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Original Research Article

A prospective, randomized, open label, comparative study of efficacy and tolerability of oral itraconazole versus combination therapy with oral itraconazole and oral terbinafine in treatment of dermatophytosis

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ABSTRACT

Background: Superficial dermatophytosis, caused by fungi like Trichophyton and Microsporum, affects skin, hair and nails, presenting as round, red, scaly patches with itching. Generally, topical antifungals are common preferred treatment, while extensive infections and immunocompromised patients often require systemic oral treatments due to frequent relapses and resistance to topical terbinafine. This study compares itraconazole monotherapy with combination therapy of itraconazole and terbinafine to optimize treatment.
Methods: The study was conducted at Kempe Gowda Institute of Medical Sciences Hospital & Research Centre, Bengaluru, the study included 152 clinical and 10% KOH smear confirmed superficial dermatophytosis patients. Participants were randomly assigned to Group A (77 received oral itraconazole 100 mg twice daily for 3 weeks) and Group B (75 received oral itraconazole 100 mg twice daily plus oral terbinafine 250 mg once daily for 3 weeks). Participants were followed -ups at 3, 6 and 9 weeks for symptoms, KOH smear test results, clinical response and rescue medication use.
Results: Group B had a higher proportion of complete recoveries without relapse (p value 0.00775). No significant differences were found between the groups in terms of symptom severity, KOH test results, clinical response or rescue medication use, indicating comparable effectiveness.
Conclusions: Combination therapy with itraconazole and terbinafine was more effective than itraconazole alone in achieving relapse-free recovery in dermatophytosis patients. Both regimens were well-tolerated, suggesting combination therapy as a potentially better approach for fungal infections. This study supports combination therapy as a cost-effective treatment for tinea infections.

Keywords: Antifungal drugs, Dermatophytosis, Itraconazole, Terbinafine

INTRODUCTION

Superficial dermatophytosis, commonly known as 'tinea' affects the skin, hair and nails. Its classification depends on the affected area: tinea pedis (foot), tinea cruris (groin), tinea corporis (body), tinea faciei (face) and tinea capitis (scalp). This fungal infection impacts 20-25% of the global population, making it a prevalent dermatological condition. In India, prevalence varies widely, ranging from 6.09% to 61.5%, with South India showing rates between 6.09% and 27.6%, while North India records significantly higher rates of up to 61.5%.[1] Tinea corporis or ringworm of the body, is primarily caused by dermatophytes from the Trichophyton and *Microsporum genera*. Recent studies confirm that Trichophyton mentagrophytes accounts for over 90% of dermatophyte isolates. A large multicentric

study found the *Trichophyton mentagrophytes*/ *Trichophyton interdigitale* complex in 93.2% of cases, while Trichophyton rubrum was detected in only 6.8%.[2]

Clinically, *tinea corporis* manifests as erythematous, scaly, ring-shaped lesions with sharp, raised edges and central clearing, often pruritic. Other tinea types provide symptoms that are similar, depending on where they are located. Dermatophyte persistence can be related to immune evasion mechanisms such as surface molecule masking, toll-like receptor recognition evasion and decoy component shedding. An Indian study demonstrated that chronic dermatophytosis patients with enhanced CD4+ cell markers of Th17 and Treg culminate in mitigated Th17/Treg ratio, sustained fungal burden and futile immune reaction.[1]

Topical antifungal agents include miconazole, terbinafine and butenafine and are commonly used to treat superficial dermatophytosis. But for extensive infections or cases not resolving with topical treatment, systemic treatment is needed including oral antifungals such as itraconazole, terbinafine, griseofulvin or fluconazole. Hepatotoxicity limits the use of ketoconazole and griseofulvin's rapid elimination from the stratum corneum increases recurrence rates. Other drug effects of fluconazole and terbinafine are effective in short-term or pulse therapy. Use of itraconazole (100 mg once daily for two weeks or 200 mg once daily for one week) is effective for the treatment of tinea capitis; however, because of high rates of relapse, extended regimens (100 mg twice daily or 200 mg once daily for three weeks) are frequently used. The first-line drug, terbinafine, is effective at 500 mg/day, but resistance and relapse cases are increasing.[3-5]

In India, dermatophytosis management has evolved, yet data on oral antifungal efficacy remains insufficient. Limited comparative studies exist, particularly regarding monotherapy versus combination therapy. This study aims to compare the efficacy and tolerability of monotherapy using oral itraconazole versus combination therapy with oral itraconazole and oral terbinafine in dermatophytosis treatment in order to determine the most effective approach for reducing relapses and improving patient outcomes.[6]

METHODS

The study was registered under CTRI/2022/12/047904 and was conducted over a period of 16 months, from August 1, 2022, to December 31, 2023. After getting approval from Institutional Ethics Committee(KIMS/IEC/D117/M/2022) all participants fulfilling inclusion and exclusion criteria and willing to give written informed consent (total of 152 eligible) were enrolled using a simple randomization method. Participants were allocated to one of the two treatment arms in a 1:1 ratio. Randomization was carried out using a computer-generated sequence to ensure unbiased allocation. The study was conducted in accordance with the international conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines, the Declaration of Helsinki (Fortaleza, 2013) and the National Ethical Guidelines for Biomedical and Health Research (Indian Council of Medical Research, 2017).

Study subjects

The study recruited participants diagnosed with superficial dermatophytosis (tinea corporis, tinea faciei, tinea cruris) from the Dermatology Outpatient Department at Kempe Gowda Institute of Medical Sciences Hospital and Research Centre, Bengaluru. Participants were randomized into two groups in a computer-generated method by principal investigator: Group A, receiving oral itraconazole 100 mg twice daily (77 participants) and Group B, receiving oral itraconazole 100 mg twice daily plus oral terbinafine 250 mg once daily (75 participants) for 03 weeks.

Study procedure

Diagnosis was confirmed through mycological examination using a 10% potassium hydroxide (KOH) smear. A one-week washout period was maintained for participants using topical antifungal and or systemic antifungal therapy before enrolment to the study. Baseline assessments included demographic details, medical history, family history, comorbidities and concomitant medications, which were recorded in a specially designed case record form. Participants aged 18 to 65 years with a clinical diagnosis of new and recurrent superficial dermatophytosis, were included in the study. Participants were excluded if they were pregnant or lactating, had a history of pre-existing liver or renal disease, HIV or were under antiretroviral therapy, had hypersensitivity to study drugs or were receiving immunosuppressive therapy. Additionally, female participants were counselled to take adequate contraceptive measures during the study period and up to 15 weeks post-treatment. Those who tested positive for pregnancy during the study were excluded and followed up until delivery to assess potential teratogenic effects.

At each visit, following clinical parameters were assessed using a 4-point scale itching, erythema, scaling.

0=none, 1=mild, 2=moderate, 3=severe

The primary endpoint of the study was to assess the complete clinical cure, which was defined as an absence of erythema and scaling (score 0) along with an itching score of 0 or 1 along with negative mycological cure. Mycological cure was also evaluated using a 10% KOH smear to confirm the absence of fungal hyphae at the end of 3 weeks. Participants were assessed at baseline and at subsequent follow-up visits at 3, 6, 9, 12 and 15 weeks. Secondary endpoints included evaluating the relapse rate, time to complete cure and the tolerability of the treatment regimens. Tolerability was assessed based on adverse

events such as gastrointestinal disturbances, headache, rash and allergic reactions. As no standardized severity scoring system was available for the study context, a study-specific composite clinical assessment was used based on key clinical parameters, which were evaluated at baseline and during follow-up visits. However, it was not a formally validated scoring tool.

Participants with partial clinical recovery or relapse at the 3-week visit (end of therapy) or at 6 weeks or beyond were administered oral itraconazole dose, dosing schedule for another 3 weeks as a rescue treatment and participants were followed until mycological cure.

Statistical analysis

Data entry and analysis were performed using Microsoft Excel. Categorical variables were expressed as frequencies (number) and percentages (%). Comparisons between groups were performed using the Chi-square test for unpaired data. A p value of <0.05 was considered statistically significant.

Sample size estimation was based on the hospital burden of dermatophytosis, resulting in approximately 75 participants per group to account for a 10% loss to follow-up. The final sample size was determined using standard statistical formulas to ensure adequate power 95% for detecting significant differences between the treatment groups.

RESULTS

A total of 210 participants were screened, with 152 meeting the inclusion criteria and being randomized. Assessments were conducted at baseline and follow-up visits at 3, 6, 9, 12 and 15 weeks until clinical cure. A total of 2 participants (2.59%) from Group A and 8 participants (10.66%) from Group B were lost to follow-up.

In this study, most participants were between 31–40 years of age, with more women affected overall. However, there was no statistical difference in age or gender between Group A and Group B. Participants largely came from the upper middle class and the most common infections were *Tinea Corporis* and *Tinea Corporis* with Cruris, both affecting areas prone to sweat and poor ventilation. In most cases, the body surface area involved was small (1–10%), matching the number of lesions seen.

Health conditions like diabetes and hypertension did not show any clear link with the infections or outcomes. A few participants (n=6, 5.3%) reported alcohol or smoking habits and this did not affect recovery. Many had a past history of Tinea, with (significant/ nonsignificant) more relapses in Group A than Group B, though most improved by nine weeks. Family history was rare and did not influence outcomes. Overall, both groups showed very similar patterns of recovery (Table 1). Table 2 presents the clinical response data for two groups (A and B) at 3 weeks, 6 weeks, 9 weeks, 12 weeks and 15 weeks. In Tinea infections the clinical response is categorized as complete response, partial response, no improvement or loss to follow-up based on the severity of symptoms like itching, redness, scaling and KOH testing. The total score for the Tinea infection symptoms is equal to or less than 1 is considered complete response, if the score is 2-10 is considered partial response and no improvement in the severity of symptoms from the beginning of the therapy is considered as no response.

In Group A, at 3 weeks, 40.25% achieved complete response, while 54.54% had partial response, 2.59% showed no improvement and 2.59% were lost to follow-up. By 6 weeks, complete responses increased to 58.44%, with 37.66% partial responses. At 9 weeks, 79.22% reached complete response, with 18.18% showing partial recovery. Rescue medication (Itraconazole 100 mg BID for 3 weeks) was administered for relapses and by 15 weeks, all participants recovered.

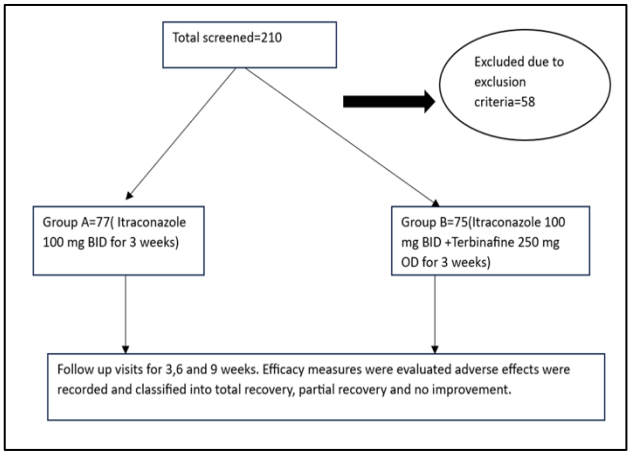

Figure 1: Participants flow diagram.

In Group B, at 3 weeks, 49.33% achieved complete response, 40% had partial response and 10.66% were lost to follow-up. By 6 weeks, complete response rose to 64% and by 9 weeks, 74.66% achieved full recovery. At 12 weeks, 13.3% continued to improve and by 15 weeks, all participants recovered with rescue medication.

Relapse analysis showed Group A had a 22.58% relapse rate at 6 weeks, compared to 16.66% in Group B (p=0.616). Lesions typically reappeared at the same sites, with one relapse linked to diabetes and hypertension in Group A. By 9 weeks, most relapsed participants recovered, though one required extended therapy. In Group B, relapses also recurred at original sites, except in one participant whose infection shifted locations (*Tinea Corporis* initially and *Tinea Cruris* subsequently. Importantly, Group B had a significant recovery rate at 9 weeks (p=0.00775). Both groups reported dizziness (n=2, 2.60 %) in Group A and (n=1, 1.33%) in Group B and the person in Group B discontinued therapy with no statistically significant distinction between the two groups. The data suggests that

both Group A and Group B showed a decrease in the use of rescue medication over time. While there were fluctuations in the response rate between the groups at different time points, not revealing any statistical differences with respect to rescue medications between the two groups. This indicates that the effectiveness or need for rescue medication did not significantly differ between the two groups receiving antifungal treatment.

Table 1: Baseline parameters.

	Group A (n=77,100%)	Group B (n=75,100%)	Total	P value (chi square test)
Age (in years)				
18-20	9 (11.68)	4 (5.3)	13	0.453
21-30	16 (20.77)	23 (30.66)	39	
31-40	22 (28.57)	20 (26.66)	42	
41-50	17 (22)	17 (22.66)	34	
>50	13 (16.88)	11 (14.66)	24	
Gender				
Females	47 (61.04)	46 (61.33)	93	0.654
Males	30 (38.9)	29 (38.6)	59	
Kuppuswamy scale				
Class				
Upper I	14 (18.18)	21 (28)	35	0.23
Upper middle II	40 (51.94)	32 (42.66)	72	
Lower middle III	18 (23.37)	18 (24)	36	
Upper lower IV	5 (6.4)	4 (5.33)	9	
Lower V	0	0	0	
Tinea				
Corporis	33 (42.85)	31 (41.33)	64	0.48
Cruris	16 (20.77)	12 (16)	28	
Faciei	3 (3.8)	5 (6.66)	8	
Corporis+Cruris+Faciei	3 (3.8)	0	3	
Corporis+Cruris	19 (24.67)	21 (28)	40	
Corporis+Faciei	1 (1.2)	4 (5.33)	5	
Cruris+Faciei	2 (2.59)	2 (2.59)	4	

Table 2: Clinical data.

Clinical response	Group A (n=77,100%)				Group B (n=75,100%)				P value (Chi-Square Test)*
	Complete response	Partial response	No improvement	Discontinued (loss to follow up)	Complete response	Partial response	No improvement	Discontinued (loss to follow up)	
3 weeks	31 (40.25)	42 (54.5)	2 (2.59)	2 (2.59)	37 (49.33)	30 (40)	0	8 (10.66)	*0.924
6 weeks	45 (58.44)	29 (37.66)	1 (0.01)	0	48 (64)	19 (25.33)	0	0	†0.734
9 weeks	61 (79.22)	14 (18.18)	0	0	56 (74.66)	11 (14.66)	0	0	‡0.146
12 weeks	11 (14.28)	3 (3.89)	0	0	10 (13.3)	1 (1.33)	0	0	§0.372
15 weeks	3 (3.89)	0	0	0	1 (1.33)	0	0	0	‖0.320

*The P value for the comparison between Group A and Group B at 3 weeks is 0.924 (95% CI;0.191, 0.295), suggesting no significant statistical difference but clinical significance is present. †The P value for the comparison between Group A and Group B at 6 weeks is 0.734 (95% CI;0.060, 0.513) suggesting no significant statistical difference but clinical significance is present. ‡The P value for the comparison between Group A and Group B at 9 weeks is 0.146 (95% CI;0.097, 0.595), suggesting no significant statistical difference but clinical significance is present. §The P value for the comparison between Group A and Group B at 12 weeks is 0.372 (95% CI;0.119, 0.1463), suggesting no significant statistical difference but clinical significance is present. ‖The P value for the comparison between Group A and Group B at 15 weeks is 0.320 (95% CI;0.098, 0.170), suggesting no significant statistical difference but clinical significance is present. Clinical response categorized as complete response, partial response, no improvement or loss to follow-up.

DISCUSSION

The study demonstrates individuals with a higher prevalence of females in 31-40 age in group A (n=22, 28.57%) and group B (n=20, 26.66%) possibly linked to climate, dress codes and hygiene practices. Similar age distribution has been found in a study comparing the efficacy and safety of orally administered Terbinafine and Itraconazole for the treatment of Tinea pedis (Dhaka) while another study found that most participants in group A (Itraconazole) were in the 21-30 age group, while most participants in group B (Terbinafine) were in the 51-60 age group (Ahmedabad, Gujarat) in treating Tinea Cruris.[7-9]

While a study for resistant Tinea infections showed female predominance (sample size 30, Dhaka), other studies demonstrate a predominance of male participants in Karnataka (sample size 270), (sample size 50, Dhaka)7,8 (Sample Size 200, Varanasi).[10-12] Studies done on resistant tinea infection and tinea cruris showed prevalence of lower socioeconomic strata (Ahmedabad, Gujarat), (Dhaka, Bangladesh) which implies higher literacy rates, better income and greater access to hospital for treatment in our study.[10,11] Tinea corporis (n=33, 42.85 and n=31, 41.33%) followed by tinea corporis and cruris are the most common types (n=19, 24.67% and n=21, 28%), primarily affecting areas prone to body moisture. In a similar study participants showed a higher prevalence of Tinea cruris and corporis followed by tinea cruris and corporis and faciei.[12] Concomitant medical conditions like Diabetes Mellitus and personal history of smoking and drinking did not bear any statistical or clinical correlation with other factors like socioeconomic status, family history, past history of Tinea infection, number and type of lesions and even treatment outcomes.

For evaluation of efficacy multiple parameters like itching severity (p value 0.574 95% CI;0.048,0.288), scaling severity (p value 0.0816 95% CI;0.064, 0.657), redness severity (p=0.152 95% CI;0.010, 0.543), clinical response (p=0.924 95% CI;0.1918, 0.295) and rescue medication (p=0.246 95% CI;0.17, 0.19) usage did not demonstrate significant changes between the groups, suggesting comparable treatment effectiveness overall.

In other studies, Itraconazole monotherapy was concluded to be the superior antifungal drug in terms of clinical remission with lowest incidence of increased erythema and scaling, followed by terbinafine and fluconazole.[10,12] Treatment regimens in our study show good safety profiles. While in the treatment of Tinea pedis, terbinafine was highlighted as a potential alternative for participants unable to take itraconazole due to contraindications or toxicity.[7,8] For resistant tinea infections both Itraconazole and Terbinafine showed high clinical improvement rates, with combination therapy in pulsed dose being effective and safe also.[10]

In conclusion, while Group B showed a higher proportion of participants achieving complete recovery without relapse compared to Group A at 9 weeks, as evidenced by the significant difference observed (p value 0.00775 95% CI; 0.14, 0.792), the overall efficacy of the treatment regimens administered to both groups appear promising. In other studies combination therapies involving these drugs have shown high efficacy in resistant tinea infections and specific conditions like chromoblastomycosis.[13-15] These studies collectively suggest that while single-drug regimens are effective, combination therapies may offer enhanced outcomes for complex or resistant cases. Therefore, optimizing treatment strategies for tinea infections with Itraconazole with Terbinafine is a cost-effective approach or a P-Drug.

Oral combination therapy of Itraconazole and Terbinafine is statistically and clinically significant at 9 weeks to Itraconazole only therapy with respect to complete recovery without relapse. However, there is no statistically significant difference between the study groups at 3 weeks and at 6 weeks as our study defines. The safety profile of these two drug regimens is good and comparable.

Limitations of the study are a single-centre study with a low sample size may not give results that can be generalised to a wider population and the short follow-up period may not adequately assess the sustainability of treatment and rates of recurrence. The study utilized a study-specific composite clinical assessment rather than a standardized, validated severity scoring system, which may limit the comparability of results with other studies. Additionally, the lack of formal validation of this assessment tool may introduce subjectivity in outcome measurement. Although literature suggests a treatment duration of 2-4 weeks, many participants required rescue medication at 3 weeks (48%), 6 weeks (31%) and 9 weeks (13.8%), indicating a need for longer treatment periods. Cost-effectiveness analysis of drug regimens could improve patient compliance, while Quality-of-Life (QOL) scales may highlight treatment impact. Cross-over studies comparing current drug regimens may yield further insights into optimizing treatment efficacy and patient outcomes.

CONCLUSION

The findings suggest that itraconazole–terbinafine combination therapy may offer improved sustained clinical outcomes compared with itraconazole monotherapy, warranting further investigation. Larger, multicentric studies with standardized outcome measures and longer follow-up are needed to establish its efficacy, safety, cost-effectiveness, and role in the management of dermatophytosis.

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