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Clinical Efficacy of Oral Terbinafine, Fluconazole and Itraconazole in the Treatment of Tinea Corporis

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Authors' contributions

This work was carried out in collaboration between both authors. Author WM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author DV managed the analyses of the study and literature searches. Both authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Context: Comparing terbinafine, fluconazole and itraconazole for its efficacy.
Aims: This study was aimed to assess the clinico-mycological efficacy of oral terbinafine, fluconazole and itraconazole in the treatment of tinea corporis in a tertiary care hospital.
Study Design: This is a randomised comparative study with a sample size of 60 patients.
Methods: Patients were enrolled after considering various inclusion and exclusion criteria into three groups. Group A (oral terbinafine 250 mg daily for 2 weeks), group B (fluconazole 150 mg once weekly for 4 weeks) and group C (itraconazole 200 mg once daily for 2 weeks). Clinical assessment was performed weekly on the basis of physician global assessment grading the severity of pruritus, erythematic, vesicle and desquamation.

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Statistical Analysis Used: Fisher exact test was used to calculate the statistical significance between the pre and post interventional results.
Results: Of the 60 patients, 51 completed the study on a comparison between the three groups terbinafine (n=15), itraconazole (n=18) and fluconazole (n=18), it was observed that terbinafine was more effective on pruritis (80%), erythema (40%) and desquamation (80%). Itraconazole showed effectiveness on vesicle (66.66%).
Conclusions: Terbinafine was better than itraconazole and fluconazole in relieving signs and symptoms during the study period.

Keywords: Desquamation; erythema; fluconazole; itraconazole; terbinafine; tinea.

Key Message: *Efficacy studies play a very pivotal role in avoiding the resistance of the drugs among patients. According to this study, terbinafine was more effective than itraconazole and fluconazole in alleviating clinical signs and symptoms particularly pruritus, erythema and desquamation, whereas itraconazole was found effective in relieving vesicle.*

1. INTRODUCTION

Dermatophytosis represents a superficial infection of the keratinised layers of hair, nail and skin caused by dermatophytic fungi [1].

Topical agents such as clotrimazole are usually well tolerated and penetrate into the systemic circulation infrequently. However, they may not penetrate well into the keratin barrier, and thus may not provide optimal treatment for dermatophyte infections located within the keratin. Furthermore, they may induce irritant or allergic contact dermatitis, and repeated application to extensive areas of skin is not always practical for patients. For these reasons, a desirable alternative for the treatment of dermatophyte infections is an oral agent with proven efficacy and minimal toxicity [2].

This study was undertaken to evaluate the clinico-mycological efficacy of three drugs fluconazole, itraconazole and terbinafine in tinea corporis and to evaluate the susceptibility of isolates to the three antifungal drugs.

2. METHODS

A randomised comparative study was conducted from August 2015-March 2016, after ethical approval by local Ethics Committee.60 untreated patients of tinea corporis were selected. All the patients are >16 years of age with the diagnosis of tinea corporis confirmed by direct microscopy (KOH preparation) or culture. Patients with extensive dermatophytosis [3] (tinea corporis with cruris, pedis and onychomycosis) were excluded. Patients already on antifungal therapy (either topical or oral), 14 days of baseline were excluded. Patients who had used topical steroids were also excluded from the study. Pregnant women and patients with hepatic or renal disease were also not included. Patients were briefed about the nature of the study and a written informed consent was obtained.

2.1 Study Design

A detailed history was taken regarding duration and progress of lesion in past and demographic details including family history, age, and sex in a predesigned Performa. A complete dermatological examination was done to assess type of lesion, morphology and distribution was done along with general physical examination. Relevant systemic examination was done and the findings were recorded along with the vital examination. The affected area was first thoroughly cleaned with 70% alcohol to remove surface contaminants. After the alcohol dried, skin scraping was placed from the border of the active lesion using a microscopic slide, moving the slide perpendicular to the skin surface where another slide was kept along to collect the specimen sample. Specimen was collected on sterile paper.

Samples of the patients were subjected to necessary investigations which include KOH test, culture test.

2.2 KOH Preparation

The specimen is placed on a clean sterilised glass slide, few drops of 20% KOH are added

and then a cover slip is placed over it. The slide was left at room temperature for 24 hours. The specimen is examined under the microscope first under low power (10X) and then under high power (40X) for hyphae and arthrospores.

2.3 Culture

All the samples irrespective of KOH results were subjected to culture on Sabouraud dextrose agar (SDA) with chloramphenicol, and Sabouraud dextrose agar with chloramphenicol + cycloheximide. The specimen was inoculated on to this media and it was incubated at room temperature. They were examined every week for the growth of colonies and were discarded after 4 weeks if there was no growth.

2.4 Clinical Assessment

Clinical assessment was performed on the basis of global physician assessment by scoring the severity of pruritus, erythematic, vesicle and desquamation from 1 to 3 (3=severe, 2= moderate, 1=mild).

2.5 Diary for Safety Assessment

Diary for safety assessment was provided to the patients of all the three groups and patients were explained all the details about diary and trained to fill the diary. Patients were also provided with Patient Information Leaflet (PIL) in the language which was understandable to them.

2.6 First Visit

Patients were screened and thus allotted the Group of treatment.

2.7 Randomisation

Patients are randomly assigned to three groups.Group 1, Group 2 and Group 3 through Simple randomisation method. All the patients were prescribed same brands of terbinafine, fluconazole and itraconazole.

(I) Group A (Daily oral terbinafine): In this group patients were given oral terbinafine (250 mg) daily at morning time after breakfast for 2 weeks [3].

(II) Group B (Weekly oral fluconazole): In this group patients were given oral fluconazole (150 mg) once weekly at morning time after breakfast for 4 weeks [3].

(III) Group C (Daily oral itraconazole): In this group patients were given oral itraconazole (200 mg) once daily at morning time after breakfast for 2 weeks [3].

2.8 Follow up and Evaluation

Patients were followed at 2nd and 3rd week wherein physical clinical assessment was performed in all their visits.

2.9 Statistical Analysis

Once the data was collected, it was coded and entered into Microsoft excel spreadsheet and analysed. Fisher exact test was used for data analysis.

3. RESULTS

In the present study 60 patients of tinea corporis were enrolled. The results and observations were as below:

Our study showed that the Incidence of tinea corporis was high in males than females with the male to female ratio of 1.8:1. Most common age group with tinea Corporis patients was 60-70 years comprised of 23.33%. Most of the patients were farmers (33%) followed by housewives (30%). In this study KOH examination for fungus was positive in 48% of the cases and negative for 52% cases. Culture positivity for fungus in the study was 53.33%.

Out of 60 patients, 51 patients completed the study whereas 9 patients were lost to follow up. In terbinafine group, 5 patients were lost to follow up, whereas in itraconazole and fluconazole groups, 2 patients each were lost to follow up. Among the total 51 patients enrolled in the study 15 patients were in the group of terbinafine and 18 each in itraconazole and fluconazole groups.

Table 1. Comparison of changes in proportion with Pruritus

Baseline visit			
Drugs	**Grade**		**Total patients(n)**
	3	**4**	
Fluconazole	8 (44.44%)	10 (55.55%)	18
Terbinafine	9 (60%)	6 (40%)	15
Itraconazole	8 (44.44%)	10 (55.55)	18
	p=0.091		

Visit 2				
Drugs	**Grade**			**Total**
	2	**3**	**4**	**patients(n)**
Fluconazole	3 (16.66%)	12 (66.66)	3 (16.66)	18
Terbinafine	8 (53.33%)	7 (46.66%)	0	15
Itraconazole	4 (22.22%)	13 (72.22%)	1 5.55%)	18
Total	p=0.599			

Visit 3				
Drugs	**Grade**			**Total**
	1	**2**	**3**	**patients(n)**
Fluconazole	0	9 (50%)	9 (50%)	18
Terbinafine	12 (80%)	3 (20%)	0	15
Itraconazole	4 (22.22%)	9 (50%)	5 (27.77%)	18
Total	16	21	14	51
	p=0.001			

Terbinafine was very effective in curing pruritus.

Table 2. Comparison of changes in proportion with erythema

Baseline visit					
Drugs	**Grade**				**Total**
	1	**2**	**3**	**4**	**patients(n)**
Fluconazole	1 (5.55%)	4 (22.22%)	10(55.55%)	3(16.66%)	18
Terbinafine	2(13.33%)	2 (13.33%)	7 (46.66%)	4 (26.22%)	15
Itraconazole	2(11.11%)	1(5.55%)	12(66.66%)	3(16.66%)	18
	p=0.765				

Visit 2				
Drugs	**Grade**			**Total patients(n)**
	1	**2**	**3**	
Fluconazole	2 (1[1].11%)	5 (27.7%)	11 (61.11%)	18
Terbinafine	4 (26.66%)	6(40%)	5(33.33%)	15
Itraconazole	2(11.11%)	13(72.22%)	3(16.66%)	18
	p=0.035			

Visit 3				
Drugs	**Grade**			**Total patients(n)**
	1	**2**	**3**	
Fluconazole	8 (44.44%)	8 (44.44%)	4 (22.22%)	18
Terbinafine	8 (53.33%)	6 (40%)	1 (6.66%)	15
Itraconazole	6 (33.33%)	11(61.11%)	1 (5.55%)	18
	p=0.435			

Terbinafine was effective in curing erythema.

Table 3. Comparison of changes in proportion with vesicles (we have not come across any patients with pustules)

Baseline visit					
Drugs	**Grade**				**Total**
	1	**2**	**3**	**4**	**patients(n)**
Fluconazole	3 (16.66%)	9(50%)	5(27.77%)	1(5.55%)	18
Terbinafine	7(46.66%)	5(33.33%)	3(20%)	0	15
Itraconazole	2(11.11%)	9(50%)	7(38.88%)	0	18
	p=0.221				

Visit 2				
Drugs	**Grade**			**Total**
	1	**2**	**3**	**patients(n)**
Fluconazole	8(44.44%)	7(38.88%)	3(16.66%)	18
Terbinafine	12(80%)	3(20%)	0	15
Itraconazole	7(38.88%)	10(55.55%)	1(5.55%)	18
	p=0.075			

Visit 3			
Drugs	**Grade**		**Total patients(n)**
	1	**2**	
Fluconazole	13(72.22%)	5(27.77%)	18
Terbinafine	15(100%)	0	15
Itraconazole	14(77.77%)	4(22.22%)	18
	p=0.072		

Itraconazole was effective in curing vesicle.

Table 4. Comparison of changes in proportion with desquamation

Baseline visit					
Drugs	**Grade**				**Total**
	1	**2**	**3**	**4**	**patients(n)**
Fluconazole	1(5.55%)	5(27.77%)	10(55.55%)	2(11.11%)	18
Terbinafine	1(6.66%)	3(20%)	11(73.33%)	0	15
Itraconazole	1(5.55%)	8(44.44%)	8(44.44%)	1(5.55%)	18
	p=0.498				

Visit 2				
Drugs	**Grade**			**Total**
	1	**2**	**3**	**patients(n)**
Fluconazole	1(5.55%)	15(83.33%)	2(11.11%)	18
Terbinafine	4(26.66%)	10(66.66%)	1(6.66%)	15
Itraconazole	8(44.44%)	8(44.44%)	2(11.11%)	18
	p=0.066			

Visit 3				
Drugs	**Grade**			**Total**
	1	**2**	**3**	**patients(n)**
Fluconazole	10(55.55%)	6(33.33%)	2(11.11%)	18
Terbinafine	13(86.66%)	2(13.33%)	0	15
Itraconazole	12(66.66%)	6(33.33%)	0	18
	p=0.276			

Terbinafine showed effective clinical improvement in G-1 from 6.66% in baseline visit to 86.66% in V-3 with overall effectiveness of 80%.

4. DISCUSSION

Considering the facts the present study was conducted to know the clinical efficacy of three antifungal drugs i.e, terbinafine, itraconazole and fluconazole with respect to understanding the disease pattern which thereby relates to clinical efficacy of the above drugs.

In the present study males were more affected. Almost two third patients (65%) were males with a male to female ratio of 1.85:1.

There was lesser variation in the male to female ratio among most of the previous studies. In a study conducted by Kumar et al in 2013, male to female ratio was 1.36:1 [4]. In contrast, Bindu et al [5] in 2002, had reported a wide variation in distribution of the disease in both the genders with a male to female ratio 2.06:1.

Overall it was observed that, in previous studies and the present study, male population is commonly greater, which may be due to the increased sweating and active workload outdoors.

In this study maximum age group patients belonged to the age 61-70yrs old (25%) with next common age groups from 21-30yrs old (23.33%).

A study by Roopa and Biradar in 2012 encountered maximum number of cases in the age group 31-40yrs (47.27%) followed by 21-30yrs (29.09%) [6].This is in contrast to our study where maximum number of patients are in the age group 61-70yrs. It may be due to the higher incidence of dermatophytes in those patients proportional to the hygienic conditions, amount of sebum production and decreased immunity with old age [3].

Occupation distribution among the patients in the study was widely varied with maximum number of patients being farmers (33.33%) followed by housewives (30%) to a lesser extent of students (15%).Overall present study observed farmers being subjected to this disease is on higher incidence which may be due to outdoor activity and excessive sweating to that of housewives because all the female patients were housewives and prevalence may be due to wet conditions or humidity [7]. In the present study maximum cases were noted from September to November (65%) with peak in the month of November. The higher incidence is during or post rainy days which may be due to humidity or moisture.

In the present study Trichophyton mentagrophytes (40.62%) was most common isolate followed by *T. rubrum* (34.37%). Study conducted by Surendran et al from Mysore found that *T. rubrum* was chief isolate organism (55.5%) followed by *T. mentagrophytes* (33.3%) [8]. Isolation rate of the distribution of different dermatophytes varies with geographical area and the course of time leading to change in the spectrum of dermatophytic isolates [9].

Change in pruritus was seen at the end of treatment phase with the comparison on the grades from baseline to visit 3 (V-3).It was noted that there were no patients with grade1 (G-1) at baseline visit and visit 2 (V-2). Whereas in V-3 there were 0% of patients treated with Fluconazole, 80% of patients treated with terbinafine and 22.22% patients treated with itraconazole. Therefore it is significant that terbinafine was very effective in curing pruritus.

At the end of treatment phase the proportion of erythema was effectively cured to G-1 from 13.33% in baseline visit to 53.33% in V-3 with effectiveness by 40% in terbinafine group followed by fluconazole 38.89% and itraconazole 20% effectiveness. Thus terbinafine was effective in curing erythema.

At the baseline visit vesicle in the itraconazole group 11.11% of patients were at G-1which was significantly increased to 77.77% with an effectiveness of 66.66% to that of terbinafine group which showed 53.34% and fluconazole 55.6% increase in resolution in G-1 Thus our study showing itraconazole was effective in curing vesicle.

Comparison of effectiveness in G-1 for desquamation terbinafine showed effective clinical improvement in G-1 from 6.66% in baseline visit to 86.66% in V-3 with overall effectiveness of 80%.

A study by Deval et al in 2014 reported that there was no significant difference in between terbinafine (79%) and itraconazole (82%) in terms of clinical cure (>70%) [10]. Furthermore a study conducted by Arca et al reported a clinical evaluation, where endpoint of the follow-up period, the clinical cure rates were 81.3% (13/16) in the terbinafine group, 77.8% (14/18) in the itraconazole group, and 37.5% (6/16) in the fluconazole group [11].

Hence the studies show that terbinafine being more effective followed by itraconazole and fluconazole.

5. WHAT'S KNOWN

Topical agents may not penetrate well into the keratin barrier, and thus may not provide optimal treatment for dermatophyte infections located within the keratin. A desirable alternative for the treatment of dermatophyte infections is an oral agent with proven efficacy and minimal toxicity.

6. WHAT'S NEW

Our study correlated the differential grading of pruritus, erythema, vesicle and desquamation. As per our knowledge, no direct comparison of terbinafine, itraconazole and fluconazole was studied for tinea corporis with respect to pruritus, erythema, vesicle and desquamation.

7. LIMITATIONS

This study involved small sample size where the study can have a larger sample size if conducted for a longer duration which may also have more number of dermatoaphyte isolates which may have been studied for the efficacy of the drugs.

8. CONCLUSION

The result of this study indicates that terbinafine is better than itraconazole and fluconazole in relieving signs and symptoms during the study period, whereas itraconazole was found effective in relieving vesicle. Fluconazole is seen to be least effective in relieving the symptoms. None of the patients complained any contact dermatitis or adverse reaction to the drug suggesting excellent safety and tolerability of terbinafine, itraconazole and fluconazole.

Comparison of added antifungals agents can be included in further studies for better safety and efficacy of various drugs. Subjects with multiple clinical diagnosis of tinea can be included in further studies. Comparison of oral and topical antifungals can be studied with respect to relapse of the infection.

CONSENT

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity.

ETHICAL APPROVAL

Ethical approval for the study was obtained from the KLE University's Ethics Committee. (Ref No: KLEUCOP/337/2015-16).

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Authors contributed equally in the development of the manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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APPENDIX

Photograph 1. Tinea corporis with irregular border, erythema and desquamation at baseline visit

Photograph 2. Tinea corporis with erythema and desquamation at baseline visit

Photograph 3. Tinea Corporis with reduced erythema and desquamation after 2 weeks of terbinafine therapy

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