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Original Research Article

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

Abstract:

Context: Comparing the three drugs for its safety and efficacy.

Aims: This study was aimed to assess the clinico-mycological efficacy and safety 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 2 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.*

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Key Message: Safety and 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. 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.

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]

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 with diagnosis of tinea corporis were selected. Patients who fulfilled the selection criteria were briefed about the nature of study and a written informed consent was obtained. All the patients > 16years of age with the diagnosis of tinea corporis were selected. Patients with severe dermatophytosis and with involvement of more than 15% body surface area were excluded. Patients already on antifungal therapy or those who used oral fungals and antibiotics 14 days ~~of~~ baseline were also excluded. Pregnant women and patients with hepatic or renal disease were also not included.

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

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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 1=absent).

Diary for safety assessment was provided to the patients of both 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.

(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.

(II) GROUP B (Weekly Oral Fluconazole)

In this group patients were given oral Fluconazole (150 mg) once weekly at morning time after breakfast for 2 weeks.

(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.

Follow up and Evaluation

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Patients were followed at 2nd week and 3rd week (after the end of treatment) 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

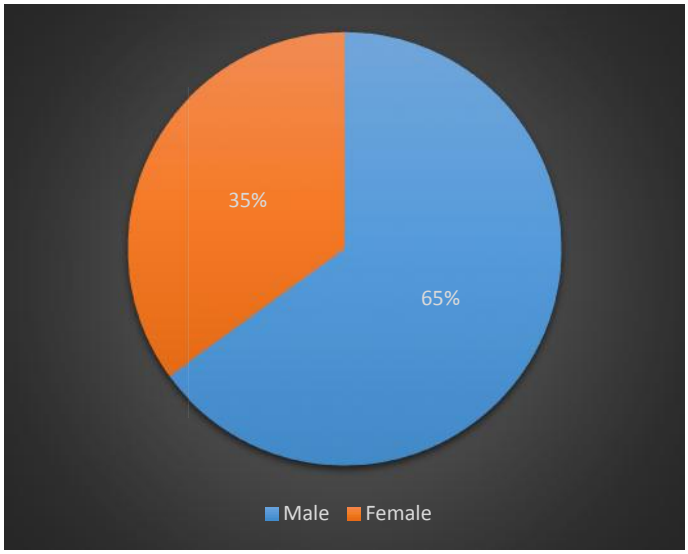
Results:

The present study was carried out in a tertiary care hospital over a period of six months. All clinically diagnosed cases of ~~T~~inea Corporis in the age groups above 16 years old and of both sexes, attending the outpatient department of Dermatology and Venereology were taken for the study and patients who were already on treatment with antifungals and antibiotics or dermatophytosis were excluded from the study.

In our study we had 60 T.corporis patients enrolled with *T.rubrum* as the most common isolate.

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 ~~Cases~~



Our study showed that the Incidence of Tinea Corporis was high in males than females with the male to female ratio of ~~13:7.~~

Figure 2: Commonly involved age group in the study

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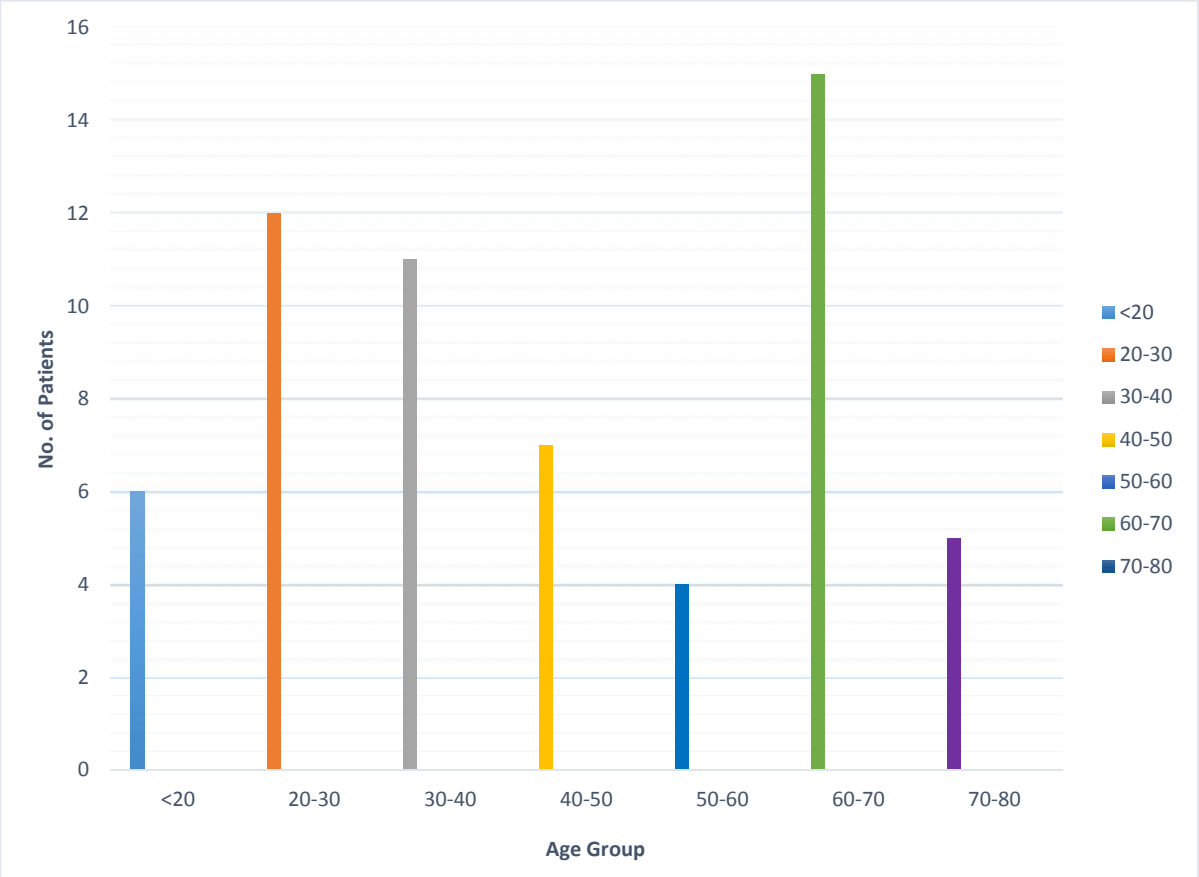

In the study, most common age group with ~~Tinea~~ Corporis patients was 60-70 years comprised of 23.33%.The Distribution of other age groups is shown in ~~Graph.~~

Figure 3: Occupation

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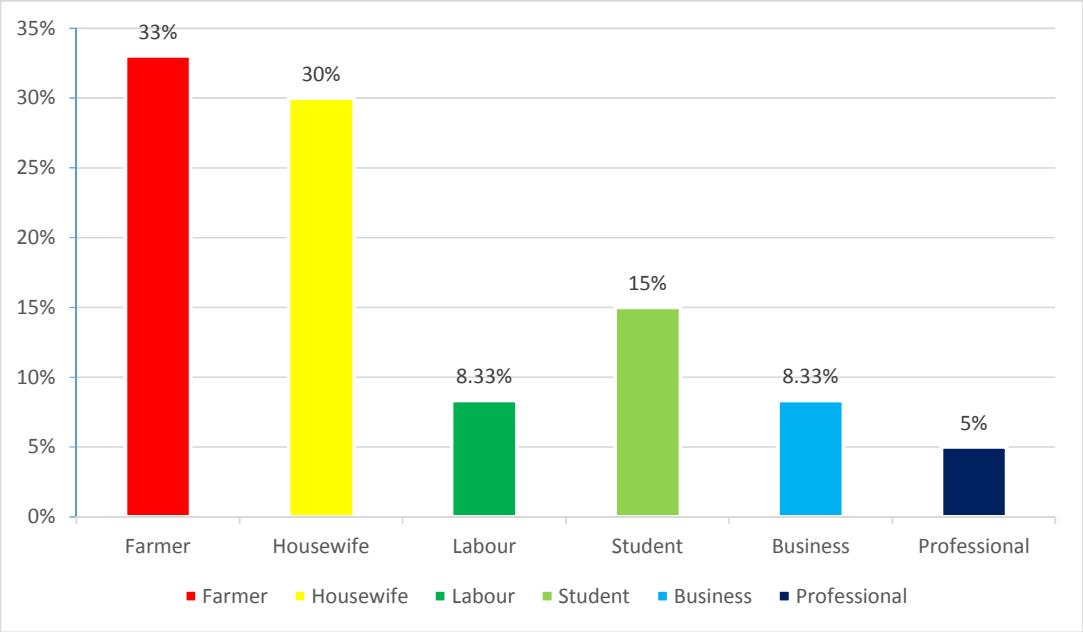
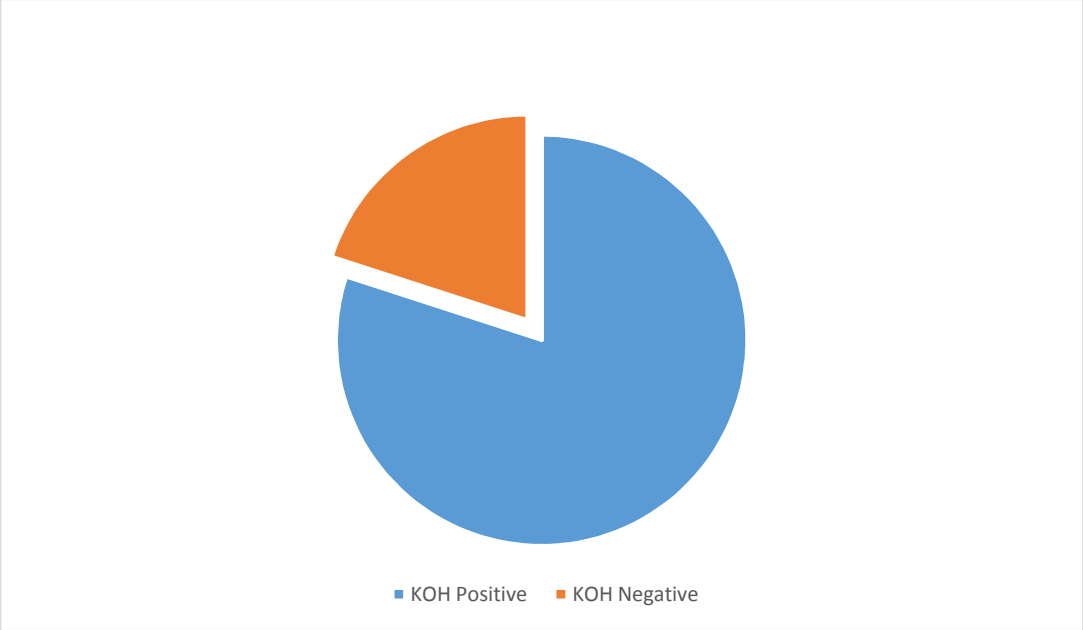


In ~~the~~ study most of the patients were ~~Farmers~~ (33%) followed by housewives (30%). The occupation of other patients is shown in ~~Graph.~~

Figure 4: KOH Status of Clinical samples



In the study KOH examination for fungus was positive in 48% of the cases and negative for 12% cases.

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Table 1: Comparison of Baseline Demographics

GENDER		
	FEMALE/MALE	TOTAL PATIENTS
FLUCONAZOLE	4/14	18
TERBINAFINE	8/7	15
ITRACONAZOLE	6/12	18
	p= 0.173	

AGE		
	MEAN±SD	RANGE
FLUCONAZOLE	45.6±18.34	17-66
TERBINAFINE	38.8±14.38	23-73
ITRACONAZOLE	40.1±17.95	17-71
	p= 0.473	

Table 2: 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			

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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 5: Comparison of changes in proportion with Pruritus

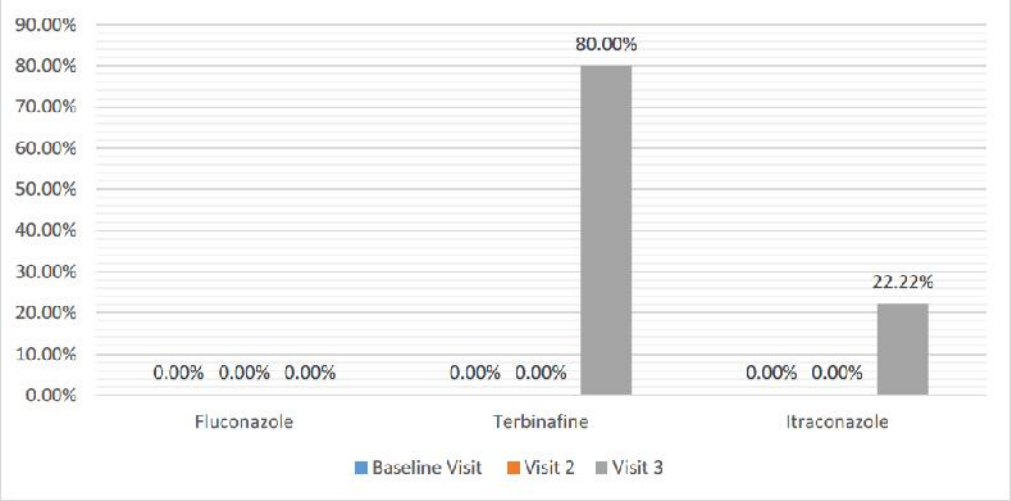

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Table 3: Comparison of changes in proportion with erythema

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			

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Figure 6: Comparison of changes in proportion with erythema

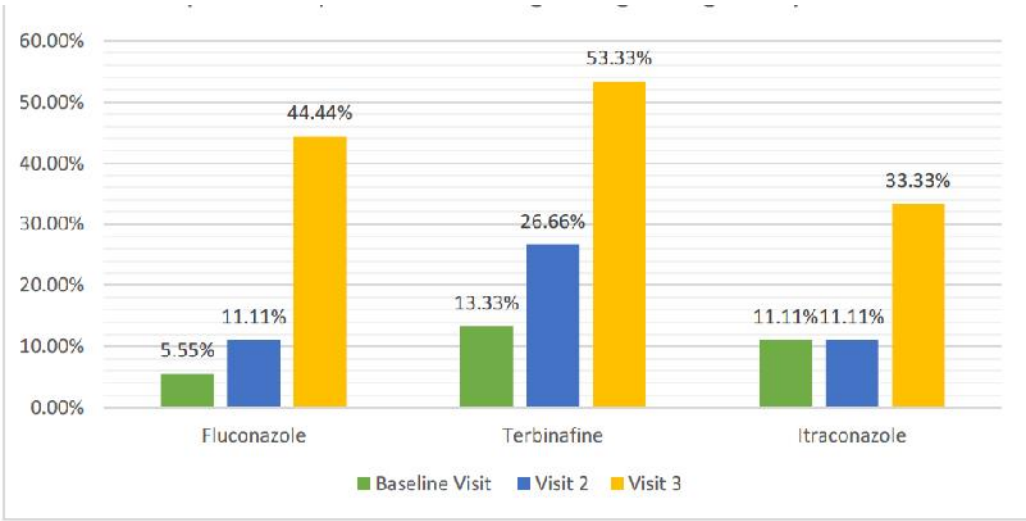

Table 4: Comparison of changes in proportion with vesicles

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

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	1	2	PATIENTS(n)
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 7: Comparison of changes in proportion with vesicles

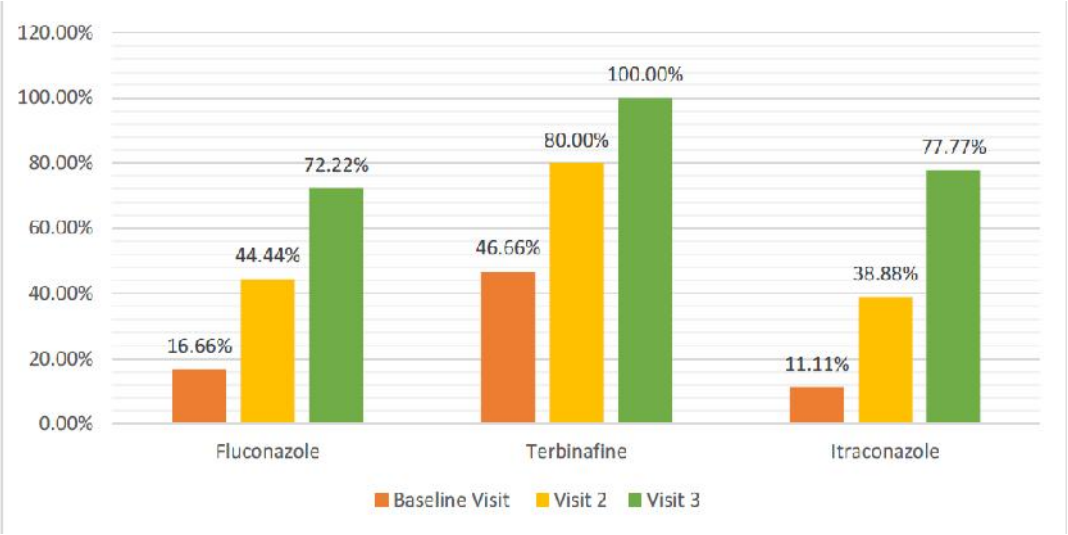

Table 5: Comparison of changes in proportion with Desquamation

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	

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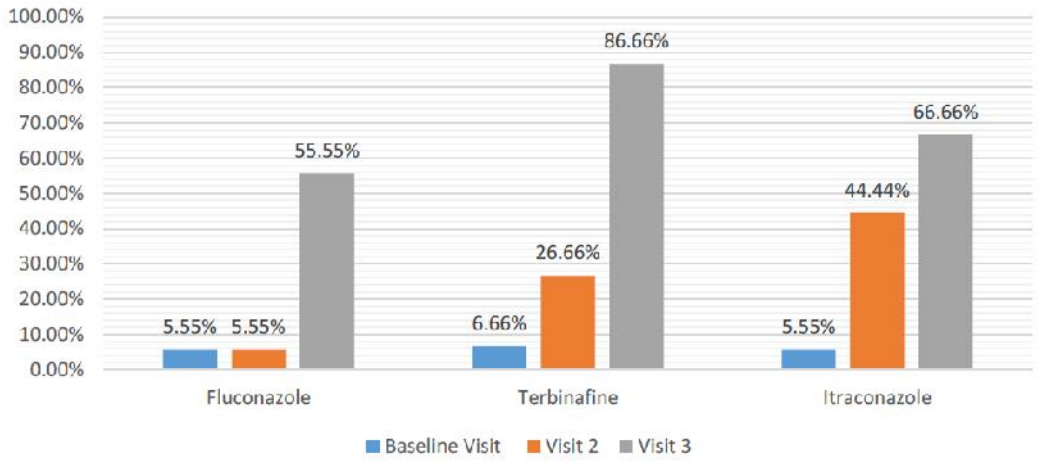
FLUCONAZOLE	1(5.55%)	15(83.33%)	2(11.11%)	18
TERBINAFINE	4(26.66%)	10(66.66%)	1(6.66%)	15
ITRACONAZOLE	8(44.44%)	8(44.44%)	2(11.11%)	18
	p=0.066			
VISIT 3				
DRUGS	GRADE			TOTAL PATIENTS(n)
	1	2	3	
FLUCONAZOLE	10(55.55%)	6(33.33%)	2(11.11%)	18
TERBINAFINE	13(86.66%)	2(13.33%)	0	15
ITRACONAZOLE	12(66.66%)	6(33.33%)	0	18
	p=0.276			

Figure 8: Comparison of changes in proportion with Desquamation



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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.[3]

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.[4]

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. [5]

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.Roopa 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.[7]

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.[8] 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.

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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 an effectiveness by 40 % in Terbinafine group followed by Fluconazole 38.89% 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% 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 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:

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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 of 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.

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. Comparision of oral and topical antifungals can be studied with respect to relapse of the infection.

Declaration of patient consent

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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.

Financial support and sponsorship

Nil.

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