Original Article

Efficacy and Safety of Oral Terbinafine versus Itraconazole in the Treatment of Dermatophytosis: A Randomized Clinical Trial

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Abstract

Background: Dermatophytosis, a common fungal infection which is typically treated with a combination of systemic and topical antifungals. However, there is an increasing trend of these infections that is not responding well to conventional treatments.

Objective: To assess the effectiveness and safety of two antifungal medications, oral Terbinafine and Itraconazole, in treating dermatophytic infections.

Methods: This randomized clinical trial was conducted at the Department of Dermatology and Venereology, Combined Military Hospital, Ghatail and comprised of 100 patients diagnosed with Dermatophytosis. They were divided into two groups: Group A received 375 mg of Terbinafine tablets daily, while Group B was given 300 mg of Itraconazole capsules daily, in two divided dose, both for a duration of 6 weeks. Follow-ups were conducted in the 3rd and 6th weeks, during which scores for erythema, pruritus, and pigmentation were documented along with cure rate and recurrence rate. Data were analyzed by SPSS v25.

Results: The mean age of the participants was 31.5±9.5 years and most were males (54%). At baseline, moderate to severe scores for erythema, pruritus, and pigmentation were noted in 49(98%), 50(100%) and 43(86%) of patients in group A and 48(96%), 49(98%) and 40(80%) of patients in group B respectively. Improvement in all the three symptoms (erythema, pruritus and pigmentation) was seen at the 6th week of treatment with no significant difference between two groups ($p>0.05$). From baseline to 6th week of treatment, there was no significant difference between the two groups in reducing erythema ($p=0.05$) and pigmentation ($p=0.06$). However, group A patients had a much better improvement in reducing pruritus compared to group B ($p=0.006$). By the 6th week of treatment, 43(87.8%) group A patients and 37(74%) group B patients were completely cured. During treatment period, a total of 28 patients reported with adverse drug reactions.

Conclusion: The results of the study indicated that over a 6-week treatment period, Itraconazole and Terbinafine provided comparable outcomes.

Key-words: Dermatophytosis, Itraconazole, Terbinafine.

Introduction

Dermatophytosis is a major global health concern, affecting a significant number of individuals worldwide. It is caused by a superficial fungus that infects and proliferates in keratinized tissues, including skin, hair, and nails, leading to considerable discomfort, potential social stigma, and further health complications if left untreated.[1] An estimated 20-25% of the global population suffers from Tinea, a condition associated with dermatophytosis.[2] The dermatophyte fungi species affecting humans are Trichophyton, Microsporum, and Epidermophyton.[3] While the range of dermatophyte infections has varied significantly over time, Trichophyton species, especially Trichophyton rubrum, have consistently been the predominant cause of dermatophyte infections for the past decades.[4] In the last forty years, there has been significant progress in the treatment of this condition, evolving from the use of basic antiseptics, which possess non-specific antifungal properties, to the present availability of specific antifungal medications.[5]

Itraconazole and Terbinafine are two pivotal antifungal medications used in treating various fungal infections. Itraconazole, belonging to the triazole class, functions by hindering the synthesis of ergosterol, a key component of fungal cell membranes, effectively slowing fungal growth.[6] This broad-spectrum antifungal is particularly potent against dermatophytes, candida, and certain non-dermatophytic molds,[7] though it may lead to side effects like gastrointestinal disturbances, skin reactions, electrolyte imbalances, and potential impacts on blood pressure and renal function.[8] In contrast, Terbinafine, an allylamine antifungal agent, acts by inhibiting squalene epoxidase, an enzyme involved in the early stages of ergosterol synthesis. This action results in the accumulation of toxic squalene within fungal cells, ultimately leading to their death.[3] It is known for its milder and generally self-limiting side effects, including headaches, digestive discomfort, and skin rashes, making it a safer option for many patients.[9] Several studies have demonstrated the effectiveness of both Itraconazole and Terbinafine in treating dermatophyte infections.[10-12] It is essential for clinicians to evaluate how these two medications compare in effectiveness within a typical clinical settings. Therefore, this study aimed to assess the safety and effectiveness of Terbinafine and Itraconazole in patients with dermatophyte infections at a tertiary care facility in Bangladesh.

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Materials and Methods

This non-blinded randomized clinical trial was conducted involving 100 Dermatophytosis patients attending the Outpatient Department (OPD) of the Department of Dermatology and Venereology at Combined Military Hospital (CMH), Ghatail from July 2023 to January 2024. The study included patients aged >18 years and less than 65 years with Tinea corporis, Tinea cruris and Tinea faciei, with a total body surface area involvement of ≥ 50%. The study excluded pregnant and lactating women, patient who were allergic to Terbinafine and Itraconazole, patients with a history of intake of oral antifungals in last one month, patients with a history of topical treatment in the last two weeks, patients with Diabetes mellitus, cardiac, renal, and hepatic disease and patients with abnormal complete haemogram, renal function test and liver function test.

Patients satisfying the inclusion criteria were enrolled in the study after obtaining informed consent from the patient. Clinical diagnosis of Dermatophytosis was confirmed by positive potassium hydroxide (KOH) test along with presence of scaling, erythema, and pruritus. Patients were randomly divided into two groups by random sampling using lottery system; each group consisting of 50 patients. Patients were divided into two groups A and B. Group A patients were given tablet Terbinafine 375 mg daily and group B patients were given capsule Itraconazole 300 mg daily in two divided dose till the resolution of lesions or a maximum of 6 weeks. All the patients were followed up at 3rd week and 6th week with repeat KOH examination from the same site, wherever necessary. At each follow up visit clinical responses were observed in erythema, pruritus and pigmentation. These three parameters were clinically scored as 0-3 in which 0-absent, 1-mild, 2-moderate, 3-severe. Topical antifungal Econazole nitrate cream and oral antihistamines were prescribed in both groups as a part of supportive care. All the information was collected in a structured questionnaire.

Primary effectiveness endpoint: The primary effectiveness endpoint was the percentage of patients achieving complete cure at the end of the treatment period from the baseline. Patient was considered cured when there was absence of erythema, pruritus and pigmentation along with negative KOH test result. Outcome measurements at the end of the treatment included 'Cured': complete clinical resolution of all lesions, 'Partially cured': more than 50% improvement of the total area involvement from the first day of visit, 'Mild cure': less than 50% improvement of the total area involvement from the first day of visit.

Secondary effectiveness endpoint: The percentage of patients achieving clinical cure at the end of the treatment period. Clinical cure was defined as absence of erythema, pruritus and pigmentation at the end of the treatment. To observe the recurrence rate, patients were followed-up an additional four weeks post-treatment completion. Safety assessment was done by analysing all the adverse events reported by the patients during the treatment and by monitoring the liver function tests.

Descriptive statistics were expressed as frequencies and percentages for categorical variables and means and standard deviations for continuous variables. Student t-test was applied to compare the mean values of quantitative variables and Chi square test was used for analysing the categorical variables. The data were analyzed using the Statistical Package for Social Sciences (SPSS) v25. A p value <0.05 was considered statistically significant in the analysis.

This study adhered to ethical guidelines and obtained clearance from the Ethical Review Committee of Combined Military Hospital (CMH), Ghatail. All participants agreed to participate in the study, by expressing their consent through a detailed informed written consent form integrated into the initial page of the questionnaire. Additionally, no incentives were provided to the participants, and their involvement was entirely voluntary, with no coercion involved in the recruitment process.

Results

The mean age of the participants was 31.5±9.5 years. In terms of gender, most were male (54%), and majority were illiterate (92%) and lower income family (99%). Tinea cruris was most common type of dermatophytic infection in group A (66%) and both Tinea cruris and Tinea corporis were common in group B (72%). Majority of the patients had the dermatophytic infection for 3-4 weeks (Group A: 56% and Group B: 56%) and none of the patients had a family history of dermatophytosis. There was no significant difference between patients taking Terbinafine and Itraconazole regrading dermatophytosis species, duration of dermatophytosis, family history of dermatophytosis (p>0.05) (Table-I).

At baseline, moderate to severe scores for erythema, pruritus and pigmentation were noted in 49(98%), 50(100%) and 43(86%) of patients in Terbinafine group (group A) and 48(96%), 49(98%) and 40(80%) of patients in Itraconazole group (group B) respectively. Statistically, there was no significant difference between two groups for symptoms erythema and pigmentation, however significant difference was observed in the pruritus symptom (p=0.04) at baseline. Improvement in all the three symptoms (erythema, pruritus and pigmentation) was seen at the 6th week of treatment with no significant difference between two groups (p>0.05) (Table-II). From baseline to 6th week of treatment, the mean percentage of improvement for symptoms erythema, pruritus and pigmentation in group A was 98.5±3.81, 97.8±4.64 and 93.3±7.40 respectively and in group B was 96.6±5.75, 94.4±7.37 and 90.2±8.65 respectively. There was

was no significant difference between the two groups in reducing erythema (p=0.05) and pigmentation (p=0.06). However, patients who took Terbinafine (group A) had a much better improvement in reducing pruritus compared to those who took Itraconazole (Group B) (p=0.006) by the end of the treatment (Table-III).

Table-I: Demographic and clinical characteristics of respondents (n=100)

	Total n(%)	Group A n(%)	Group B n(%)	p-value*
Age (years)				0.37
19-28	43(43)	22(44)	21(42)	
29-38	37(37)	15(30)	22(44)	
39-48	17(17)	11(22)	6(12)	
>48	3(3)	2(4)	1(2)	
Mean ±SD	31.5±9.51	32.1±10.2	30.9±8.87	0.51**
Gender				0.69
Male	54(54)	26(52)	28(56)	
Female	46(46)	24(48)	22(44)	
Educational status				1.00
Illiterate	92(92)	46(92)	46(92)	
Literate	8(8)	4(8)	4(8)	
Socio-economic status				0.32
Lower income	99(99)	49(98)	50(100)	
Middle income	1(1)	1(2)	0(0)	
Upper income	0	0	0	
Occupation				0.15
Service holder	50(50)	22(44)	28(56)	
Housewife	43(43)	24(48)	19(38)	
Student	4(4)	1(2)	3(6)	
others	3(3)	3(6)	0	
Dermatophytosis species				
T. cruris	69(69)	33(66)	36(72)	0.52
T. corporis	64(64)	28(56)	36(72)	0.09
T. faciei	0	0	0	-
T. corporis et cruris	25(25)	15(30)	10(20)	0.25
T. corporis et cruris et faciei	1(1)	0	1	0.32
T. corporis et faciei	0	0	0	-
Duration of dematophytosis				0.60
1-2 weeks	43(43)	21(42)	22(44)	
3-4 weeks	56(56)	28(56)	28(56)	
>4 weeks	1(1)	1(2)	0(0)	
Family of dematophytosis				-
Yes	0	0	0	
No	100(100)	50(100)	50(100)	

**p-value obtained by chi-square test; **p-value obtained by student t test*

Table-II: Comparison of clinical characteristics of patients in group A and group B at baseline, 3rd week and 6th week (n=100)

	Group A n(%)				Group B n(%)				p-value
	No	Mild	Moderate	Severe	No	Mild	Moderate	Severe	
At baseline									
Erythema	0	1(2)	28(56)	21(42)	0	2(4)	25(50)	23(46)	0.74
Pruritus	0	0	35(70)	15(30)	0	1(2)	23(46)	26(52)	0.04
Pigmentation	0	7(14)	38(76)	5(10)	0	10(20)	34(68)	6(12)	0.66
At 3rd week									
Erythema	0	38(76)	12(24)	0	1(2)	29(58)	20(40)	0	0.07
Pruritus	0	36(72)	14(28)	0	1(2)	26(52)	23(46)	0	0.05
Pigmentation	0	45(90)	5(10)	0	1(2)	39(78)	10(20)	0	0.15
At 6th week									
Erythema	39(78)	10(20)	1(2)	0	30(60)	20(40)	0	0	0.17
Pruritus	37(74)	12(24)	1(2)	0	30(60)	20(40)	0	0	0.21
Pigmentation	30(60)	19(38)	1(2)	0	23(46)	27(54)	0	0	0.24

**p-value obtained by chi-square test*

Table-III: Comparison of percentage of improvement in clinical characteristics from baseline to 6th week (n=100)

	Overall percentage of improvement Mean±SD	**Group A** Mean±SD	**Group B** Mean±SD	**p-value***
Erythema	97.6 ± 4.95	98.5 ± 3.81	96.6 ± 5.75	0.05
Pruritus	96.1 ± 6.37	97.8 ± 4.64	94.4 ± 7.37	0.006
Pigmentation	91.7 ± 8.16	93.3 ± 7.40	90.2 ± 8.65	0.06

***p-value obtained by student t test*

Of all the 100 patients, 80 patients were cured completed, 19 patients were cured partially and 1 patient did not get cure at all. By the 6th week of treatment, 43(87.8%) patients in Terbinafine group and 37(74%) patients in Itraconazole group had complete resolution of symptoms and 6 (12.2%) patients in Terbinafine group and 13 (26%) patients in Itraconazole group was partially cured. While assessing the recurrence rate, in 15 patients the dermatophytic infection recurred again, of which 7 patients were in Terbinafine group and 8 patients were in Itraconazole group (Table-IV).

Table-IV: Comparison of cure rate and recurrence rate between studied groups at the end of treatment (n=100)

	Total n(%)	**Group A n(%)**	**Group B n(%)**	**p-value***
Cure rate				0.08
Cured	80(80)	43(87.8)	37(74)	
Partially cured	19(19)	6(12.2)	13(26)	
Not cured	1(1)	1(2)	0	
Recurrence rate				0.78
Recurred	15(15)	7(14)	8(16)	
Not recurred	85(85)	43(86)	42(84)	

**p-value obtained by chi-square test*

During treatment period, a total of 28 patients reported adverse drug reactions. In group A, 16(32%) patients experienced headache, while in group B, 9(18%) patients experienced headache during the treatment period. In group A, 3(6%) patients reported having pruritus. No other adverse reactions were reported in either group (Table-V).

Table-V: Comparison of adverse events between studied groups (n=100)

	Overall	**Group A** n(%)	**Group B** n (%)	**p-value***
Loss of appetite	0	0	0	-
Headache	25(25)	16(32)	9(18)	0.11
Yellow skin	0	0	0	-
Elevated liver enzymes	0	0	0	-
Hypersensitivity	0	0	0	-
Pruritus	3(3)	3(6)	0	0.08
Diarrhea	0	0	0	-
Loin pain	0	0	0	-
Vomiting	0	0	0	-

**p-value obtained by chi-square test*

Discussion

Antifungal medications are crucial for managing dermatophytes, available in both topical and oral forms. Several antifungal drugs have been developed, with ongoing exploration for better treatment. In this study, we aimed to compare the effectiveness of oral Itraconazole (300 mg) to oral Terbinafine (375 mg) in treating dermatophyte infections. We opted for a 6-week treatment regimen using both drugs administered twice a day. This dosage and duration regimen was chosen to ensure both safety and optimal performance in treating dermatophyte infections of the skin. Terbinafine is particularly prominent for its widespread use in treating superficial fungal infections due to its broad-spectrum fungicidal activity.[13] In this study, Terbinafine did not significantly outperform Itraconazole in terms of clinical cure rates (p=0.08), but it did significantly reduce the symptom of itching (p=0.006) in patients with dermatophytic infection.

In the present study, the mean age of the participants were 31.5±9.5 years and most were male (54%). Notably, 57% of the cases had dermatophytosis lasting more than 2 weeks. These findings align with a study by Ramesh et al which reported a mean

participant age of 36.5 years[1] and in studies by Singh et al[14] and Sharma et al[13] male predominance was reported at 74.1% and 70% respectively. The differences in gender distribution could be attributed to factors such as the study population's nature, cultural disparities or variations in sample size.

In the past, Terabinafine consistently demonstrated effectiveness against dermatophytes with cure rates exceeding 90% when taken at a daily dose of 250mg over two weeks.[15] Lately, the emergence of resistance to Terbinafine at previously established doses has prompted some doctors to either increase the dosage or resort to combination treatments.[16] The findings of the present study, showed a slightly better efficacy of Terbinafine over Itraconozole in terms of symptom resolution particularly pruritus, however, when it came to the overall rate of cure, both drugs performed similarly. The study by Majid et al reported a relatively low cure rate of 43% after a treatment period of two weeks with a daily dose of 250mg of Terbinafine for dermatophytosis[17] which is considerably lower than the 87.8% cure rate observed in this study. However, this is in line with other research findings that documented mycological cure rates for Terbinafine at 74%[18] and 71%.[19] Contrarily, Singh et al found Itraconazole to be more efficacious than Terbinafine.[14] Furthermore, another study demonstrated that a three-week regimen of Terbinafine at 250 mg/day resulted in a 35% cure rate, whereas Itraconazole at 200 mg/day achieved a 50% cure rate.[13]

Previous research has shown that the rate of recurrence with Itraconazole is typically very low when treating dermatophytosis.[20,21] However, in this study, we observed a higher rate of recurrence with Itraconazole (16%) compared to Terbinafine (14%). This may be due to Itraconazole's fungistatic action which inhibits fungal growth without necessarily killing the fungus. Conversely, Terbinafine's fungicidal properties, along with its ability to remain in the stratum corneum for several months after treatment has ended, likely contribute to its lower rate of relapse.[22,23]

The limitations of this study include its small sample size and the brief duration of follow-ups. Additionally, the reliance on fixed dosages also posed a constraint. The results of this study should be considered within the particular framework of the drug dosage and treatment duration used. Further research involving different dosages and treatment lengths to determine the most effective dosing strategies, drug choices, and treatment durations, as well as to ensure adequate post-treatment follow-up period to assess the two drug's effectiveness in preventing recurrence is recommended.

Conclusion

The results of the study indicated that over a 6-week treatment period, Itraconazole and Terbinafine provided comparable outcomes. While the differences in response rates between the two drugs were not statistically significant, Terbinafine showed a slightly better proportional response compared to Itraconazole. Future research involving a larger number of participants might more effectively ascertain the statistical significance of these observed differences.

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