

“To assess the clinical efficacy of oral Terbinafine, Fluconazole and Itraconazole in the treatment of tinea corporis in a tertiary care hospital”.

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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 and Material: Patients were enrolled after considering various inclusion and exclusion criteria into three groups. Group A (oral Terbinafine 250mg daily for 2 weeks), group B (Fluconazole 150mg once weekly for 4 weeks) and group C (Itraconazole 200mg 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.

Statistical analysis used: Paired t- test was used to calculate the statistical significance between the pre and post interventional results. The software used was SPSS version 20.

Results: Of the 60 patients, 51 completed the study on 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.

Key-words: *Desquamation, Erythema, Fluconazole, Itraconazole, Terbinafine, Tinea.*

Key Message: Efficacy studies plays 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 in pruritus, erythema and desquamation, whereas Itraconazole was found effective in relieving vesicle.

Introduction:

Dermatophytosis infection represents a superficial infection of the keratinized layers of hair, nail and skin caused by dermatophytic fungi.¹ Dermatophytosis in India have received increasing attention in recent years from different parts of the country.

Topical agents such as clotrimazole are usually well tolerated and penetrate into the systemic circulation infrequently. However, topical agents may not penetrate well into the keratin barrier, and thus may not provide optimal treatment for dermatophyte infections located within the keratin. Furthermore, topical agents 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.

Subjects and Methods:

A Randomised comparative study was conducted from August 2015- March 2016. Ethical approval for the study was obtained from the local Ethics Committee. 60 untreated patients of tinea corporis were selected. All the patients > 16years of age with the diagnosis of tinea corporis confirmed by KOH or culture were selected. Patients with extensive dermatophytosis³ (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 study and a written informed consent was obtained.

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 of the subject. The affected area was first thoroughly cleaned with 70% alcohol to remove surface contaminants. After the alcohol dried, skin scraping was collected 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.

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 0=absent).

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.

First Visit

Patients were screened and thus allotted the Group of treatment.

Randomization

Patients will be randomly assigned to three groups Group1, Group 2 and Group3 through Simple Randomization 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 (200mg) once daily at morning time after breakfast for 2 weeks.³

Follow up and Evaluation

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

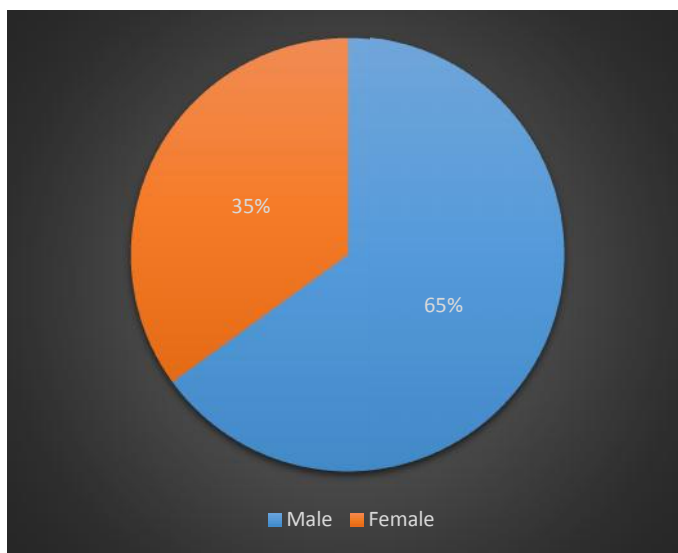
Statistical Analysis:

Once the data was collected ANOVA Fisher exact p test was used for data analysis

Results:

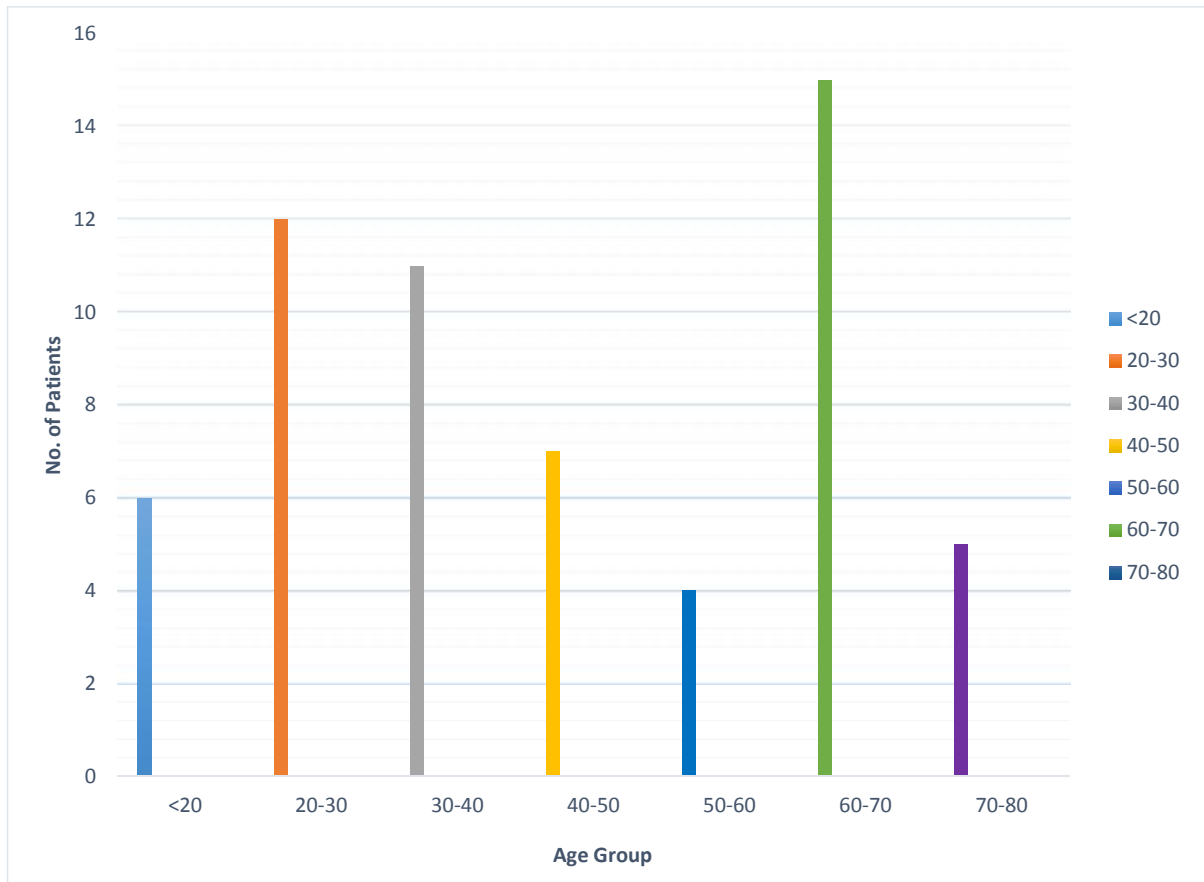
In the present study 60 patients of tinea corporis were enrolled. The data obtained was coded and entered into Microsoft excel spreadsheet and analyzed. The results and observations were as below:

Figure 1: Sex Wise Distribution of patients



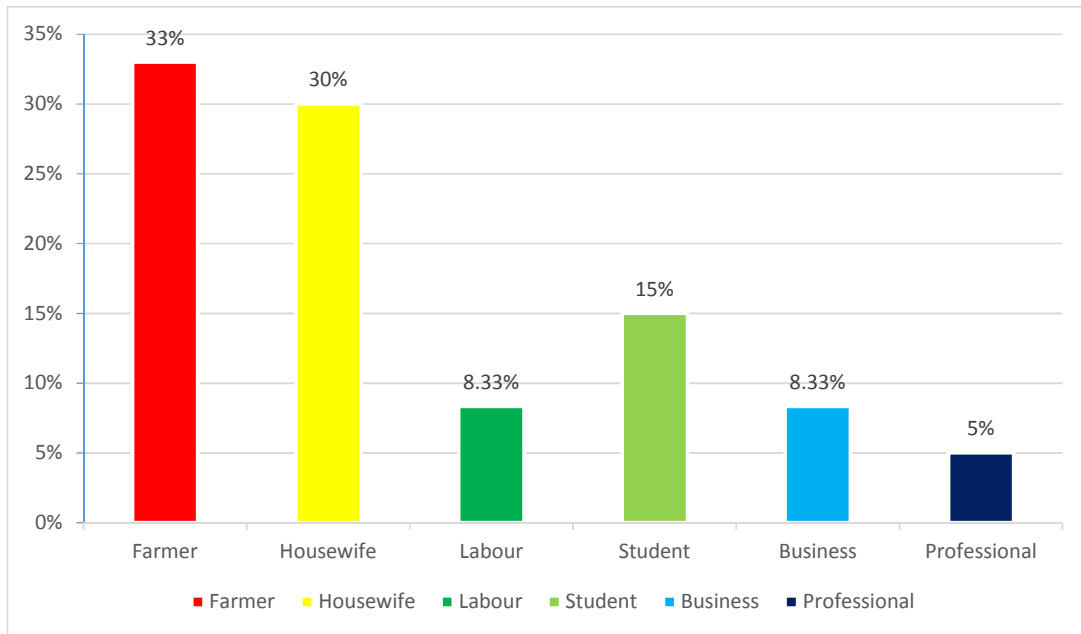
Our study showed that the Incidence of Tinea Corporis was high in males than females with the male to female ratio of 1.8:1

Figure 2: Commonly involved age group in the study



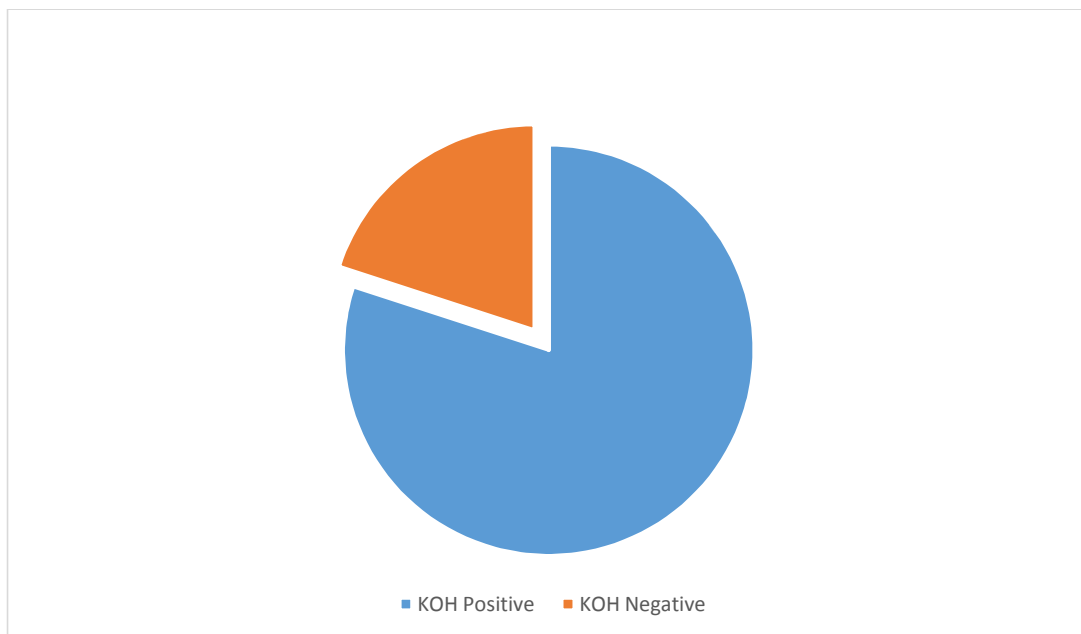
In the study, most common age group with tinea Corporis patients was 60-70 years comprised of 23.33%. The Distribution of other age groups is shown in figure 2.

Figure 3: Occupation



In this study most of the patients were farmers (33%) followed by housewives (30%). The occupation of other patients is shown in figure 3.

Figure 4: KOH Status of Clinical samples



In this study KOH examination for fungus was positive in 48% of the cases and negative for 52% cases.

Figure 5: Culture Status of Clinical samples



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 flucanazole groups.

Table 1: Comparison of changes in proportion with Pruritus

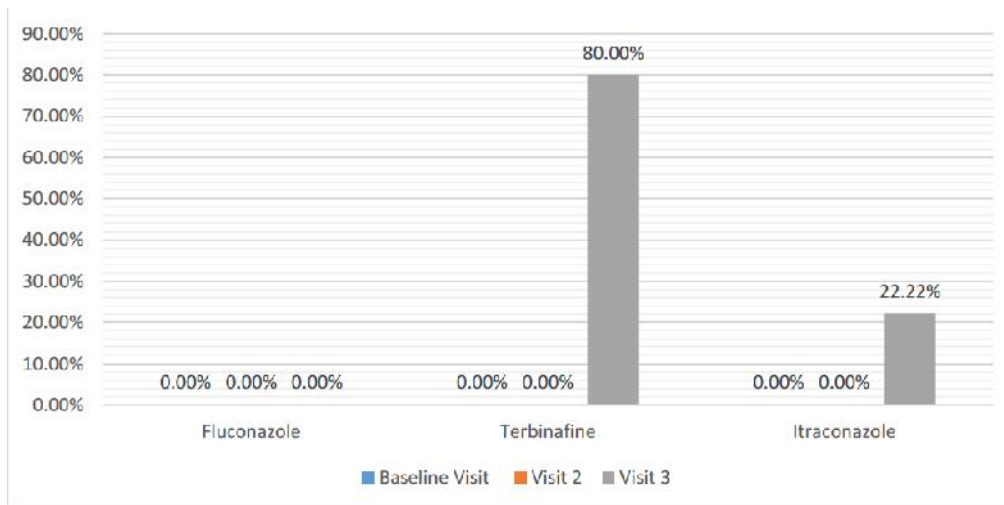
BASELINE VISIT			
DRUGS	GRADE		TOTAL PATIENTS(n)
	3	4	
FLUCONAZOLE	8 (44.44%)	10 (55.55%)	18
TERBINAFINE	9 (60%)	6 (40%)	15

ITRACONAZOLE	8 (44.44%)	10 (55.55)	18
	p=0.091		

VISIT 2				
DRUGS	GRADE			TOTAL PATIENTS(n)
	2	3	4	
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 PATIENTS(n)
	1	2	3	
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			

Figure 6: Comparison of changes in proportion with Pruritus



Terbinafine was very effective in curing pruritus.

Table 2: Comparison of changes in proportion with erythema

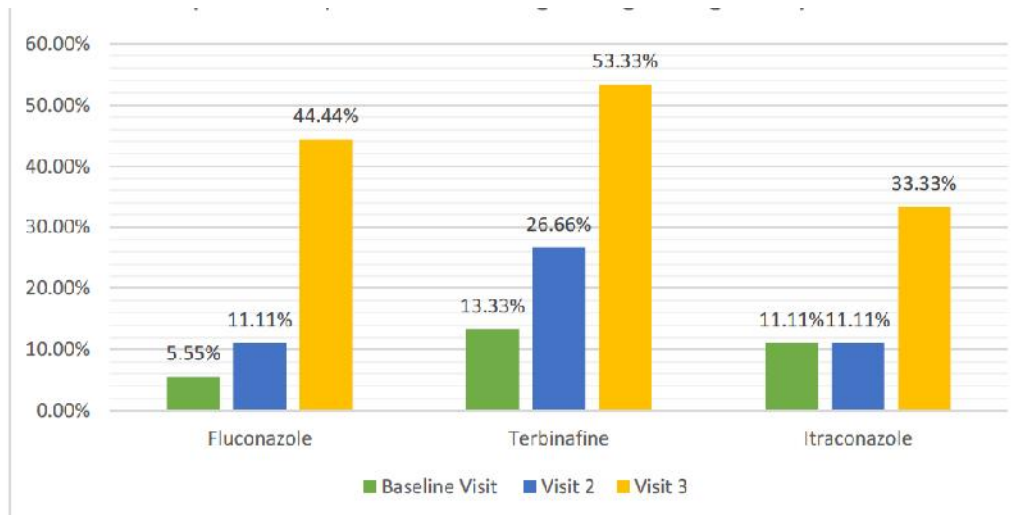
BASELINE VISIT					
DRUGS	GRADE				TOTAL PATIENTS(n)
	1	2	3	4	
FLUCONAZOLE	1 (5.55%)	4 (22.22%)	10(55.55%)	3(16.66%)	18
TERBINAFINE	2(13.33%)	2 (13.33%)	7 (46.66%)	4 (26.22%)	15
ITRACONAZOLE	2(11.11%)	1(5.55%)	12(66.66%)	3(16.66%)	18
	p=0.765				

VISIT 2				
DRUGS	GRADE			TOTAL PATIENTS(n)
	1	2	3	
FLUCONAZOLE	2 (11.11%)	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			

Figure 7: Comparison of changes in proportion with erythema



Terbinafine was effective in curing erythema.

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

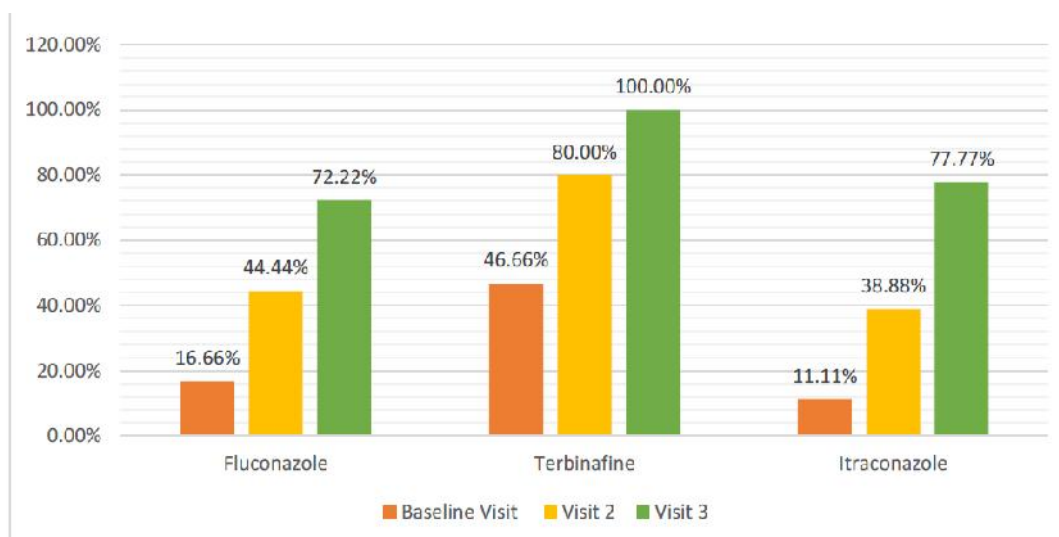
BASELINE VISIT					
DRUGS	GRADE				TOTAL PATIENTS(n)
	1	2	3	4	
FLUCONAZOLE	3 (16.66%)	9(50%)	5(27.77%)	1(5.55%)	18
TERBINAFINE	7(46.66%)	5(33.33%)	3(20%)	0	15
ITRACONAZOLE	2(11.11%)	9(50%)	7(38.88%)	0	18
	p=0.221				

VISIT 2				
DRUGS	GRADE			TOTAL PATIENTS(n)
	1	2	3	
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		

Figure 8: Comparison of changes in proportion with vesicles



Itraconazole was effective in curing vesicle.

Table 4: Comparison of changes in proportion with Desquamation

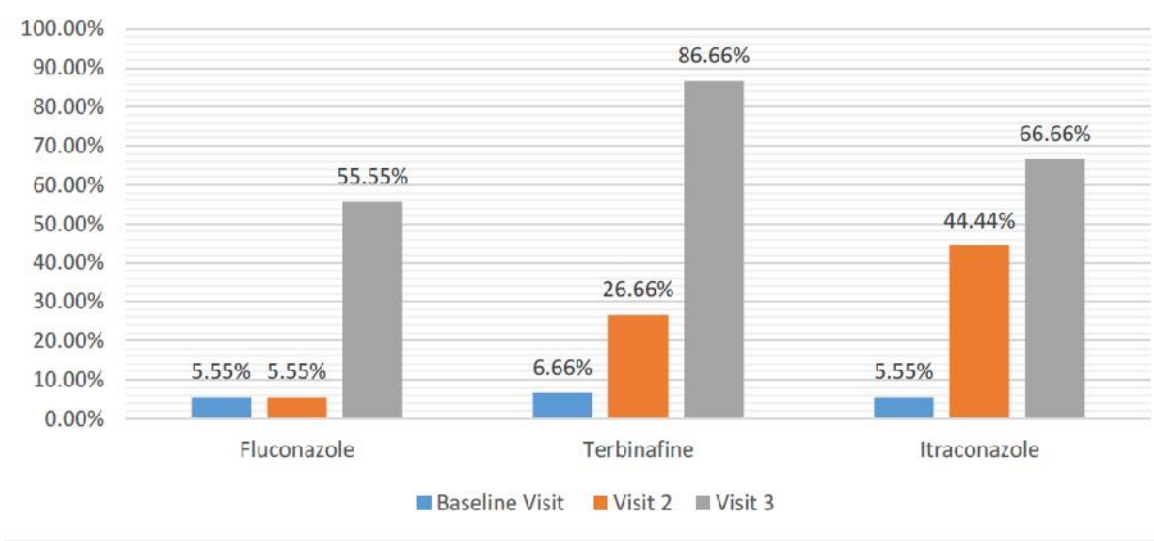
BASELINE VISIT					
DRUGS	GRADE				TOTAL PATIENTS(n)
	1	2	3	4	
FLUCONAZOLE	1(5.55%)	5(27.77%)	10(55.55%)	2(11.11%)	18
TERBINAFINE	1(6.66%)	3(20%)	11(73.33%)	0	15
ITRACONAZOLE	1(5.55%)	8(44.44%)	8(44.44%)	1(5.55%)	18
	p=0.498				

VISIT 2				
DRUGS	GRADE			TOTAL PATIENTS(n)
	1	2	3	
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 PATIENTS(n)
	1	2	3	
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			
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Figure 9: Comparison of changes in proportion with 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%.

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 previous studies. A study conducted in Farukkabad, Uttar Pradesh Amit Kumar et al reported male to female ratio of 1.36:1 in 2013.⁴

In contrast, Bindu V et al from Vishakapatnam reported almost wide variation distribution of the disease in both the genders with a male to female ratio 2.06:1.⁵

Overall the previous studies including present study observed 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%).

Study conducted by C.Roopaa and Sunil Kumar Biradar in Raichur Karnataka in 2012 where maximum number of cases encountered in the age group 31-40yrs (47.27%) followed by 21-30yrs (29.09%).⁶

In our study the maximum number of patients were 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 KAK et al from Mysore found that T.rubrum was chief isolate organism (55.5%) followed by T.mentagrophytes (33.3%). Neetu J et al conducted a study in Jaipur reported T.rubrum (22.22%) followed by T.mentagrophytes (15.55%) which also relates to other studies conducted in India and other

countries. 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.⁸

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 grade 1 (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 an effectiveness by 40 % in Terbinafine group followed by Fluconazole 38.89% and itraconazole 20% effectiveness. Thus Terbinafine being effective in curing erythema.

At the baseline visit vesicle in the Itraconazole group 11.11% of patients were at G-1 which 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 being 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%.

In a study conducted by Deval N Vora et al in Gujarat, reported that there was no significant difference in between terbinafine and itraconazole in terms of clinical cure where therapy of terbinafine v/s itraconazole, clinical cure rate (>70%) were 79% and 82% respectively.⁹ Furthermore a study conducted by E. 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.¹⁰

Hence the studies show that Terbinafine being more effective followed by Itraconazole and Fluconazole.

Whats 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.

What's new: Our study correlated the differential grading of clinical signs and symptoms 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.

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 dermatophyte isolates which may have been studied for the efficacy of the drugs.

Conclusion: The result of this study indicates that Terbinafine was more effective than Itraconazole and Fluconazole in alleviating clinical signs and symptoms particularly in pruritus, erythema and desquamation, whereas Itraconazole was found effective in relieving vesicle. Fluconazole was seen as 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.

FUTURE DIRECTIONS

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.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) 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)

Acknowledgments

All authors contributed equally in the development of the manuscript.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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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

