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Original Research Article

A comparative study on efficacy of oral terbinafine and itraconazole on dermatophytic infections

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ABSTRACT

Background: The increased cases of dermatophyte infections and their poor response to oral drugs with current doses and duration of treatment is common. So, we conducted the study with a goal to assess the efficacies of two antifungal drugs with their increased dosages and duration.
Methods: A prospective comparative study was done on 145 patients belonging to age group 18-60 years which were both clinically and microbiologically confirmed cases of tinea cruris and tinea corporis. Patients were randomized into two groups A and B. Group A patients were given capsule itraconazole 100 mg twice daily and group B were given tablet terbinafine 250 mg twice daily, both for 6 weeks. Patients were followed up at 2, 4 and 6 week and at each visit, scores for 3 parameters (erythema, scaling and pruritus) were recorded and were analysed.
Results: A total 140 patients completed the study with 72 patients in group A and 73 patients in group B. In group A 72.5% patients achieved complete remission compared to 67.6% in group B. At each follow up patients were evaluated based on total symptom score (erythema, scaling and pruritus) which had shown significant improvement with negative potassium hydroxide results. None of the patients had severe side effects.
Conclusions: Study showed that Itraconazole has higher clinical and mycological cure rates as compared to terbinafine. So itraconazole is superior to terbinafine in treatment of tinea corporis and cruris.

Keywords: Dermatophyte, Tinea, Itraconazole, Terbinafine

INTRODUCTION

Dermatophytes are group of filamentous fungi that require keratin for growth. The condition produced as a result of dermatophyte infection is commonly known as dermatophytosis. The dermatophyte infections can cause cutaneous changes in the skin by forming ring shape lesions with a clear center and inflammatory edge and owing to this they are often also termed as ringworm.[1,2] Dermatophyte infections are quite common among human beings and affect people at different age groups and both the genders.[3,4] The dermatophyte fungi species affecting humans are *Epidermophyton* spp., *Microsporum* spp. and *Trichophyton* spp. respectively. Though spectrum of dermatophyte infections has shown a considerable variation over time, however, over the last one century, *Trichophyton* spp. in general and *Trichophyton rubrum* in particular has remained the most dominant dermatophyte infection.[5]

Itraconazole is a triazole class of broad-spectrum antifungal that is successfully being used for treatment of various types of fungal infections. It acts by slowing down the growth of fungi through inhibition of ergosterol synthesis that helps to maintain the cell membrane in the fungi.[6] It has been found to be highly effective against dermatophytes, candida, and on some non dermatophytic molds.[7] Side effects includes most commonly

gastrointestinal upset where as others are rashes/pruritus, hypokalemia, headache, hypotension, leukocytopenia as well as renal impairment.[8]

Terbinafine, on the other hand is an allylanine antifungal antibiotic that acts like triazoles by inhibiting the ergosterol synthesis but it does so by its further upstream by inhibiting squalene epoxidase. As a result, the ergosterol depletion takes place and accumulation of toxic squalene takes place which results in fungal death. Unlike itraconazole, Terbinafine has relatively much mild and self-limiting side effects such as headaches, gastrointestinal symptoms, and rashes.[9] Thus terbinafine has a relatively safer profile.[10]

The efficacy of itraconazole as well as terbinafine in management of dermatophyte infections has been reported in a number of studies.[11,12-16] From a clinician point of view, it would be important to judge which of the two drugs is better under standard clinical scenario.

Hence, the present study was planned to compare the clinical efficacy of oral itraconazole (100 mg BD) and terbinafine (250 mg BD) in treatment of dermatophytic infection of skin at a tertiary care centre in North India.

METHODS

Study design

The study design was of prospective, randomized and comparative.

Place of study

Study carried out at department of dermatology, Era's Lucknow medical college and hospital, Lucknow.

Study period

The duration of the study was of 24 months (Nov. 2019-Oct.2021).

Study population

Patients attending the skin clinic of department of dermatology, Era's Lucknow medical college and hospital, Lucknow presenting with dermatological infections.

Sample size estimation

Sample size estimation was done at department of community medicine, Era's Lucknow medical college and hospital, Lucknow. Sample size calculations were based on a previous study by Bhatia et al.[23]

Sample size was calculated on the basis of 6-week success rate of the two study drugs using the formula:

$$N=\left(\frac{Z_\alpha+Z_\beta)^2}{[In(1-e)]^2}\right)[1-\frac{p_1}{p_1}+1-\frac{p_2}{p_2}]$$

Where, p_1= 0.918, The 6 week success rate of the first drug, p_2=0.743 The 6 week success rate of the second drug, risk ratio e=0.20, considered to be clinically significant, type I error, α=5%, type II error β=10% for setting power of study 90%, lost to follow up=20%.

The sample size was calculated to be n=70 each group. However, a total of 145 patients were included in the study for randomization.

Inclusion criteria

Freshly diagnosed patients of aged 18 years and above with clinical diagnosis of tinea corporis and tinea cruris confirmed by potassium hydroxide (KOH) test attending dermatology OPD at ELMC and H included in study.

Exclusion criteria

Previously treated patients, patients with pre-existing renal disease hepatic disease and cardiac disease and pregnant and lactating women were excluded.

Method of sampling

Sequentially numbered opaque sealed envelope (SNOSE) technique.

A randomized, prospective comparative study was done in which total of 145 freshly diagnosed tinea corporis and tinea cruris patients of age 18 years and above attending the dermatology OPD at ELMC and H were included. Clinical diagnosis was confirmed by potassium hydroxide (KOH) test. Patients were divided into two groups A and B. Group A patients were given capsule Itraconazole 100 mg twice daily and group B were given tablet terbinafine 250 mg twice daily, both for 6 weeks. Patients were followed up at 2nd, 4th and 6th week.

In group A each patient will be given oral itraconazole 100 mg twice daily till the resolution of lesions or a maximum of 6 weeks. In group B each patient will be given oral terbinafine 250 mg twice daily till the resolution of lesions or a maximum of 6 weeks. At each follow up visit clinical responses were observed in scaling, erythema and pruritus these three parameters as were clinically scored as 0-3 in which 0-absent, 1-mild, 2-moderate, 3-severe. Patient were considered cured when there was absence of scaling, erythema and pruritus with negative KOH.

Statistical analysis

Data analysed using IBM SPSS 21.0 software. Chi-square, independent samples 't'-test and Mann-Whitney U test were used to compare data. Kaplan-Meir survival analysis done to compare time taken for resolution.

RESULTS

A total of 145 patient were assigned treatment using sequentially numbered opaque sealed envelope (SNOSE) technique for random distribution of patients in both groups. Five patients loss to follow up because of COVID pandemic, therefore a total of 140 patients were completed the study which includes 69 patients in group A and 71 patients in group B. Group A patients were given oral itraconazole 100mg twice daily and group B patients were given terbinafine 250mg twice daily. Demographic profile and diagnosis of patients of are shown in Table 1. The mean age of patients was 31.97±12.14 and 31.25±10.13 years respectively, in group A and group B. Group A had 52 (72.2%) males and 20 (27.8%) females, while in group B there were 50 (68.5%) males and 23(31.5%) females. Majority of patients were males (72.2%). Tinea corporis et cruris (59 patients in group A and 48 patients in group B) was most common type of dermatophytic infection followed by tinea cruris (8 patients in group A and 15 patients in group B) and tinea corporis (5 patients in group A and 10 patients in group B). Majority of the patients in both group were students and homemaker followed by farmers.

At baseline, moderate to severe scores for erythema, scaling and pruritus were noted in 70 (97.2%), 60 (83.3%) and 69 (95.8%) of patients in Itraconazole group and 73 (100%), 63 (86.3%) and 71 (97.3%) of patients in Terbinafine group. Statistically, there was no significant difference between two groups for symptom scores for all the three symptoms at baseline. Improvement in all the three symptoms (erythema, scaling and pruritus) was seen from the first follow-up at 2 weeks itself. No significant difference in pattern of resolution of all the three symptoms was observed between two groups at first follow up. By second follow up (4 weeks) two patients in Itraconazole group and one patient in Terbinafine group had complete resolution of symptoms. The clinical improvement seen in both the groups. At final follow-up (6 weeks) resolution of symptoms erythema, scaling and pruritus seen in 76.1%, 95.6% and 76.6% of itraconazole and 68.6%, 85.7% and 65.7% of terbinafine group patients. Statistically, there significantly better response to treatment in itraconazole group for scaling. The findings of the present study thus show that with respect to resolution of symptoms, Itraconazole had a slight edge over terbinafine. Itraconazole tended to show a faster resolution of symptoms as compared to terbinafine.

Table 1: Demographic profile and diagnosis of patient.

Characteristic	Group A, (n=72)	Group B, (n=73)	Statistical significance
Mean age±SD (range) (years)	31.97±12.14 (18-64)	31.25±10.13 (18-61)	't'=0.391; p=0.696
Sex			
Male	52 (72.2)	50 (68.5)	χ^2=0.242; p=0.623
Female	20 (27.8)	23 (31.5)	
Diagnosis			
Tinea corporis	5 (6.9)	10 (13.7)	
Tinea cruris	8 (11.1)	15 (20.5)	χ^2=4.921; p=0.085
Tinea corporis and cruris	59 (81.9)	48 (65.8)	
Occupation			
Unskilled worker/ farmer	15 (20.8)	16 (21.9)	
Skilled worker/ vendor	11 (15.3)	16 (21.9)	
Clerk/ shopkeeper/ teacher	11 (15.3)	10 (13.7)	
Officer/ professional	1 (1.4)	3 (4.1)	χ^2=2.771; p=0.735
Homemaker	14 (19.4)	10 (13.7)	
Student	20 (27.8)	18 (24.7)	

Table 2: Clinical parameters in Group A (Itraconazole) and B (Terbinafine).

Characteristics	Group A, (n=72) (%)				Group B, (n=73) (%)				Statistical significance (Mann-Whitney U test) 'p' value
	No	Mild	Mod	Sev	No	Mild	Mod	Sev	
At enrolment (Baseline)	**(n=72)**				**(n=73)**				
Erythema	0	2 (2.8)	19 (26.4)	51 (70.8)	0	0	30 (41.1)	43 (58.8)	z=1.351; p=0.177
Scaling	0	12 (16.7)	55 (76.4)	5 (6.9)	0	10 (13.7)	54 (74.0)	9 (12.3)	z=0.997; p=0.319
Pruritus	0	3 (4.2)	69 (95.8)	0	0	2 (2.7)	71 (97.3)	0	z=0.469; p=0.639

Continued.

Characteristics	Group A, (n=72) (%)				Group B, (n=73) (%)				Statistical significance (Mann-Whitney U test) 'p' value
	No	Mild	Mod	Sev	No	Mild	Mod	Sev	
First follow-up	**n=72**				**n=71**				
Erythema	1 (1.4)	19 (26.4)	49 (68.1)	3 (4.2)	1 (1.4)	19 (26.8)	45 (63.4)	6 (8.5)	z=0.336; p=0.737
Scaling	11 (15.3)	53 (73.6)	8 (11.1)	0	6 (8.5)	50 (70.4)	15 (21.1)	0	z=1.907; p=0.057
Pruritus	0	6 (8.3)	59 (81.9)	7 (9.7)	3 (4.2)	60 (84.5)	8 (11.3)	0	z=0.814; p=0.416
Second follow-up	**n=69**				**n=71**				
Erythema	15 (21.7)	48 (69.6)	6 (8.7)	0	14 (19.7)	43 (60.6)	14 (19.7)	0	z=1.266; p=0.206
Scaling	56 (82.4)	11 (16.2)	1 (1.5)	0	41 (57.7)	30 (42.3)	0	0	z=3.063; p=0.002
Pruritus	13 (18.8)	35 (50.7)	21 (30.4)	0	2 (2.8)	42 (59.2)	27 (38)	0	z=1.986; p=0.047
Third follow-up	**n=67**				**n=70**				
Erythema	51 (76.1)	16 (23.9)	0	0	48 (68.6)	22 (31.4)	0	0	z=0.983; p=0.326
Scaling	65 (95.6)	3 (4.4)	0	0	60 (85.7)	10 (14.3)	0	0	z=1.978; p=0.048
Pruritus	52 (76.5)	12 (17.6)	4 (5.9)	0	46 (65.7)	19 (27.1)	5 (7.1)	0	z=1.330; p=0.183

Table 3: Potassium hydroxide (KOH) test at the end of study.

Characteristics	Group A, (n=69) (%)	Group B, (n=71) (%)	Statistical significance (Mann - Whitney U test), 'p' value
KOH positivity at final assessment			
KOH positivity at 3rd follow-up	18/69 (26.1)	24/71 (33.8)	χ^2=0.992; p=0.

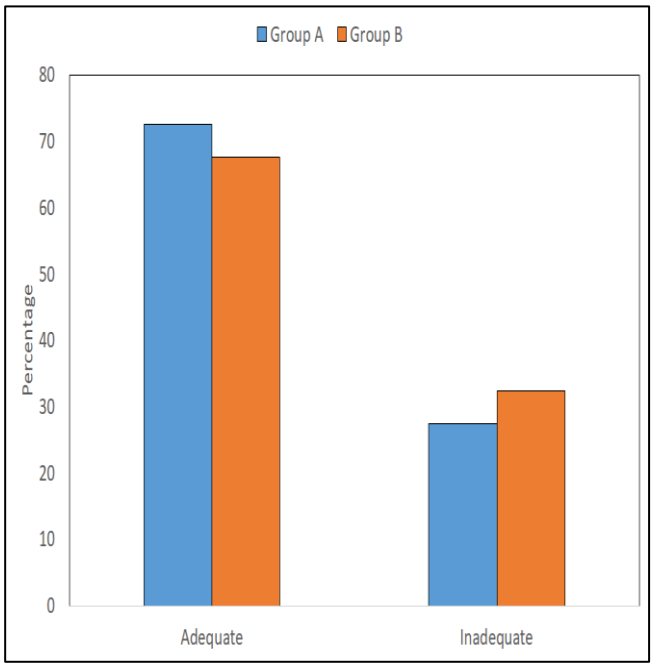

Figure 1: Comparison of final outcome between two study groups.

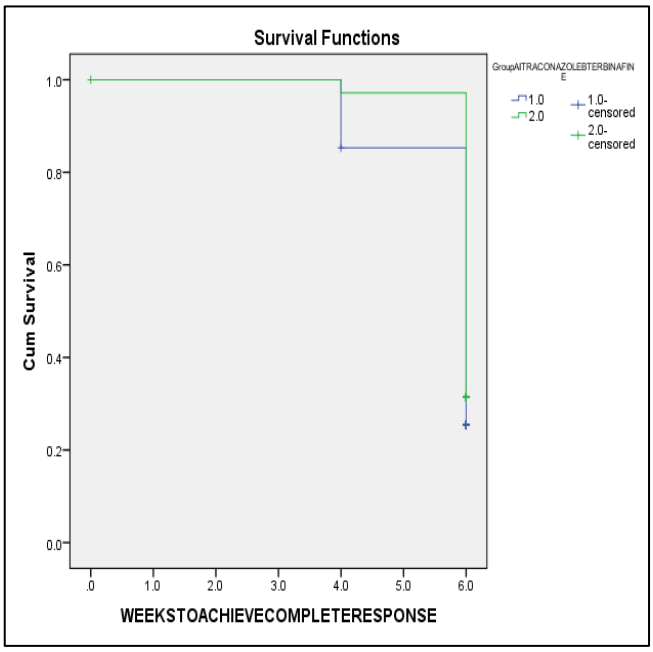

Figure 2: Test of equality of survival distributions for the different levels of group (A-itraconazole, B- terbinafine).

Median time taken for complete response was 6 weeks in both the groups and did not show a significant difference between two groups (p=0.113).

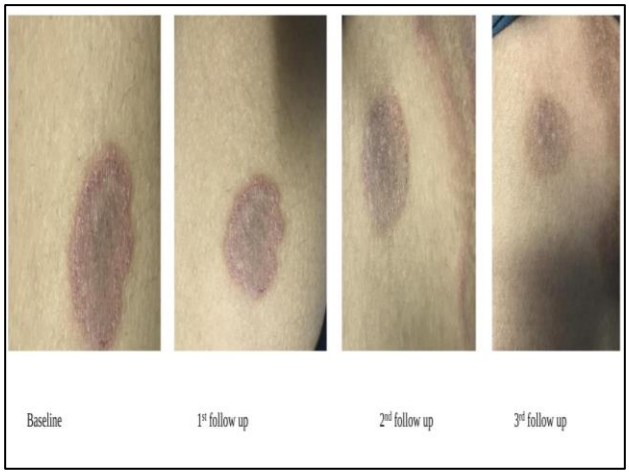

Figure 3: Single annular erythematous plaque with scaling.

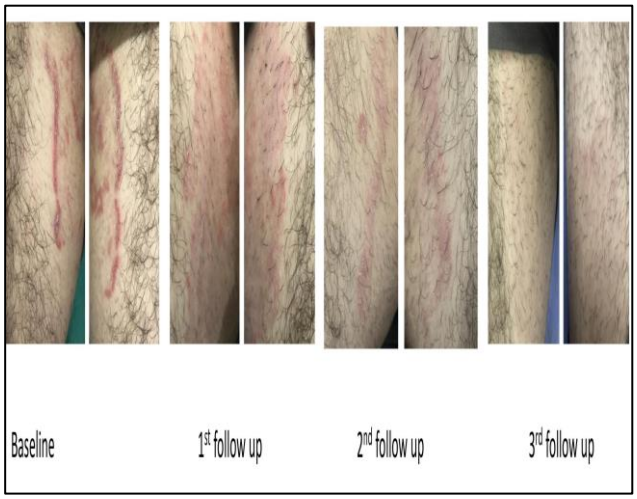

Figure 4: Erythematous plaque over bilateral groin.

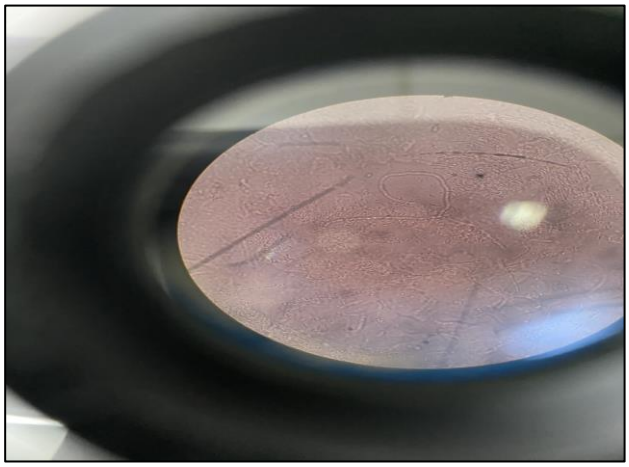

Figure 5: Multiple, branched, refractile, septate hyphae seen under 40X.

DISCUSSION

Dermatophytic infections of skin are caused by a group of fungi that affect the superficial layer of skin. Antifungals are the mainstay of medical management of dermtophytes both in topical as well as oral form. Triazoles-particularly Itraconazole is one of the most commonly used antifungals that has been reported to be highly effective against dermatophytes.[7] A number of studies in the past have compared Itraconazole and Terbinafine for their efficacy in treatment of dermatophyte infection.[17-32] However, there is still controversy regarding the projection of better of these two modalities and what should be the appropriate drug-dose regimen to obtain the optimum results with minimal adverse effects.

Itraconazole is generally well tolerated. However, certain side effects have been reported with its use. Most commonly encountered side effects were Gastrointestinal upset followed by rashes/ pruritus, headache, hypotension in small number of patients.[8]

Terbinafine resistance when given in the standard doses (250 mg OD for 2 weeks) is increasingly leading to partial or no response for treatment of dermatophytic infection.[33] Hence, higher dosage regimen for longer duration has been found to be more effective. The most common adverse events associated with terbinafine tend to be mild and self-limited. These include headaches, gastrointestinal symptoms, and rash.[10]

In the present study, we attempted to compare oral itraconazole (100 mg BD) to oral terbinafine (250 mg BD) for treatment of dermatophyte infections of skin. The selection of the dosage of the two drugs being compared was based on two criteria-first was safety and second was performance. On reviewing the literature we find an extreme variability in drug-dose selection and duration of treatment. In the present study we used a 6-week long regimen of two drugs with twice a day regimen.

The findings of the present study, thus show a slightly better efficacy of itraconazole over terbinafine in terms of symptom resolution, however, the two drugs were comparable in terms of overall response rate. The findings of the present study must be viewed in specific context of drug-dose combination and duration of treatment. Further studies on variable drug-dose combinations and duration of treatment are recommended to settle the issue of optimum dosing, drug selection and duration of treatment and a sufficient post-treatment follow-up to evaluate the efficacy of two drugs to study their efficacy in terms of recurrence prevention.

Limitations

Despite of 6 weeks course of capsule itraconazole 100 mg twice daily and terbinafine 250 mg twice daily, there

were 19 patients and 23 patients who could not completed treatment and were further required treatment for complete resolution of symptom and negative potassium hydroxide test.

CONCLUSIONS

At final assessment, KOH positivity rate was higher in terbinafine group (33.8%) as compared to that in Itraconazole group (26.1%) but difference between the two groups was not significant statistically. On overall assessment, adequacy of treatment was seen in 50 (72.5%) of Itraconazole as compared to 48 (67.6%) of terbinafine group patients. Statistically, this difference was not significant statistically. Median time taken for complete response was 6 weeks in both the groups and did not show a significant difference between two groups. The findings of the study showed that for a 6-week regimen, both itraconazole and terbinafine offered similar response. Though statistically non-significant yet a proportional response to treatment was better in itraconazole as compared to terbinafine. Further studies with larger sample size could determine the statistical significance of these differences in a better way.

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Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

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