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Efficacy and Safety of Terbinafine and Itraconazole in Different Doses and Formulations and in Combination in the Treatment of Tinea Infection

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ABSTRACT

Background: Tinea (dermatophytosis) is a common superficial fungal infection with increasing chronicity and treatment failure, particularly in tropical regions. Rising antifungal resistance has reduced the effectiveness of conventional monotherapy, highlighting the need for higher doses, newer formulations, and combination regimens of commonly used agents such as terbinafine and itraconazole. This study aimed to compare the effectiveness and safety of terbinafine and itraconazole administered in different doses, formulations, and combinations in the treatment of tinea infection.

Methods: This prospective comparative study was conducted in the Departments of Pharmacology and Dermatology at Santosh Medical College and Hospital. A total of 246 KOH-positive patients with clinically diagnosed tinea infection were enrolled and divided into six treatment groups (n=41 each) receiving terbinafine, conventional itraconazole, super-bioavailable itraconazole, or their combinations. Clinical assessment using the Disease Severity Score (DSS) was performed at baseline and during three follow-up visits over 8 weeks.

Results: All groups were comparable at baseline for age, BMI, and DSS ($p>0.05$). Follow-up assessments showed significant intergroup differences, with maximum DSS reduction in Group 6, followed by Groups 5 and 3 ($p<0.01$). The shortest time to negative KOH was observed in Group 6 (2.6 days), while Group 1 showed the longest duration (5.53 days), indicating faster mycological cure with advanced and combination therapies ($p<0.01$).

Conclusion: This study concludes that itraconazole regimens, particularly those containing higher doses and the so-called super-bioavailable preparations, and combination with terbinafine are more effective in faster and complete clinical and mycological cure of tinea infections without undermining safety

Key-words: Tinea infection, Itraconazole, Terbinafine, Combination antifungal therapy, Antifungal efficacy

INTRODUCTION

Tinea, also known as ringworm, is the most common superficial fungal infection. It is widespread across the globe and negatively affects the quality of life of people and brings about social stigma.

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Tinea is a topical fungus induced by dermatophytes that infiltrate the targeted tissue (skin, hair, nails), producing multiplication. The infection is the most common fungal infection globally that involves the legs, arms, and trunk. The susceptibility to infections varies among individuals with genetic and familial predispositions that are linked to innate and adaptive immunity [1,2].

The most frequently seen fungal infection due to trichophyton, epidermophyton, and microsporum is tinea, which has a prevalence of 20-25% of the population worldwide and diffuses variably across

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different geographic regions. The prevalence has increased over the last few years, particularly in tropical nations, with chronic and recurrent cases of dermatophytosis also being on the increase [3]. These conditions can be treated using oral or topical antifungal drugs, depending on the intensity of the symptoms. Drugs like terbinafine, itraconazole, fluconazole, and luliconazole are being tested as clinical trial drugs to cure fungal diseases. Terbinafine and itraconazole have been the most widely used antifungal agents to date, with their favorable pharmacokinetic properties and a wide range of antifungal activity [4].

Terbinafine is an antifungal agent that is an allylamine, a drug, and is treated as the first line of treatment of tinea in case of Trichophyton infections due to fungicidal characteristics. Its fungicidal properties make it normally used in short-term treatment and are highly effective against dermatophytes [5]. On the other hand, the triazole itraconazole functions by inhibiting the Lanosterol 14α-demethylase enzyme, which is a fungal cytochrome P450-dependent enzyme. This is by inhibiting the process of changing lanosterol to ergosterol, which disrupts the fungal cell walls, and is of a broader spectrum of antifungal activity against yeasts and dermatophytes [6].

When the standard doses and durations are applied, resistance to these drugs increases dramatically. This can be explained by the fact that the effective concentration of terbinafine and itraconazole is reduced due to their widespread distribution in the skin and adipose tissue [7]. Therefore, the high rates of resistance to traditional antifungals and the rise in the rates of clinical failure are leading to the need to develop a successful combination of antifungal agents that will allow obtaining a fast clinical and mycological remission. Consequently, combination treatment is a highly developed principle of enhancing therapeutic performance and addressing drug resistance through a combination of synergistic and additive effects of two or more medications. *In vitro,* terbinafine and itraconazole are known to have synergistic interaction with a broad spectrum of dermatophytes and non-dermatophyte fungi [8]. The objective of the present study is to evaluate the safety and efficacy of itraconazole and terbinafine in the treatment of tinea when used in various dosages and formulations.

MATERIALS AND METHODS

Research design- The study is a comparative study regarding the efficacy and safety of terbinafine and itraconazole drugs for the tinea problem. The study was conducted in the Department of Pharmacology, which is in association with the Department of Dermatology, situated in the Santosh Medical College and Hospital. The study has been continued till the size of the sample has been achieved. The patients have been selected based on the visitors in the OPD centre of the dermatology department, specifically for the treatment of tinea. The patients have been selected based on certain inclusion and exclusion criteria. The proper ethical approval is needed for the study, and both informed and written consent are required for the study's conduction.

Inclusion criteria

1. Only patients of 40 to 80 kg have been selected for the study.
2. Patients visiting the OPD centre for tinea infections only are considered.
3. Well-informed and written consent is required for the study.

Exclusion criteria

1. Any pregnant women or women in their lactating stage are not allowed for the study.
2. Less than 40kg or more than 80kg
3. Weight is not considered for the study.
4. Drug reaction or any allergy to the two drugs is not considered for the study.
5. The pre-history of any oral antifungal agents within one month is excluded.
6. Severe comorbid patients with cardiovascular problems, liver or renal disorders, which can get severe during the study, are excluded.

Methodology- Demographic data, including age, weight, height, sex, and body mass index (BMI), were recorded for all participants. Dermatophytosis was diagnosed clinically and confirmed using potassium hydroxide (KOH) smear examination. Skin scrapings from the infected area were collected on a grease-free slide, prepared as a KOH wet mount, and examined microscopically for fungal hyphae, which appeared as hyaline, broad, aseptate branches with right-angle

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branching. Participants were divided into six treatment groups (n=41 each). Group 1 received terbinafine 500 mg twice daily; Group 2 itraconazole 100 mg twice daily; Group 3 itraconazole 200 mg twice daily; Group 4 super-bioavailable itraconazole 70 mg twice daily; Group 5 super-bioavailable itraconazole 130 mg twice daily; and Group 6 a combination of itraconazole 100 mg and terbinafine 250 mg twice daily. No topical antifungal agents were used. Baseline investigations included complete blood count, liver and renal function tests, and electrocardiography. Patients were followed every 2 weeks for 8 weeks or until lesion clearance. Clinical assessment was based on scaling, erythema, and pruritus scores (0–3). Cure was defined as the absence of clinical signs with a negative repeat KOH smear.

Sample Size

The Sample size was calculated by using the following formula

$$SS=(Z\text{-score})^2 * p*(1-p) / (e)^2$$

where Z=1.96 (at 95% confidence level)

p= 80% i.e. prevalence based on the previous study, Singh *et al*. [1] e=5% i.e. margin of error

$$Z=(1.96)^2*0.80*(1-0.80) / (0.05)^2=246$$

Thus, the sample size calculated for each of the groups is 41 subjects, which includes all the dropouts, the withdrawals, and the missed follow-up.

Statistical Analysis- The statistical analysis has been done by SPSS-27 or 29 software. Continuous variables were expressed as means with standard deviations, while categorical variables were summarised as frequencies and percentages. Intergroup comparisons for continuous outcomes were performed using one-way analysis of variance, and associations between categorical variables were assessed using Pearson's chi-square test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Fig. 1 presents the gender distribution in six different groups. The male population within all groups is always higher than the female one, and it means that there is a strong male dominance in the study population. The number of males varies between 25 and 32 across the groups, with Group 2 and Group 6 having the highest number of males and Group 4 having the lowest number of males. The female counts in comparison are relatively lower, with an average of 13-20 females, with the highest figure of females being recorded in Group 4 and the lowest in Group 2.

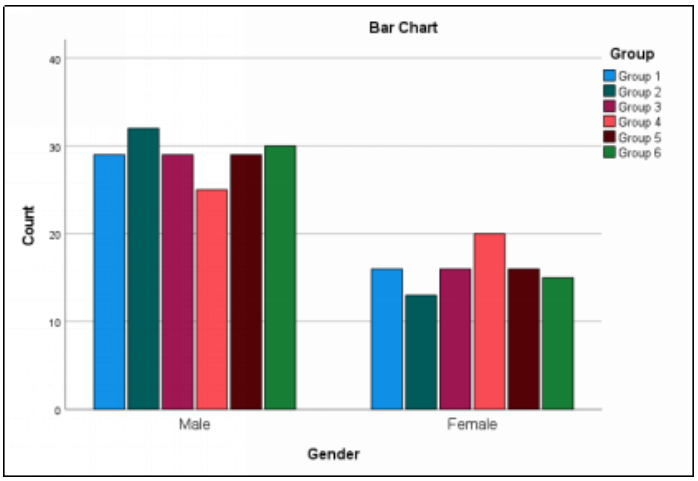

Fig. 1: Sex distribution of the patients in each group

Table 1 showed that the six groups were comparable with respect to baseline age and body mass index. The mean age varied minimally across groups, ranging from 30.29 years in Group 1 to 31.71 years in Group 4, with an overall mean of 31.11±8.56 years. One-way ANOVA demonstrated no statistically significant difference in age distribution among the groups (F=0.17, p=0.97), indicating homogeneity in age. Similarly, mean BMI values were narrowly distributed, from 21.89 kg/m² in Group 3 to 22.25 kg/m² in Group 5, with an overall mean BMI of 22.05±1.27 kg/m². The intergroup comparison for BMI was also non-significant (F=0.41, p=0.84). These

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findings confirm that both age and BMI were evenly matched across groups, minimizing their potential confounding effect on subsequent clinical and laboratory comparisons.

Table 1: Age and BMI of the patients and their analysis

Parameters	Group	N	Mean	Std. Deviation	F-value	p-value
Age	Group 1	45	30.28	9.10	0.17	0.97
	Group 2	45	31.42	8.75		
	Group 3	45	30.77	7.89		
	Group 4	45	31.71	8.27		
	Group 5	45	31.55	8.60		
	Group 6	45	30.91	9.06		
	Total	270	31.11	8.56		
BMI	Group 1	45	22.06	1.29	0.41	0.841
	Group 2	45	21.98	1.17		
	Group 3	45	21.89	1.28		
	Group 4	45	22.10	1.33		
	Group 5	45	22.25	1.32		
	Group 6	45	22.01	1.22		
	Total	270	22.05	1.26		

Table 2 shows that baseline disease severity score (DSS) was comparable across all six groups, with mean values ranging narrowly from 24.78 to 25.58 and no statistically significant intergroup difference (F=0.44, p=0.81), indicating uniform baseline disease severity. At the first follow-up, DSS demonstrated a marked and statistically significant reduction with clear intergroup differences, as mean scores declined from 23.64–23.82 in Groups 1 and 2 to 13.89 in Group 6 (F=63.99, p<0.01). This divergence became more pronounced at the second follow-up, where Group 6 showed the greatest improvement (mean DSS 8.82) compared with persistently higher scores in Groups 1 and 2 (F=69.96, p<0.01). By the third follow-up, DSS values approached near-complete resolution in Groups 5 and 6, while Groups 1 and 2 retained higher residual scores, yielding a highly significant difference (F=779.20, p<0.01). Time to negative KOH test also differed significantly among groups, decreasing progressively from 5.53 days in Group 1 to 2.6 days in Group 6 (F=242.78, p<0.01), reflecting faster mycological clearance in later groups.

Baseline DSS was comparable across all groups (p=0.81), confirming equivalent initial disease burden. At the first follow-up, Groups 6 and 5 demonstrated the greatest reduction in DSS, while Groups 1 and 2 showed minimal improvement, with highly significant intergroup differences (p<0.01). This pattern persisted and intensified at the second and third follow-ups, where Group 6 achieved near-complete clinical resolution, followed closely by Group 5 and Group 3, whereas Groups 1 and 2 retained comparatively higher residual scores (p<0.01 at all follow-ups). The time to a negative KOH test further corroborated these findings, with the shortest duration observed in Group 6 and the longest in Group 1 (p<0.01).

Table 2: Baseline DSS and follow-up DSS and Time taken to obtain a negative KOH Test

Parameters	Group	Mean	Std. Deviation	F-value	p-value
DSS_Baseline	Group 1	25.28	3.22	0.44	0.81
	Group 2	25.17	3.03		
	Group 3	25.57	3.45		
	Group 4	24.86	3.11		

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	Group 5	24.77	3.23		
	Group 6	25.46	3.15		
	Total	25.19	3.19		
DSS_first_followup	Group 1	23.82	3.30	63.99	<0.01
	Group 2	23.64	3.03		
	Group 3	18.73	3.75		
	Group 4	21.17	3.31		
	Group 5	19.15	2.05		
	Group 6	13.88	2.94		
	Total	20.07	4.58		
DSS_second_followup	Group 1	17.42	1.80	69.96	<0.01
	Group 2	23.64	3.03		
	Group 3	18.73	3.75		
	Group 4	21.17	3.31		
	Group 5	19.15	2.05		
	Group 6	8.82	7.56		
	Total	18.15	6.13		
DSS_third_followup	Group 1	10.55	1.13	779.20	<0.01
	Group 2	7.4	1.57		
	Group 3	1.51	1.16		
	Group 4	5.8	0.81		
	Group 5	0.26	0.83		
	Group 6	0	0		
	Total	4.25	4.08		
KOH_Time (days)	Group 1	5.53	0.50	242.78	<0.01
	Group 2	5.46	0.50		
	Group 3	4	0.70		
	Group 4	4.46	0.50		
	Group 5	3.11	0.31		
	Group 6	2.6	0.49		
	Total	4.19	1.21		

Terbinafine 500 mg twice daily showed the least reduction in disease severity (mean DSS change 14.73), indicating limited efficacy. Conventional itraconazole 100 mg twice daily produced moderate improvement (mean DSS reduction 17.78), offering only incremental benefit over terbinafine. Increasing itraconazole to 200 mg twice daily resulted in a markedly greater reduction in disease severity (mean DSS change 24.07). Super-bioavailable itraconazole 70 mg twice daily achieved an intermediate effect (mean DSS reduction 19.07), superior to lower-dose conventional regimens but inferior to higher-dose therapies. Super-bioavailable itraconazole 130 mg twice daily produced near-maximal benefit (mean DSS reduction 24.51). The combination of itraconazole 100 mg and terbinafine 250 mg twice daily showed the greatest efficacy, with the highest mean DSS reduction (25.47).

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Overall, the mean DSS change of 20.94 demonstrates substantial clinical improvement and a clear efficacy gradient favoring combination therapy and higher-dose or super-bioavailable itraconazole over conventional monotherapy (Fig. 2).

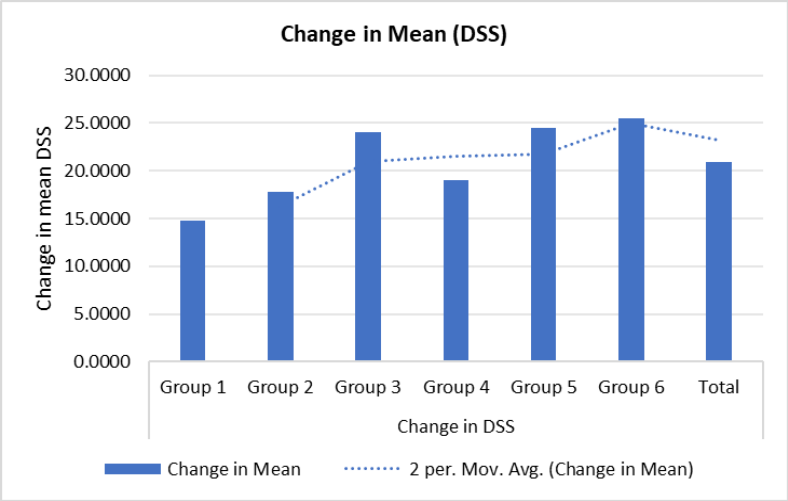

Fig. 2: Change in Mean DSS in each group

DISCUSSION

Dermatophyte infection is increasingly becoming common, particularly in the tropics. It has been noted that the antifungals are no longer as effective as before. The efficacy of terbinafine and itraconazole alone or in combination with various doses was determined in the treatment of tinea infection. It appears that itraconazole is superior to terbinafine. In the treatment of tinea, there is no use of an increase in dose or a combination regimen. It takes a long time to be cured completely [9].

The study aimed to compare the effectiveness of terbinafine and itraconazole in higher doses and durations in the treatment of *Tinea corporis* and tinea cruris. The randomized comparative study involved patients having *Tenia cruris* and *T. corporis* who were randomly paired in two groups of 160 patients who received oral itraconazole (Group II) and oral terbinafine (Group I) during the 4-week period. It appears that itraconazole and terbinafine are equally effective and safe for the treatment of *T. cruris* and *T. corporis* [10].

Efficacy and safety of a single daily dose of oral terbinafine 250 mg versus 500mg in combination with topical clotrimazole in the treatment of tinea infections were compared in a study. Every group of subjects was given 250 mg or 500 mg of terbinafine orally daily for four weeks, including topical clotrimazole. Terbinafine (oral 250mg daily) showed a poor cure rate of *T. cruris* and *T. corporis* after 4 weeks of therapy, and no added effect of a higher dosage of 500 mg was found [11].

A study assessed the effectiveness and safety of terbinafine 500 mg during the administration of a single dosage of 500mg daily in patients with superficial dermatophytosis. The study found that terbinafine at a dose of 500 mg per day administered as a single dose was both effective and safe in management of dermatophytosis among patients in a study of three groups who were categorized based on duration of therapy; Group A - terbinafine 500 mg 2 weeks, Group B - terbinafine 500 mg 4 weeks, and Group C - terbinafine 500 mg 6 weeks [12].

A study compared the effectiveness and safety of oral terbinafine and itraconazole combination therapy in dermatophytosis treatment. *Corporis*/Cruris/Faciei patients diagnosed clinically and positive for KOH were randomly separated into three groups and provided with terbinafine 250 mg, itraconazole 200 mg, and a combination of both at the same time and on the same day over 3 weeks. Systemic terbinafine and itraconazole therapy could be considered as a safe and effective treatment choice in the treatment of dermatophytosis [13].

The effectiveness of itraconazole 100, 200, and 400mg/d in the treatment of TCC was compared in terms of cure rates, treatment durability, safety profiles, and relapse rates. High overall efficacy was also found in 3 itraconazole doses used in the treatment of TCC in the randomized clinical trial, but the time of treatment was prolonged with high rates of relapse. The 200- and 100-

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mg dosage treatments were not significantly different in their effectiveness or periods of treatment, but the 400-mg treatment scored higher on these measures than the other 2 measures. It involves significant extra expense in terms of accomplishing cure with the 200- and 400-mg doses [14].

A study evaluated the efficacy and safety of high doses of terbinafine compared to itraconazole at the standard dose. Ciclopirox olamine was used on the topical areas of both arms. Either terbinafine 250mg twice a day or itraconazole 100mg twice a day was used over a period of 4 weeks. It was demonstrated that a combination of topical ciclopirox and high dose of terbinafine is effective and safe in treating *T. corporis* et cruris [15].

CONCLUSIONS

This study concludes that itraconazole regimens, particularly those containing higher doses and the so-called super-bioavailable preparations, and combination with terbinafine, are more effective in faster and complete clinical and mycological cure of tinea infections without undermining safety. The itraconazole-terbinafine combination regimen led to the best disease severity score reductions, the shortest time to negative KOH status, and nearly perfect clinical resolution, suggesting an apparent effective gradient, with the use of optimized itraconazole-based regimens. In general, a higher-dose or super-bioavailable itraconazole and combination therapy are recommended in tinea patients, especially in light of increasing antifungal resistance and recurrent or persistent dermatophytosis, which is necessary to achieve quick clearance and better therapeutic performance.

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