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Original Research Article

The use of fluconazole in the treatment of superficial fungal infections- A meta-analysis

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ABSTRACT

The study evaluated the efficacy of the once-weekly dose of oral fluconazole 150 mg therapy in dermatophytosis in comparison to placebo or comparator in the adult patient. A systematic literature search was conducted to identify relevant studies published from 2011 until March 2021. Two reviewers independently abstracted data and assessed study quality. Oral fluconazole 150 mg tablet per week is effective in reducing dermatophytosis after 4 weeks (OR 0.14 95% Cl -1.81-1.82). The heterogenicity test shows no substantial changes between the two studies included in the meta-analysis (Chi^2=2.36, df=1, I^2=56.68%; P=0.124). Weekly treatment of fluconazole 150 mg by oral route for 4 weeks is effective against dermatophytosis.

1. Introduction

The most common dermatomycoses are dermatophytosis and tinea is caused by fungi like trichophyton, Microsporum, and Epidermophyton. These dermatophytes can infiltrate keratinized tissues (skin, hair, and nails).[1] Some dermatophytes are widespread, while others are restricted to a specific geographic area. Dermatophytes are typically transmitted through direct or indirect contact when shared objects such as a towel, brush, or sheet. However, some risk factors must be present, such as long-term corticosteroid therapy and chronic diseases.[2,3]

Dermatophytosis usually causes mild symptoms and is rarely a life-threatening problem for patients. The American Academy of Dermatology's clinical practice guidelines suggests that the treatment of superficial mycotic infections of the skin, such as tinea pedis, tinea cruris, and tinea corporis, is the same regardless of the site of infection. Treatments with topical antifungals, which are widely available without a prescription in most places, are frequently effective. Furthermore, these drugs are easily accessible and appealing to patients because they are less expensive than oral formulations and have fewer side effects.[4–6]

Fluconazole is a triazole antifungal agent which interacts with fungal cytochrome P450 dependent enzyme lanosterol 14-alpha demethylase and selectively inhibits the conversion of lanosterol to ergosterol. The fungal membrane is majorly composed of ergosterol, and fluconazole inhibits the synthesis of ergosterol thereby increases cellular permeability. It also helps in the prevention of endogenous respiration and the formation of yeast. Demethylation processes that occur in the mammalian cell are less sensitive to inhibition by fluconazole and help the human body to counteract causative agents of fungal infection.

Fluconazole is available for oral as well as intravenous treatment of localized and disseminated

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mycoses/dermatophytosis. The pharmacokinetic properties are similar after intravenous or oral administration; intravenous administration is useful in patients with impaired gastrointestinal absorption or motility. Fluconazole absorption is unaffected by food or gastric pH, and oral fluconazole has a bioavailability of more than 90% when compared to intravenous administration.[7]

We carried out a systematic review and meta-analysis of the effectiveness, compared with placebo or comparator, of weekly fluconazole therapy for 4 weeks for dermatophytosis, analyzing the clinical outcome of fluconazole oral therapy in an adult patient.

2. Materials and Methods

2.1. Inclusion & exclusion criteria

We included randomized controlled trials which enrolled patients with superficial dermatophytosis (tinea pedis, tinea manus, tinea corpora, and tinea cruris) aged between 18 to 60 years and receiving oral fluconazole 150 mg for 4 weeks & compared with placebo for 4 weeks. The articles published in English between 2011 to March 2021 were included for meta-analysis. Studies including oral continuous or intermittent therapy of fluconazole 150 mg with or without topical agents as one of the arms were included in the meta-analysis.

Studies focusing on pharmacokinetic parameters, drug-drug interaction, studies that enrolled patients with human immunodeficiency virus infection/acquired immunodeficiency syndrome, cancer, hematologic malignancy; those who underwent bone marrow or organ transplantation; and those who received immunosuppressive therapy were excluded. We also excluded studies enrolling patients with tinea versicolor & tinea capitis (prevalent in children). Furthermore, follow up studies also excluded.

2.2. Search strategy

The goal was to find all relevant trials, regardless of publication status or language. From 2011 to March 2021, electronic databases – Medline, Pubmed, Embase, BIOSIS, LILACS, Scopus, and IBECS – were searched for randomized controlled trials. The reference lists of identified articles were also screened and experts in the field were contacted. We used the following terms, both as text words and, as appropriate Medical Subjects Heading (MeSH) or equivalent subject heading/thesaurus terms: “randomized control trial”, “dermatophytosis”, “tinea pedis”, “tinea manus”, “tinea corpora” and “tinea cruris”. This sensitive filter was created by combining three filters for the identification of diagnostic studies via the Boolean operators “OR” and “AND”. We manually scanned the reference lists of all identified articles.

2.3. Data extraction

Two reviewers (P.S. and A.D.) independently selected studies from the search results, with the initial selection based on the study title and abstract. For all trials that met the eligibility criteria, baseline characteristics, treatment intervention, drug regimen, and efficacy data were extracted.

The methodologic quality of each included RCT was assessed using a method assessment tool developed by Jadad et al considers the suitability of randomization, blinding, and lost and withdrawn descriptions. Only studies with a score of 3 or higher were considered for analysis.[8]

2.4. Statistical analysis

Meta-essential 1.5 was employed. Odds ratios (ORs) and 95% CIs were calculated to compare the total effective rates of patients with dermatophytosis. The risk of bias assessment chart of meta-essential 1.5 was utilized to assess the included articles. Each effect was represented by a 95% CI. a fixed-effects model (FEM) was adopted for the meta-analysis.

3. Results

3.1. Search results and included studies

We have found 43 articles during database search; 20 articles were excluded after the title and extract evaluation. Additional 21 studies were excluded due to not qualifying inclusion criteria. The quality of the remaining 2 articles was evaluated based on Jaded criteria and included in the study for meta-analysis (Figure 1).

3.2. Meta-analysis result of fluconazole 150 mg efficacy in dermatophytosis

Two articles were analyzed for the total effective rate of the clinical trials. There were 238 participants enrolled in the trial (comprising 102 patients in the fluconazole group & 93 patients in the comparator group). Fluconazole 150 mg was found to be useful in reducing dermatophytosis after 4 weeks of oral treatment (OR 0.14 95% Cl -1.81-1.82). An overall heterogeneity test was performed & there was no substantial heterogeneity between the two included studies (Chi^2=2.36, df=1, I^2=56.68%; P=0.124). The results of Thaker et al [2013] occupied the highest percentage (53.008%) of the final combined results.

Figure 4 shows a funnel plot of fluconazole 150 mg oral dose efficacy in dermatophytosis. The circles in the two studies were mostly dispersed towards the midline and were symmetrical, indicating that the trials were accurate, the publishing was not biased, and the conclusions were trustworthy.

Table 1: Details of clinical trials included in the study

Study	Comparators	Additional Therapy	Dose & Duration	Total Subjects	Mean age (years)	Causative Agent	Time to follow
Kumar et al. (2013)	Fluconazole	-	150 mg once weekly	116	30.32 ± 6.67	Trichophyton species	4 Weeks
	Terbinafine	-	250 mg daily		30.36 ± 6.64		
Thaker et al (2013)	Fluconazole	Whitefield Ointment	150 mg once weekly	120	-	Trichophyton mentagrophytes	4 Weeks
	1% Butenafine	-	Twice week		-		

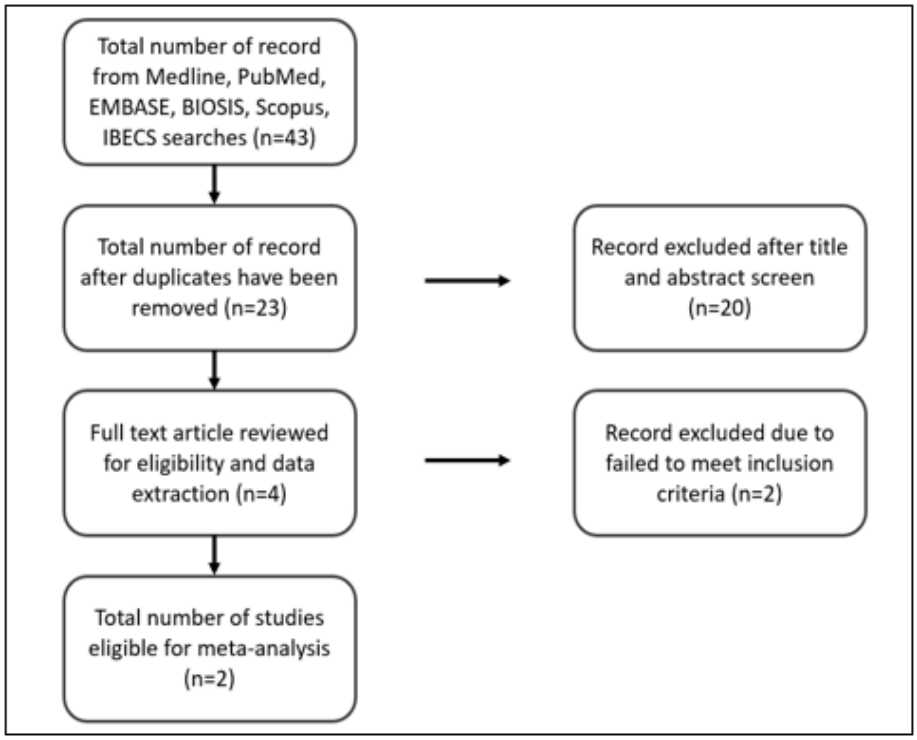


Fig. 1: Schematic for identifying eligible studies for meta-analysis.

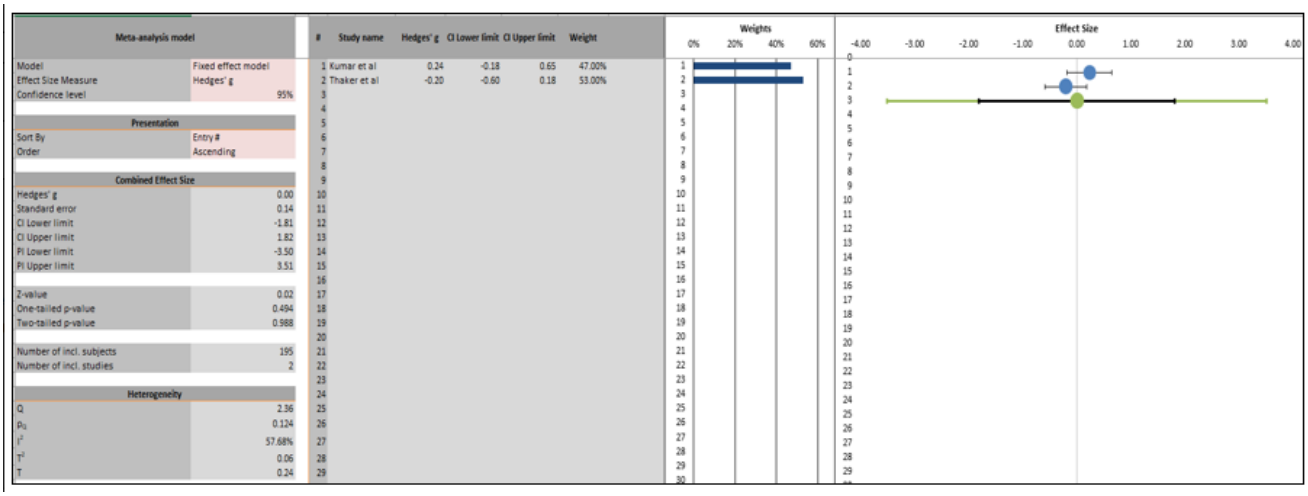
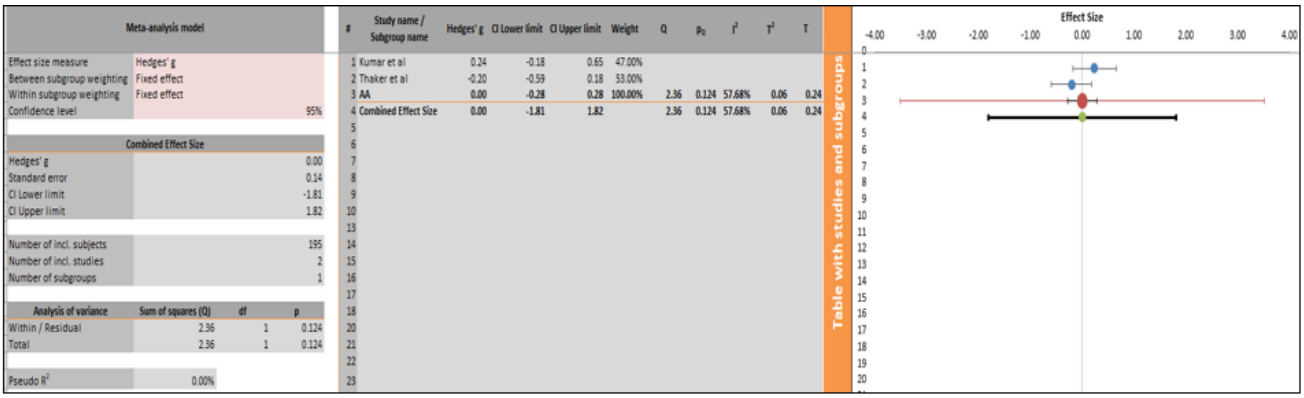


Fig. 2: Forest plot of the efficacy of Fluconazole 150 mg in dermatophytosis under the fixed effective model



Meta-analysis model	
Effect size measure	Hedges' g
Between subgroup weighting	Fixed effect
Within subgroup weighting	Fixed effect
Confidence level	95%

Combined Effect Size	
Hedges' g	0.00
Standard error	0.14
CI Lower limit	-1.81
CI Upper limit	1.82
Number of incl. subjects	195
Number of incl. studies	2
Number of subgroups	1

Analysis of variance	Sum of squares (Q)	df	p
Within / Residual	2.36	1	0.124
Total	2.36	1	0.124
Pseudo R^2	0.00%		

#	Study name / Subgroup name	Hedges' g	CI Lower limit	CI Upper limit	Weight	Q	p_Q	I^2	T^2	T
1	Kumar et al	0.24	-0.18	0.65	47.00%					
2	Thaker et al	-0.20	-0.59	0.18	53.00%					
3	AA	0.00	-0.28	0.28	100.00%	2.36	0.124	57.68%	0.06	0.24
4	Combined Effect Size	0.00	-1.81	1.82		2.36	0.124	57.68%	0.06	0.24

Table with studies and subgroups

Fig. 3: Sub-group analysis of fluconazole 150 mg in dermatophytosis

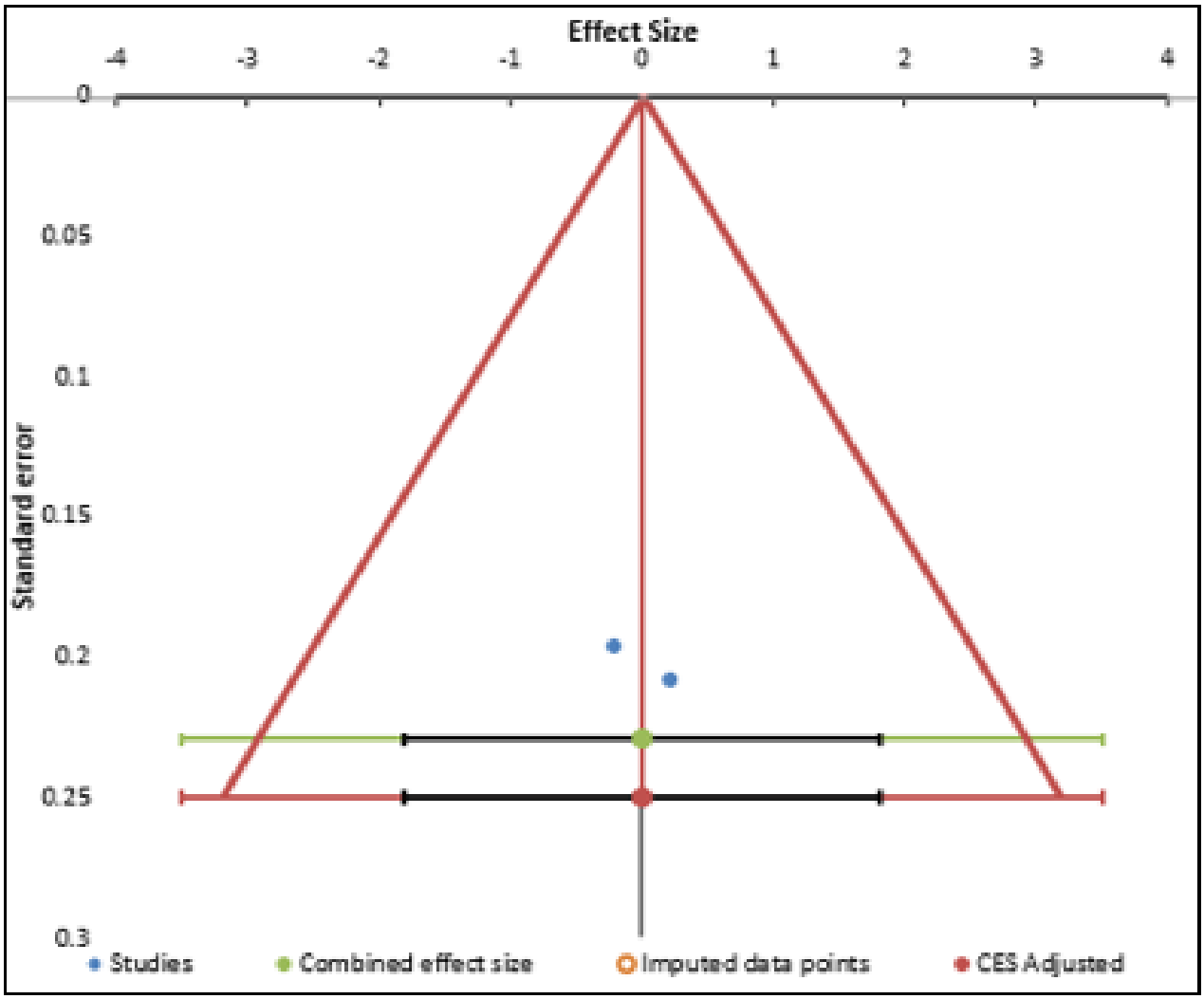


Fig. 4: Publication bias analysis during meta-analysis

4. Discussion

The current review compared the effectiveness of weekly fluconazole 150 mg oral tablet in reducing dermatophytosis in the adult patient. During review only two studies which could meet the criteria. The result of the study showed a significant effect of fluconazole 150 mg in the treatment of dermatophytosis over the period of 4 weeks.

Fluconazole and other triazoles have a stronger affinity for fungal enzymes. Fluconazole has a longer half-life; therefore, it requires less frequent doses. The fungal cytochrome P450 oxidase-mediated production of ergosterol (conversion of lanosterol to ergosterol) is inhibited by azole antifungals. Ergosterol is an essential component of the fungal cytoplasmic membrane. Fluconazole is particularly effective against Candida albicans.[9,10]

Fluconazole levels increase rapidly in the skin after oral dosing & accumulate in the sweet, diffuses rapidly and extensively into the stratum corneum. It was eliminated from there 2 to 3 times more slowly than from serum or plasma. Also, the drug attained in vitro MICs for most pathogens involved in superficial cutaneous mycoses. Therapeutic levels of the drug were still noted 1 week after treatment. In another study of fluconazole levels after weekly pulse dosing, the high stratum corneum concentrations of the drug (7.1 μg/g) was present 1 week after the second weekly dose of 150 mg. The usual MIC for most dermatophytes is 0.0015 to 0.01 μg/mL or μg/g.[11,12]

For the treatment of glabrous tinea, experts from the Indian Association of Dermatologists, Venereologists, and Leprologists (IADVL) Task Force against Recalcitrant Tinea (ITART) concluded that fluconazole should be administered for a longer time than Itraconazole or Terbinafine.[13]

When other oral antifungals like terbinafine or itraconazole have failed, systemic antifungals such fluconazole (150mg/week) can be utilized, according to the Expert Consensus on The Management of Dermatophytosis in India (ECTODERM India). According to the existing dermatophytosis situation in India, antifungal medicines should be recommended for a further two weeks after the clinical cure.[14]

Oral fluconazole is an appropriate treatment for tinea capitis, according to American Family Physician (AFP) recommendations, with shorter treatment periods than griseofulvin (Evidence rating A).[15]

5. Conclusion

Dermatophytosis is known as an infection caused by dermatophytes such as Trichophyton, Microsporum, and Epidermophytonosis on hair, nail, and skin. The common dermatological conditions which may arise from this infection include Tinea pedis, tinea corporis, tinea cruris, etc. The most prevalent causal agents, dermatophytes, are gaining prominence in emerging countries such as India. These fungi can be invasive, producing deeper and disseminated infections, even though they are usually painless and superficial. They should not be ignored. The lesions may spread, causing severe negative social, psychological, and occupational health consequences as well as a major reduction in quality of life. Dermatophytosis can be effectively cured with an oral or topical antifungal agent depending on the severity and nature of the infection. The therapeutic agents for the treatment of superficial infection are prescribed infrequently due to hepatotoxicity potential. A new agent such as fluconazole is generally preferred which possesses broad-spectrum action against dermatophytes and yeast infection.[16,17]

Fluconazole is a long-acting anti-fungal agent with improved efficacy, a safer adverse event profile, and increased patient compliance as compared with the older agents. Fluconazole 150 mg once weekly by the oral route is found to be effective when compared to topical as well as an oral anti-fungal agent during 4-week therapy. The result of the current meta-analysis suggests that a single dose of oral fluconazole (150 mg) per week for 4 weeks is effective in the treatment of superficial fungal infections such as dermatophytosis.

6. Details of Ethics Approval

No ethical approval was required for this review as all data were already published in peer-reviewed journals. No patients were involved in the design, conduct or interpretation of our review.

7. Conflict of Interest

None.

8. Source of Funding

None.

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