MeSH) for Pubmed; (("Tinea Versicolor"[Mesh]) AND "Itraconazole"[Mesh]) and keywords "pityriasis versicolor" or "tinea* versicolor" and "itraconazole" for other databases.

INCLUSION CRITERIA

TYPES OF PARTICIPANTS

We considered all randomized controlled trials in which participants were diagnosed with extensive PV.

TYPES OF INTERVENTIONS

We included RCTs of oral itraconazole for extensive PV, the dose, and the duration of administration of the therapies.

OUTCOME MEASURES

The primary outcome was clinical cure defined as disappearance of skin lesions by Wood's lamp examination. The secondary outcome was mycological results which included no hyphi in a direct microscopic potassium hydroxide preparation.

EXCLUSION CRITERIA

We did not have specific exclusion criteria in the present review.

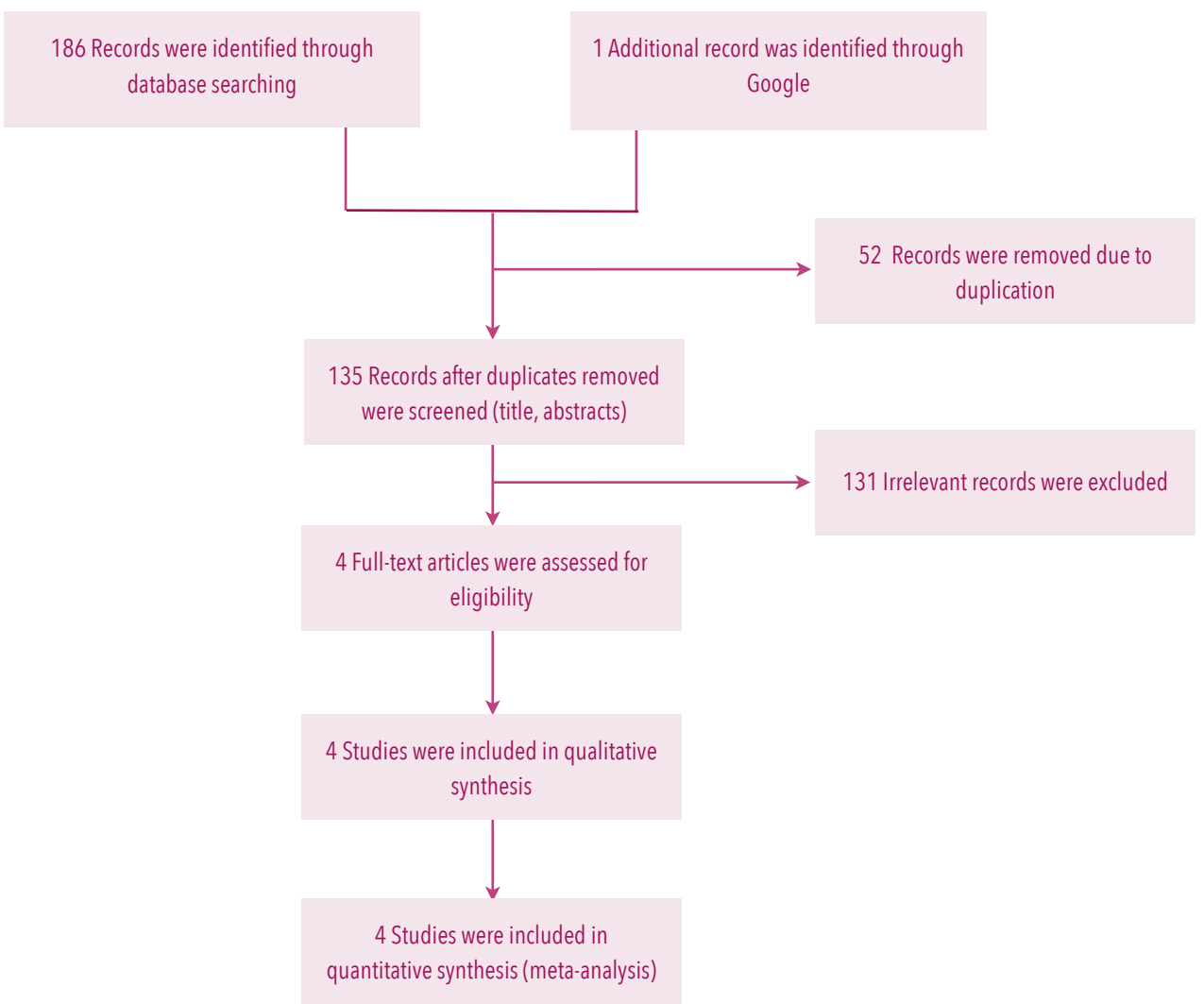

Figure 1. Study flow diagram

DATA SELECTION

Three authors individually searched for all relevant RCTs that assessed the association between the treatment outcomes of those with extensive PV and dose of itraconazole; a single dose vs. the extended dose. We independently screened the titles and abstracts to exclude irrelevant articles then the full-text relevant ones were read and were selected into the present review. Any disagreements among the authors were resolved by discussion.

DATA EXTRACTION

All review authors extracted and recorded data individually from the included studies in relation to

criteria of diagnosis, inclusion and exclusion criteria, interventions (dose of itraconazole, follow up period), number of participant and outcome measures (skin lesion). We extracted data into simple standard spreadsheet.

QUALITY OF REPORTING AND RISK OF BIAS

Our three review authors independently assessed the methodological quality using the Cochrane risk of bias tool. Each included study was regarded to sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other potential sources of bias. Disagreements were resolved by discussion with our senior advisor. The authors of original articles were contacted, if necessary.

DATA ANALYSES

For outcome measures, the clinical cure and mycological results were expressed as risk ratios with 95% confidence intervals calculated by Review Manager V5.3 (RevMan, the programme provided by the Cochrane Collaboration). Heterogeneity in the results was evaluated by means of X^2 test and I^2 test. High heterogeneity was considered when $P<0.05$ in statistically X^2 test and I^2 statistic more than 50%. A random effect model was used for the meta-analysis when heterogeneity was statistical significance and funnel plots were created to showing the standard error and the random effect size to identify potential of publication bias. X^2 test and I^2 test were calculated from Review Manager version 5.3 (Revman); The Cochrane Collaboration's software.

RISK OF BIAS ACROSS STUDIES

A funnel plot was created to identify publication bias.

RESULTS

STUDY SELECTION

Our search strategies recognized 187 publications, 52 were removed due to duplication, 131 were excluded in the assessment because titles and abstracts were not relevant (Figure 1). The remaining four studies were included in the qualitative analysis and included to the meta-analysis.

We identified and included 4 RCTs with 287 patients who had extensive PV. Details of all trials were showed in (Table 1). All trials compared the clinical cure (disappearance of skin lesions by Wood's lamp examination) between a single dose and the extended dose of itraconazole. They were all published between 2002 and 2012.

BIAS RISK ASSESSMENT

The quality of all studies was assessed by Cochrane Collaboration's tool (Figure 2, Panel A). The risk of bias graph and summary is shown in Figure 2, Panel A and B.

RANDOM SEQUENCE GENERATION

All included studies did not report the methods of generating random sequence and they were classified as "unclear risk".

ALLOCATION CONCEALMENT

All did not report details on allocation concealment and were classified as "unclear risk".

Table 1. Characteristics of studies included in systematic review

Study	Country	Study design	Participants	Intervention	Outcome
A Kokturk et al. 2002	Turkey	RCT	60 Patients with extensive PV	20 patients (Group I) received itraconazole 400 mg/day in two doses for 1 day; 20 patients (Group II) received itraconazole 200 mg/day in two doses for 5 days; 20 patients was another group.	Group I had lower rate of clinical cure than that of Group II at 6th week. Group I had lower rate of negative hyphi than that of Group II at 6th week.
Maytham M et al. 2012	Iraq	RCT	117 Patients with extensive PV	20 patients (Group I received itraconazole 400 mg single dose; 19 patients (Group II) received itraconazole 200 mg/day for one week; 78 patients were others group that received other regimens.	Group I had lower rate of clinical cure than that of Group II at 6th week. Group I had similar rate of relapse as that of Group II at 6th week.
O Kose et al. 2002	Turkey	RCT	50 Patients with extensive PV	24 patients (Group I) received itraconazole 400 mg single dose; 26 patients (Group II) received 200 mg itraconazole daily dose for one week.	Group I had same rate of clinical cure as that of Group II at 6th week. Group I had similar rate of negative hyphi as that of Group II at 6th week.
Wahab MA et al. 2010	Bangladesh	RCT	60 Patients with extensive PV	30 patients (Group I) received itraconazole 400 mg single dose; 30 patients (Group II) received itraconazole 200 mg 7 days.	Group I had similar rate of clinical cure as that of Group II at 4th week. Group I had similar rate of negative hyphi as that of Group II at 4th week.

PV= pityriasis versicolor; RCT= randomized controlled trial

BLINDING OF PARTICIPANT AND PERSONNEL

All did not report details on blinding of participant and personnel and were classified as "unclear risk".

BLINDING OF OUTCOME ASSESSMENT

All did not report details on outcome blinding assessment and were classified as "unclear risk".

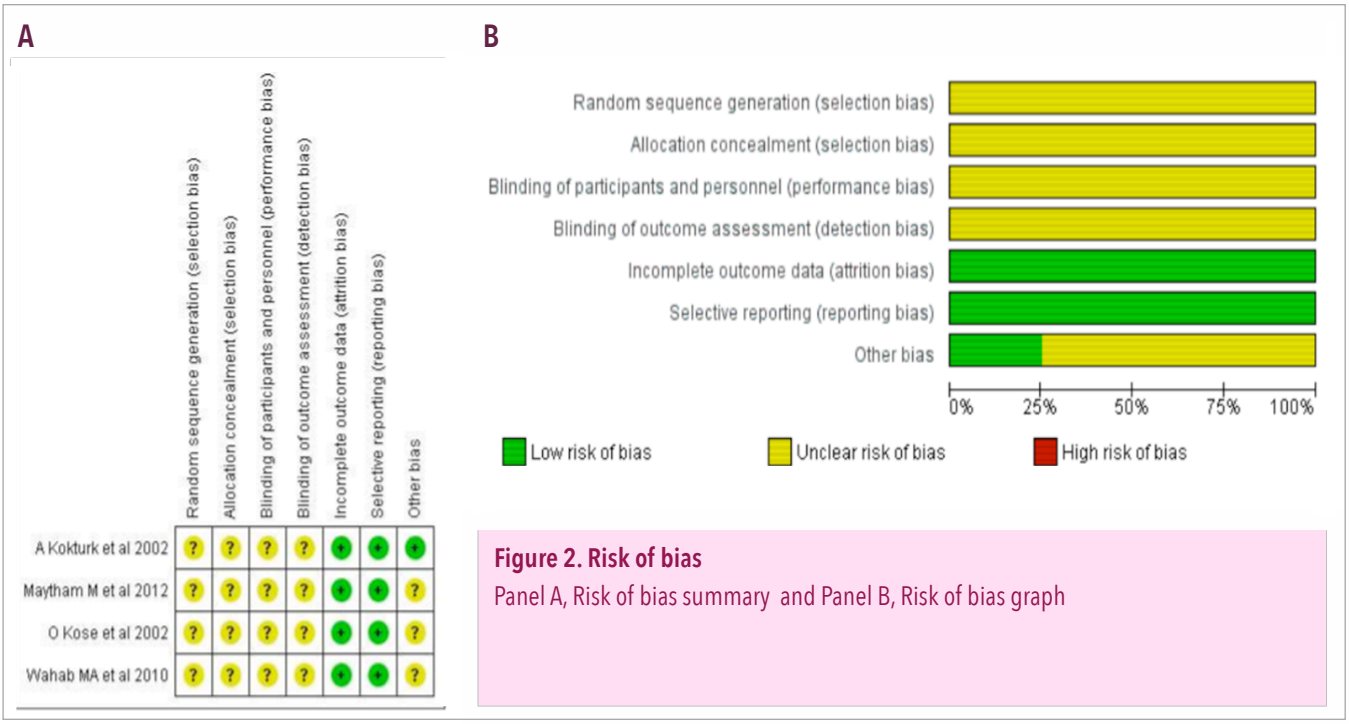

Figure 2. Risk of bias
Panel A, Risk of bias summary and Panel B, Risk of bias graph

INCOMPLETE OUTCOME DATA

All included studies reported the incomplete outcome data or dropped-out patients and they were classified as "low risk".

SELECTIVE REPORTING

All included studies properly described the clinical cure and mycological results. They were classified as "low risk".

OTHER POTENTIAL SOURCES OF BIAS

One studies reported that non-industry-sponsored and it was classified as "low risk". The others did not report about potential sources of bias so they were classified as "unclear risk".

PRIMARY SECONDARY OUTCOME

The single dose of itraconazole had a similar rate of the patient with clinical cure evaluated at 4th to 6th week as that of the extended dose of itraconazole (61.7% vs. 85.3%; RR, 0.67; 95% CI, [0.42 to 1.09]; I^2=86%) (Figure 3). However, the high heterogeneity was observed

SECONDARY OUTCOME

The single dose of itraconazole had a similar rate of negative hyphi mycological results evaluated at 4^{th} to 6^{th} week as that of the extended dose of itraconazole (60.8% vs. 78.9%; RR, 0.77; 95% CI, [0.50 to 1.20]; I^2=75%) (Figure 4). The high heterogeneity was also observed

DISCUSSION

MAJOR FINDINGS

In our systematic review showed the non-statistical difference between the proportion of patient with clinical cure in the single dose of itraconazole

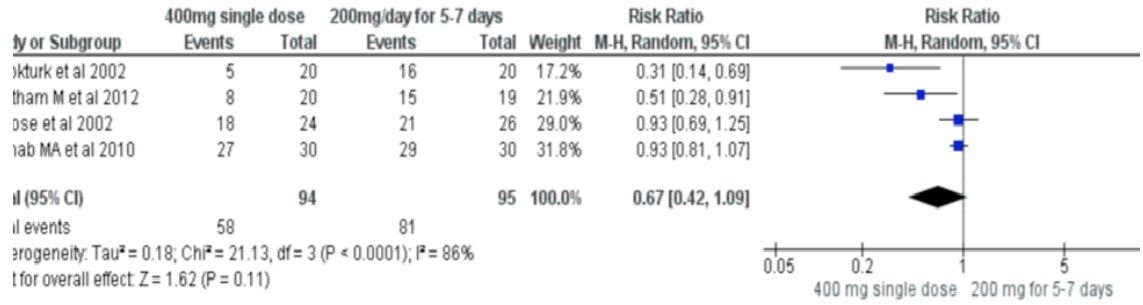

Figure 3. The Forest Plot of Comparison: Single Dose (400 mg oral) versus Extended Dose (200 mg/day oral 5-7 days), Outcome: Clinical Cure

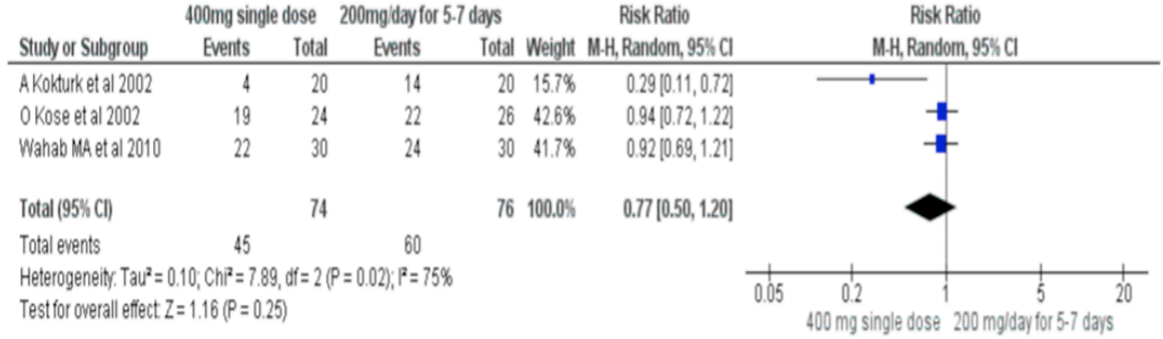

Figure 4. The Forest Plot of Comparison: Single Dose (400 mg oral) versus Extended Dose (200 mg/day oral 5-7 days), Outcome: Negative Hyph

group and that of the extended dose of itraconazole group. Moreover, there was high heterogeneity. We found a non-statistically significant difference of proportion of patients with negative hyphi in those using 400 mg single dose of itraconazole compared with that of 200 mg/day of itraconazole for more 5 days. Furthermore, its high heterogeneity was observed. Implication of the results should be careful.

STRENGTH AND LIMITATION OF THE REVIEW

This systematic review has intermediate strength. Three reviewers searched for eligible randomized controlled trial by screening all titles and abstracts and read full-text articles to assess relevant studies, then we got proper studies and can be assured not to missed important data. The data extraction has been performed by individual reviewers and independently.

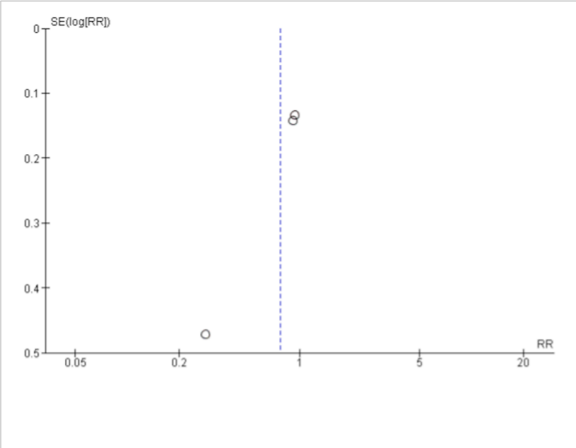

Figure 5. The Forest Plot of Comparison: Single Dose (400 mg oral) versus Extended Dose (200 mg/day oral 5-7 days), Outcome: Clinical Cure.

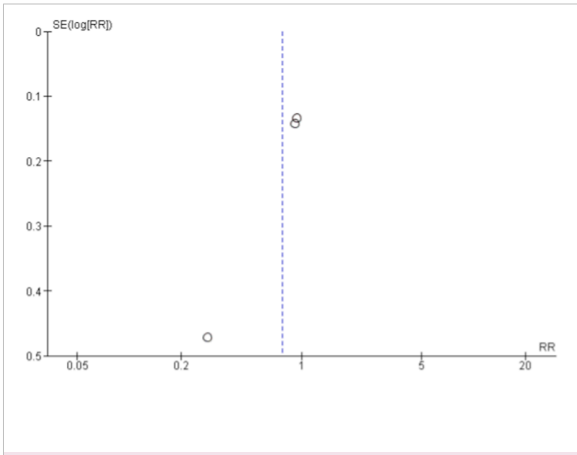

Figure 6. Funnel plot of comparison: Single Dose (400 mg oral) versus Extended Dose (200 mg/day oral 5-7 days), Outcome: Negative Hyphi.

The limitation of this review is that our conclusion was based on low-quality RCTs. All studies had many unclear risks of bias. Moreover, included studies had a small number of participants and outdated; the oldest study was published in 2002. Each study had different methods of outcome measurement as the time to follow up patients with clinical cure and negative hyphi. In the primary outcome, there were three studies evaluated the outcome at 6th week while only one at 4th week. Interpretation of the combination of the results should be careful. This pattern was also found in the evaluated time of the secondary outcome as 2 RCTs followed up patients at 4th week and only one followed up at 6th week. The funnel plots of both outcomes (Figure 5 and Figure 6) suggested the potential of unpublished bias.

COMPARISON WITH OTHER STUDIES

Our systematic review showed that there was no statistically significant difference between a single dose and the extended dose of itraconazole for treatment PV based on the included four RCTs. However, in 2015 there was also a systematic review reported the same findings as ours, however, it included only two RCTs without meta-analysis.[9]

CONCLUSION

Our systematic review and meta-analysis showed that the single dose of itraconazole for treating extensive PV had a similar rate of clinical cure and negative hyphi as that of the extended dose of itraconazole. However, there was no clinical implication for practice, due to low-quality, small number of participants and high heterogeneity of the included studies. We, thus, suggest a further multi-center double-blind controlled trial comparing the single dose and the extended dose of itraconazole in patients with extensive PV should be conducted for the better precision of their effects estimation.

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COMPETING INTERESTS: This study has no competing on interest.
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