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A Randomized Open Label Comparative Study of Once a Week Therapy of Oral Fluconazole with Once Daily Therapy of Oral Terbinafine in Patients with Extensive Tinea Corporis.

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Abstract:
Introduction: *Dermatophytes are a group of taxonomically related fungi which includes members of the genera Trichophyton, Microsporum and Epidermophyton. All of them causes skin or nail infection called Tinea or ringworm. Clinically, dermatophyte infections are classified by body region and infections of the trunk is defined as Tinea corporis.*
Objective: *To compare the therapeutic efficacy, compliance, adverse drug reactions & cost effectiveness of oral Fluconazole given once a week with oral Terbinafine given once daily in patients with extensive tinea corporis.*
Methodology: *Adult patients with extensive Tinea corporis attending the outpatient Dermatology department of Government Stanley medical college Hospital were recruited between Aug 2012 and July 2013. The total study duration comprised of 12 weeks including treatment and follow-up. Sixty eligible subjects (30 patients in each group) were included in the study. The primary end point of the study was to assess the clinical efficacy by efficacy scoring and mycological cure by skin scrapping and culture while compliance, adverse drug reactions & cost effectiveness were the secondary end point.*
Results: *At the end of 2 weeks, the severity of symptoms were reduced significantly in terbinafine group when compared with fluconazole group ($p < 0.001$).However at the end of 4 weeks the severity of symptoms were reduced equally in both the groups ($p > 0.05$) with no serious adverse effects.*
Conclusion: *Based on the outcome of this study it's been concluded that oral terbinafine administered once daily for 2 weeks is more efficacious than fluconazole as observed from the rapid improvement in the clinical symptoms and effective mycological cure. But fluconazole given once a week is a cost effective agent with better patient compliance.*
Key words: *Dermatophytes, Tinea corporis*

I. Introduction:

Fungi are a large and diverse group of organisms that may exist as saprophytes, parasites, or commensals. There are thousands of known species, though less than 100 are human pathogens[1]. Dermatophytes are a group of taxonomically related fungi and they have the ability to form molecular attachments to keratin and by using it as a source of nutrients, it allows them to colonize keratinized tissues including the stratum corneum of the epidermis, hair, nail and the horny tissues of animals[2]. Dermatophytes thrive at surface temperatures of 25–28^{o} C and infection of the human skin is supported by warm and humid conditions. For these reasons, superficial fungal infections are relatively common in tropical countries like India and are exacerbated by the wearing of occlusive clothing[3]. In addition, the frequency of dermatomycoses is greater in communities with low socioeconomic status. Crowded living conditions provide multiple opportunities for skin-to-skin contact and close proximity to animals, while hygiene may be suboptimal[4]. Dermatophytes include members of the genera Trichophyton, Microsporum and Epidermophyton. All of them causes skin or nail infection called Tinea or ringworm[8].

Tinea corporis or infection of the relatively hairless skin of the body (glabrous skin), may have a variable appearance depending on the extent of the associated inflammatory reaction. Typical infections have an annular appearance that patients refer to as "ringworm". Tinea corporis normally manifests as well-demarcated, annular, pruritic, scaly lesions that usually undergoes central clearing[5]. For isolated lesions of tinea corporis, topical agents such as the allylamines, Imidazoles, tolnaftate, butenafine, or ciclopirox are effective. Most of them are applied twice daily for 2 to 4 weeks. Oral antifungals are reserved for widespread or more inflammatory lesions[6].

II. Scope Of Present Study:

Dermatophyte infections are classified by body region and infections of the trunk is defined as Tinea corporis. Dermatophytes produce a variety of disease patterns that vary with the location and species[9]. India

being a tropical country, the incidence of fungal infections in particular tinea corporis is high[10]. Since a large number of families belonging to the lower socioeconomic status reside around our institution, the case load of superficial fungal infections are high. So any study pertaining to this will benefit the community at large.

Comparative studies in adults with extensive tinea corporis shows that fluconazole 150 mg weekly for 4 to 6 weeks, itraconazole 100 mg daily for 15 days, and terbinafine 250 mg daily for 2 weeks are as effective as griseofulvin 500 mg daily for 2 to 6 weeks, with no significant differences in adverse events[7]. So it's been decided to compare fluconazole, a azole group with terbinafine, an allylamine group, for patients with extensive tinea corporis.

III. Aim & Objective

The aim of this study is to compare the therapeutic efficacy, compliance, adverse drug reactions & cost effectiveness of oral Fluconazole 150mg given once a week with oral Terbinafine 250mg given once daily in patients with extensive tinea corporis. The primary end point of the study was to assess the clinical efficacy and mycological clearance, while patient's compliance, adverse drug effects and cost effectiveness were assessed as secondary end point of the study.

IV. Materials & Methods

This was a randomized, open label, prospective, comparative study. Adult patients diagnosed with extensive Tinea corporis (multiple site, surface area > 100cm²) attending the outpatient Dermatology department of Stanley Medical College were recruited between August 2012 and July 2013.
The study duration comprised of 12 weeks of treatment and follow-up. Sixty subjects who fulfilled the following eligibility criteria (30 patients in group I and 30 patients in group II) were included in the study.

Inclusion criteria:

- Age: 15– 60 yrs.
- Both sexes
- Newly diagnosed patients with tinea corporis.
- Patients who were willing to give informed consent to the study.

Exclusion criteria:

- Age below 15 yrs and above 60 yrs.
- Pregnant and lactating women.
- Children.
- Patients having pre-existing renal, liver and cardiac illness.
- Patients already on treatment with antifungal agents.
- Patients not willing to give informed consent.

The study was carried out after approval from Institutional Ethics Committee, Stanly Medical College. Written informed consent was obtained from all the subjects recruited in the study. Subjects fulfilling the inclusion criteria were recruited in the study and were randomized to receive either oral Fluconazole 150mg or oral Terbinafine 250mg. The selected patients were divided into two groups of 30 each.

Group I	Oral Fluconazole 150 mg once a week for 4 weeks.
Group II	Oral Terbinafine 250mg once daily for 2weeks.

The results of this study were analysed both subjectively and objectively

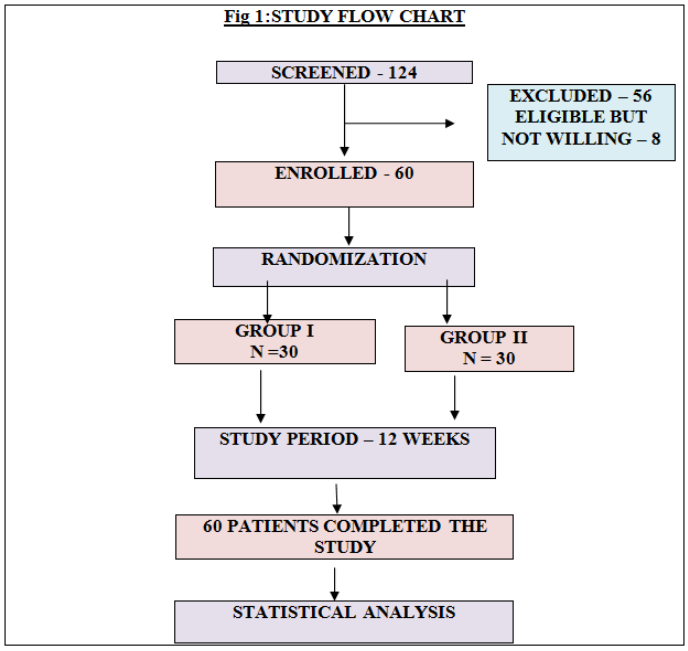
- **Basic Investigations like hemogram, renal function test and liver function test were done before and after the study period.**

The effectiveness of the treatment was assessed by the clinical efficacy scoring(-1 = severe ; 0 = No improvement ; 1 = Mild improvement ; 2 = Moderate improvement ;3 = completely cured) which includes the clearance of pruritus, erythema, vesicle & desquamation.

- **Mycological cure was assessed by Skin scraping with KOH mounts & fungal culture.**

After enrolment, study patients were evaluated for efficacy of test drugs by clinical efficacy score and mycological cure. Clinical efficacy scoring was done at the end of 1st week, 2nd week, 3rd week, 4th week, 5th week, and 6th week and at the end of 12 weeks. Mycological cure which includes skin scrapping and culture was done before (baseline) and after giving test drugs (6th week).
The obtained data was subjected to statistical analysis. Age distribution was analyzed using T-test and sex distribution was assessed by Chi square test. Biochemical studies were conducted at baseline and at the end of

12 weeks. The differences within groups before and after treatment were assessed using Student's paired t-test. P value <0 .05 was considered to be statistically significant.
The study methodology is summarized in Fig :1



V. Results:

The mean age(yrs) in groups I & II were 32.10 and 32.60 respectively as shown in table No.1 .Statistical analysis was done by using student independent t –test and the p value was not significant. There was even distribution of age in both the groups. Table No.2 shows, the sex distribution in both the groups. Statistical analysis was done using Chi-Square Test and the p value was not significant. Out of 30 patients in group I, 12 were male and 18 were female. In group II, 10 were male and 20 were female. There was no significant difference in the sex distribution between the two groups. Even though there is no difference in sex distribution between groups, most of the patients (18 in group I & 20 in group II) were found to be female.

Table No.1: Shows the age group of the patients who participated in the study

Group	N	Mean (Age in years)	Std. Deviation	Student independent t-test
Fluconazole	30	32.10	6.630	p = 0.783
Terbinafine	30	32.60	7.365	

Table No.2: Sex distribution of the patients who participated in the study

			Group		
			Fluconazole	Terbinafine	Total
Sex	Male	Count	12	10	22
		% within Sex	54.5%	45.5%	100.0%
		% within Group	40.0%	33.3%	36.7%
	Female	Count	18	20	38
		% within Sex	47.4%	52.6%	100.0%
		% within Group	60.0%	66.7%	63.3%
Total		Count	30	30	60
		% within Sex	50.0%	50.0%	100.0%
		% within Group	100.0%	100.0%	100.0%

p = 0.592 - not significant

The effect of drug treatment on pruritus in both the groups is shown in Table No.3 and also depicted graphically in Fig.No:3. At the end of 1st week and 2nd week, there was significant reduction in pruritus in terbinafine group compared to the fluconazole group as evident by increase in mean score. The mean score at the end of 1st week was 0.50 and 1.93 respectively in the fluconazole and terbinafine groups, with p value of 0.000 which is very highly significant. At the end of 2nd week, the mean score in group I was 1.43 and 2.97 in group II with a p value of 0.000, which is very highly significant. At the end of 3rd week, the mean score in group I was 2.33 and in group II it was 2.97 with p value of 0.000, which is very highly significant. After 4 th week the mean scores were almost the same in both the groups and the p value was not significant. At the end of 12 weeks, the mean scores were 2.83 and 2.97 respectively in group I & II with p value of 0.085 which is not significant. Similarly the effect of drug treatment on erythema, vesicle and desquamation in both the groups were shown in Table No.4,5&6 and also depicted graphically in Fig.No:4,5& 6.

Table No.3: Statistical analysis of Pruritus in Group I (Fluconazole) and Group II (Terbinafine)

	GROUP				
	Fluconazole		Terbinafine		
	Mean	SD	Mean	SD	p value
Base line	0.00	0.000	0.00	0.000	
week 1	0.50	0.509	1.93	0.254	p=0.000***
week 2	1.43	0.568	2.97	0.183	P=0.000***
week 3	2.33	0.606	2.97	0.183	p=0.000***
week 4	2.83	0.379	2.97	0.183	p=0.085
week 5	2.83	0.379	2.97	0.183	p=0.085
week 6	2.83	0.379	2.97	0.183	p=0.085
Week 12	2.83	0.379	2.97	0.183	p=0.085

* P< 0.05 significant ** highly significant P<0.01 *** Very high significant P<0.001

Fig.No:3 Assessment Of Pruritus Between The Groups

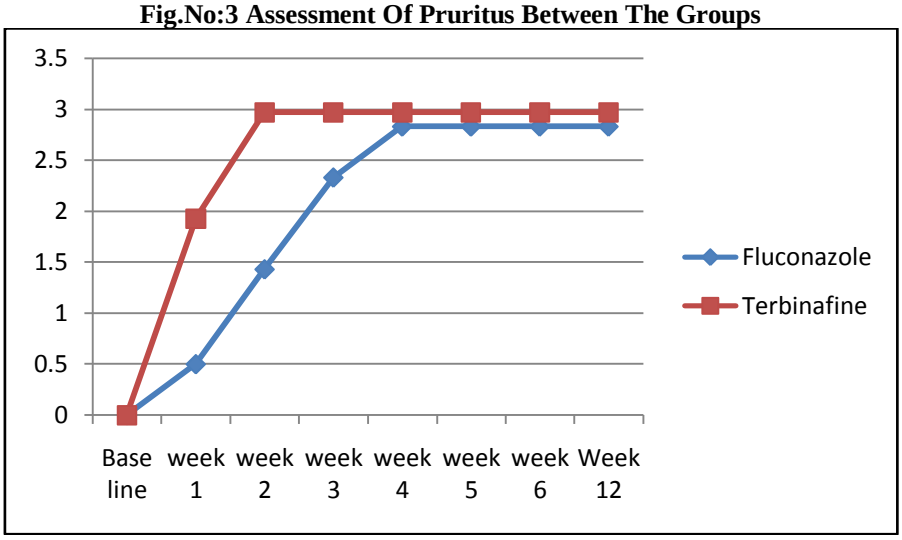


Table No.4 Statistical analysis of Erythema in Group I (Fluconazole) and Group II (Terbinafine)

	GROUP				
	Fluconazole		Terbinafine		
	Mean	SD	Mean	SD	p value
Base line	0.00	0.000	0.00	0.000	
week 1	0.47	0.507	1.87	0.434	p=0.000***
week 2	1.30	0.466	2.73	0.450	P=0.000***
week 3	2.20	0.551	2.73	0.450	p=0.001**
week 4	2.80	0.407	2.73	0.450	p=0.542
week 5	2.80	0.407	2.73	0.450	p=0.542
week 6	2.80	0.379	2.73	0.450	p=0.542
Week 12	2.80	0.379	2.73	0.450	p=0.542

Fig .No:4 Assessment Of Erythema Between Groups

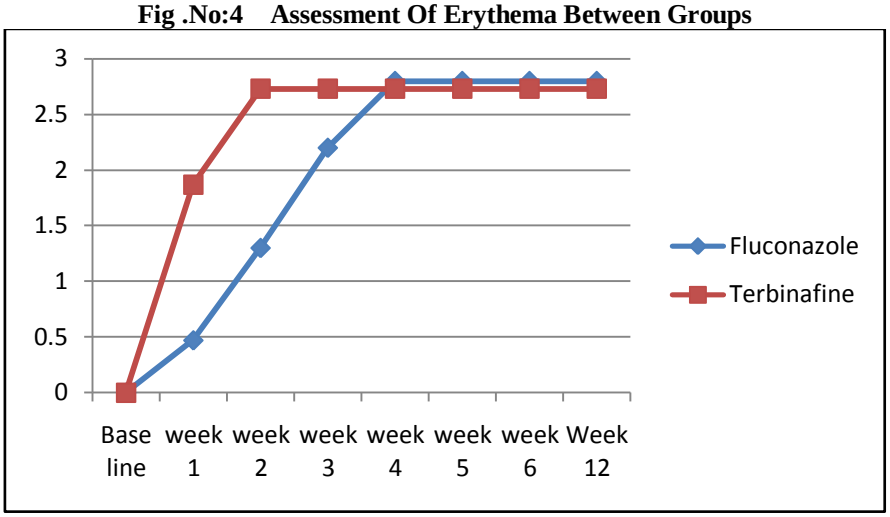


Table No.5 Statistical analysis of vesicle in Group I (Fluconazole) and Group II(Terbinafine)

	GROUP				
	Fluconazole		Terbinafine		
	Mean	SD	Mean	SD	p value
Base line	0.00	0.000	0.00	0.000	
week 1	0.57	0.504	1.80	0.484	p=0.000***
week 2	1.53	0.571	2.80	0.407	P=0.000***
week 3	2.47	0.629	2.80	0.407	p=0.061
week 4	2.83	0.379	2.80	0.407	p=0.739
week 5	2.83	0.379	2.80	0.407	p=0.739
week 6	2.83	0.379	2.80	0.407	p=0.739
Week 12	2.83	0.379	2.80	0.407	p=0.739

Fig.No:5 Assessment Of Vesicle Between Groups

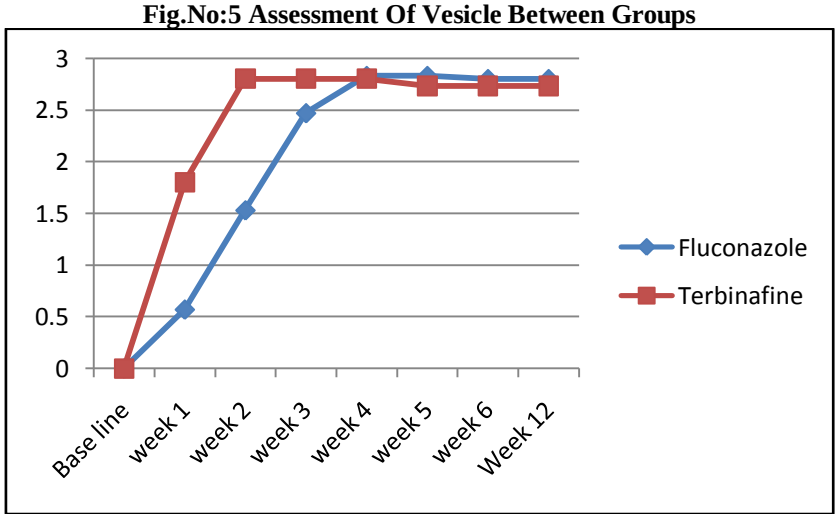
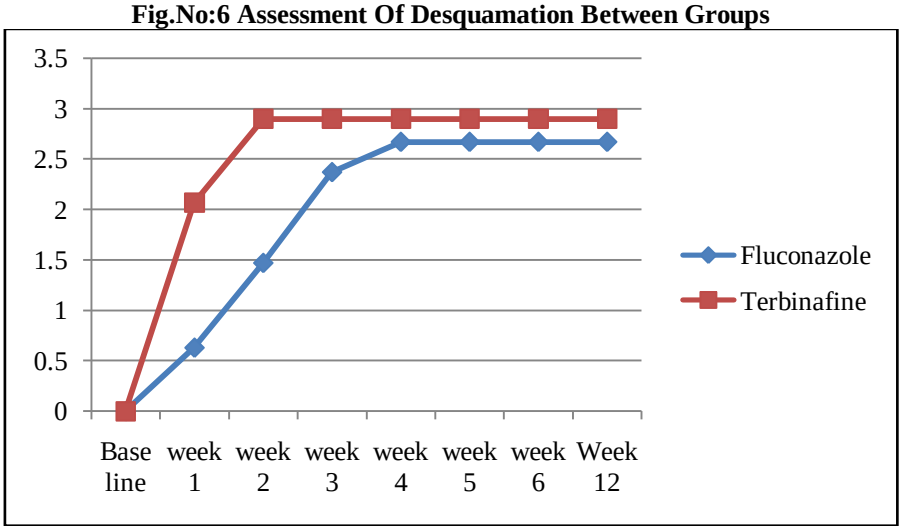


Table No.6 Statistical analysis of desquamation in Group I (Fluconazole) and Group II (Terbinafine)

	GROUP				
	Fluconazole		Terbinafine		
	Mean	SD	Mean	SD	p value
Base line	0.00	0.000	0.00	0.000	
week 1	0.63	0.490	2.07	0.450	p=0.000***
week 2	1.47	0.681	2.90	0.305	p=0.000***
week 3	2.37	0.765	2.90	0.305	p=0.008
week 4	2.67	0.661	2.90	0.305	p=0.211
week 5	2.67	0.661	2.90	0.305	p=0.211
week 6	2.67	0.661	2.90	0.305	p=0.211
Week 12	2.67	0.661	2.90	0.305	p=0.211

Fig.No:6 Assessment Of Desquamation Between Groups



Tables 7 & 8 shows statistical analysis of skin scraping before and after treatment between the groups. Before treatment, all patients in group I and group II showed presence of fungal hyphae in scraping. After treatment from the table it's clear that all the patients in both the groups turned negative for presence of fungal hyphae in skin scraping. Table 9 & 10 shows fungal culture before and after treatment between groups. From the table it was clear that all patients in both groups I & II had fungal culture conversion at the end of 6 th week.

Table no .7 Skin Scraping **Before** Treatment Between The Groups

			Group		
			Fluconazole	Terbinafine	Total
scraping-	Present	Count	30	30	60
		% within Culture -	50.0%	50.0%	100.0%
		% within Group	100.0%	100.0%	100.0%
Total		Count	30	30	60
		% within Culture -	50.0%	50.0%	100.0%
		% within Group	100.0%	100.0%	100.0%

Table no. 8 Skin Scraping **After** Treatment Between The Groups

			Group		
			Fluconazole	Terbinafine	Total
Scrapping –	Absent	Count	30	30	60
		% within Scraping – W6	50.0%	50.0%	100.0%
		% within Group	100.0%	100.0%	100.0%
Total		Count	30	30	60
		% within Scraping – W6	50.0%	50.0%	100.0%
		% within Group	100.0%	100.0%	100.0%

Table no. 9 Culture Before Treatment Between Groups

			Group		
			Fluconazole	Terbinafine	Total
Culture -	Yes	Count	30	30	60
		% within Culture -	50.0%	50.0%	100.0%
		% within Group	100.0%	100.0%	100.0%
Total		Count	30	30	60
		% within Culture -	50.0%	50.0%	100.0%
		% within Group	100.0%	100.0%	100.0%

Table no. 10 **Culture Aftertreatment Between Groups**

			Group		
			Fluconazole	Terbinafine	Total
Culture	No	Count	30	30	60
		% within Culture – W6	50.0%	50.0%	100.0%
		% within Group	100.0%	100.0%	100.0%
Total		Count	30	30	60
		% within Culture – W6	50.0%	50.0%	100.0%
		% within Group	100.0%	100.0%	100.0%

Table 11 : Basic Hematological Investigations Before And After The Study

Parameter	Group	Baseline		End of study		Student paired t-test
		Mean	SD	Mean	SD	
Hb	Group I	10.79	.95	10.95	.70	P=0.07
	GroupII	10.82	.76	10.84	0.60	P=0.42
Total Wbc count	Group I	8153.33	766.422	8123.33	627.905	P=0.63
	Group II	7463.33	502.740	7560.00	589.915	P=0.42
ESR	Group I	11.30	1.236	11.57	1.478	P=0.43
	Group II	12.00	1.531	12.03	1.426	P=0.87
Urea	Group I	22.07	2.828	21.67	2.006	P=0.44
	Group II	21.33	2.820	21.13	2.240	P=0.65
Serum creatinine	Group I	0.85	0.138	0.817	0.1621	P=0.25
	Group II	0.81	0.124	0.787	0.1629	P=0.59
SGOT	Group I	19.77	2.208	20.10	1.117	P= 0.31
	Group II	19.63	2.059	20.40	1.734	P=0.13
SGPT	Group I	23.77	1.675	23.73	1.530	P=0.93
	Group II	23.70	1.822	23.40	1.610	P=0.19

*P≤0.05 significant, ** P≤0.01 highly significant, *** P≤0.001 very high significant

Table 11 shows the basic hematological investigations before and after the study in both the groups. Paired t test was used for analysis. There is no significant change between baseline and at the end of the study value

VI. Discussion

This study was conducted to compare the efficacy of once a week therapy of oral fluconazole with once daily therapy of oral terbinafine in patients with extensive tinea corporis. Data was compiled and the results were statistically analysed.

From the results it is clear that at the end of 1st week and 2nd week, the severity of all the clinical parameters (pruritus, erythema, vesicle& desquamation) were significantly reduced in terbinafine group when compared with fluconazole group(vide tables3,4,5&6) The p value was very highly significant(<0.001). However at the end of the 3rd week the severity of all the clinical parameters (pruritus, erythema, vesicle and desquamation) were equally reduced in both the groups (vide tables 3, 4, 5&6). After the end of 4th week, the mean score of all the parameters were almost the same in both the groups and the p value was also not significant. This shows that both terbinafine and fluconazole were equally efficacious in treating tinea corporis infection. The difference is the duration of treatment.

Our study shows that oral Fluconazole 150mg once a week brings about a cure in 4 weeks whereas oral terbinafine 250mg given once daily effects a cure in 2 weeks itself.The severity of symptoms is not only reduced progressively but also at a faster rate in Terbinafine group. But the drawback was patient's affordability. Terbinafine is costlier than fluconazole. Also patient has to consume only 4 tablets of fluconazole while in the terbinafine group patients have to take 14 tablets.

The regular followup at the end of the 6th week and 12th week showed that there was no evidence of recurrence in both the groups. This was confirmed by mycological cure (fungal culture and skin scrapings) indicating that all patients in both the groups were cured both clinically and mycologically.

Side effects like nausea and indigestion was reported in 4 patients in terbinafine group while 2 patients complained of nausea in fluconazole group, which was statistically not significant. No serious adverse effects like hepatotoxicity or neutropenia was reported in both the groups.

The overall results of our study showed that at the end of 2 weeks, terbinafine is more efficacious than fluconazole as evident by the rapid cure. But results at the end of 4 weeks showed that, both fluconazole and terbinafine were equally efficacious in reducing the severity of symptoms without producing any serious side effects.

Immunocompromised patients (eg. DM) are more prone to many infections including fungal infection. So similar type of study can be done in such patients, with a much larger and diverse population to find out the efficacy of these drugs.

VII. Conclusion

Based on the outcome of this study it's been concluded that oral Terbinafine administered once daily for 2 weeks is more efficacious than Fluconazole as observed from the rapid improvement in the clinical symptoms and effective mycological cure. But fluconazole given once a week is a cost effective agent with better patient compliance.

Conflict of Interest

No conflict of interest

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