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Original Research Article

Study of effect of oral itraconazole with 2% sertaconazole cream versus oral terbinafine with 2% sertaconazole cream in dermatophytosis

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ABSTRACT

Background: Dermatophytosis is a common dermatological problem. Recent studies have reported an increase in the prevalence of the disease. Management of dermatophytosis thus has become challenging for both dermatologists and patients due to their resistance to treatment and their refractory nature. Currently the management of dermatophytic infection includes both oral and topical antifungals. The study compared the clinical efficacy and adverse effect profile of systemic with topical drugs.
Methods: Patients were randomly divided into two groups of 90 each. They were given oral Itraconazole 100 mg twice daily with Sertaconazole 2 % cream twice daily (Group A) and oral Terbinafine 250 mg once daily with Sertaconazole 2 % cream twice daily (Group B) till complete resolution of lesions or a maximum of six weeks. The response was assessed by the improvement in signs and symptoms of each of the clinical parameter, pruritus, erythema, scaling.
Results: At week 6, mycological cure was seen in 92.9% in Group A as compared to 86.9% of patients in Group B. There was a significant improvement in percentage change in pruritus, erythema, and scaling in both the groups from 0 to 6 weeks (p-value: <0.0001). Mild adverse effects such as gastrointestinal upset, headache, and raised transaminases were observed which were comparable in both the groups.
Conclusions: On comparison of the groups, we observed that both were effective but Itraconazole with Sertaconazole 2% cream was more efficacious in terms of both clinical (pruritus, scaling, and erythema) and mycological cure.

Keywords: Tinea, Itraconazole, Terbinafine, Sertaconazole, Efficacy, Dermatophytosis

INTRODUCTION

Superficial fungal infections are among the most frequent forms of human infections. They affect about 20-25% of the global population[1]Dermatophytes are the most common causative agents of superficial fungal infections in humans.[2] Dermatophytes are fungi that invade and multiply within keratinized tissues of body (skin, hair, and nails).[3] Based upon their genera, dermatophytes can be classified into three groups: *Trichophyton* (which causes infections of skin, hair, and nails), *Epidermophyton* (which causes infections of skin and nails), *Microsporum* (which causes infections of skin and hair). Various topical and systemic antifungal agents are available for the treatment of dermatophytic infection. Most used topical azoles in dermatophytic infections are imidazoles-clotrimazole (1%), econazole (1%), miconazole (1%) and sertaconazole (2%) cream/lotion used once or twice daily for 4-6 weeks.[4]

Sertaconazole, one of the newer azoles, is structurally unique due to lipophilic benzothiophene ring which help in its penetration into the keratinized layers of the skin without absorption into systemic circulation.[5]It has dual mechanism of action. Firstly, it inhibits ergosterol synthesis by blocking the P450- dependent enzyme pathway which results in the inhibition of conversion of lanosterol to ergosterol, a major constituent of fungal cell wall membranes.[6]Secondly, it binds directly to the fungal cell membrane which leads to an increased permeability and leakage of intracellular components particularly adenosine triphosphate leading to immediate cell death. Thereby it exhibits both fungicidal and fungistatic activities.[7]Sertaconazole also has additional anti-inflammatory and antipruritic actions.[8] It has shown great efficacy even against dermatophyte isolates resistant to other azoles.[9]

Itraconazole is an antifungal drug which acts by inhibiting cytochrome P-450 dependent enzyme, thereby interfering with demethylation of lanosterol to ergosterol. The medication is better absorbed orally when it is consumed with an acidic drink (such as orange juice). It takes about one to three days for half of the medication to be cleared from the blood stream. The rest of the drug is eliminated in the faeces and urine after conversion by the liver into inactive compounds. It has shown good results in the treatment of dermatophytosis at doses of 100 mg once a day for 2 weeks.[10,11] Mild side effects like gastric upset, headache, taste alteration, and jaundice has been observed. Rarely, it can cause serious side effects like hypokalaemia, torsades de pointes, and heart failure.[12,13]

Terbinafine is a member of the allylamine class of antifungal drugs. Allylamines inhibit squalene epoxidase of the ergosterol synthesis pathway, thereby block the conversion of squalene into squalene-2, 3-epoxide, which is a precursor of ergosterol. The resultant accumulation of squalene is toxic to the fungal cell membrane and is responsible for the fungicidal activity of allylamines.[14,15] Approximately 80% of terbinafine's metabolites are excreted by the kidney while the remaining fraction is eliminated through feces. Terbinafine related adverse events are mild to moderate and includes gastrointestinal complaints (e.g., nausea, abdominal pain, vomiting, diarrhoea), cutaneous eruptions, weight gain, appetite changes, headaches, and vertigo. Serious adverse drug reactions are very few, most commonly involving the liver and the hematologic system, they are only rarely reported with terbinafine use (0.04%). However, in the current scenario, there is an increase in the incidence of terbinafine resistance with increasing numbers of clinical failures and relapses.[16,17] Currently, fluconazole resistance is at 40%, terbinafine at 10-20%, itraconazole at 2%, and griseofulvin at 40%. Voriconazole, sertaconazole, luliconazole remain susceptible as reported in India.[18,19] Antifungal resistance in dermatophytosis could be due to the presence of efflux pumps, mutation in genes encoding for drug target enzyme, biofilm formation.[20] Because of the increase in the number of resistant and recalcitrant cases in recent times, the previous recommendations which was mentioned in western textbooks of dermatology on the dosage and duration of treatment are now considered inadequate.[21]Therefore, longer duration of treatment is required by most of the patients. As treatment is prolonged it can lead to an increased toxicity, increased cost, potentially serious drug interactions and adverse effects like hepatotoxicity in the patients.[22]

These factors decrease the patient's compliance to treatment with an increased risk of resistance and treatment failure. Despite an increase in resistance to various topical and oral antifungals in the current scenario, most of the higher azoles are still reserved for severe life-threatening invasive systemic mycoses.[2] Many studies have been done in the recent past especially in India on the efficacy, safety, and drug resistance profile of various first line topical and systemic antifungal therapies individually in dermatophytosis. However, none of the studies have been conducted comparing the combined efficacy of a systemic and topical antifungal drug in dermatophytosis which is the treatment protocol in the clinical practice. This will be the first study comparing the efficacy and safety profile of oral Itraconazole with topical Sertaconazole 2% cream and oral Terbinafine with topical Sertaconazole 2% cream in treatment of dermatophytosis.

Objectives

The objective was to evaluate the efficacy and safety of oral Itraconazole with Sertaconazole cream 2% and Terbinafine with Sertaconazole cream 2% in the management of dermatophytosis.

METHODS

Study type, duration and location

The study was a hospital-based randomized controlled trial. The study was done from September 2021 to December 2022. The study was performed at the Jawaharlal Nehru Medical College and Hospital, Aligarh, India. Total sample size obtained was 164 with a confidence interval and power at 95% and 80% respectively. On adding a correction factor of 10%, it came out to be 180.4. Rounding off to whole numbers, total sample size of 180 was kept with 90 in each group.[23] Written inform consent in a language understandable by the patient was obtained from each patient. As per the sample size, patients of dermatophytosis were enrolled in the study after detailed consent and were randomized into two groups, group A and group B. Randomization was done using "box and chit "method.

Inclusion criteria

All clinically diagnosed cases of dermatophytosis attending the Dermatology OPD, Aged 18 years and above were included.

Exclusion criteria

Exclusion criteria were; Inflammatory type of tinea, Steroid modified tinea, Tinea capitis and onychomycosis, Patients on some topical or systemic antifungal medications in the past 4 weeks, Patients with history of hypersensitivity to the study medications, Pregnant and lactating females, Immunocompromised patients and Patients refusing consent.

A detailed history of each patient was taken and recorded in proforma designed for the study regarding demographic data of the patients (name, age, sex, education, occupation, marital status, residence), mode of onset, progression, duration, any past treatment taken for dermatophytic infection in the form of topical or systemic therapy. General physical and systemic examination was performed. A thorough cutaneous examination was done in all patients regarding site, size, distribution, and number of lesions. Patients showing following clinical features were selected for the study: Erythematous well defined annular plaques with central clearing and itching affecting glabrous skin, groin, palms, soles, and face. Following investigations wherever deemed necessary were performed: Complete blood count (CBC), liver function test (LFT), renal function test (RFT), blood sugar, potassium hydroxide (KOH) & fungal culture (in case of doubt), dermatoscopy. In group A patients received oral Itraconazole 100 mg twice daily with Sertaconazole 2% cream twice daily for six weeks while group B patients received oral Terbinafine 250 mg once daily with Sertaconazole 2% cream twice daily for six weeks. Photographic documentation was done before the initiation of therapy and at each follow-up. At each visit, clinical response was noted in pruritus, erythema, and scaling. These were rated as clinical score of 0-3, in which 0-absent, 1-mild, 2-moderate, and 3-severe with a cumulative maximum score of 9.

The investigator was blinded and assessed the response to treatment by means of Physicians Global Assessment Scale (PGAS). On the last follow-up, patients were asked to grade their overall satisfaction as-Unsatisfied - <25%, slightly satisfied- 25-50%, satisfied- 51-75%, very Satisfied - >75%. All the immediate and late adverse effects were evaluated after each treatment session. All the patients were followed up every two weeks for six weeks.

The statistical analysis included profiling of patients on different demographic and clinical parameters. The Shapiro-Wilk test was used for testing of normal distribution of the study parameters. Descriptive analysis of quantitative parameters was expressed as means and standard deviation. Categorical data were expressed as absolute number and percentage. Independent Student t – test was used for testing of mean difference between two independent groups. Cross tables were generated, and Chi square test was used for testing of associations. P-value < 0.05 is considered statistically significant. All analysis was done using SPSS software, version 24.0.

RESULTS

A total of 180 patients with tinea infection were included in the study.

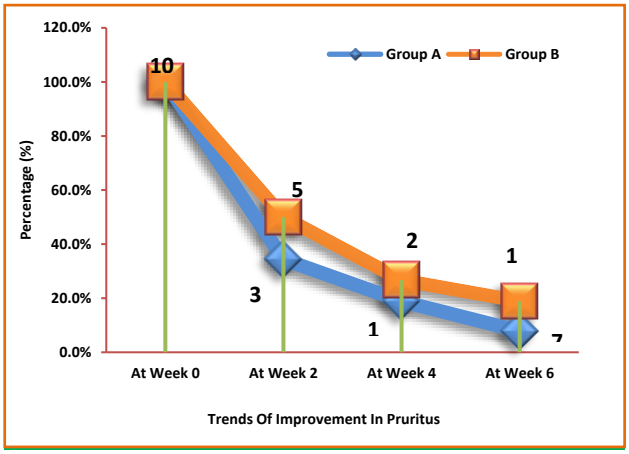

Figure 1: Trends of improvement in pruritus in patients.

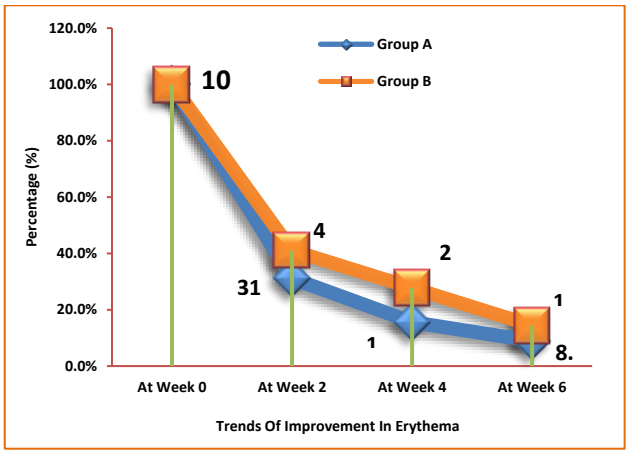

Figure 2: Trends of improvement in erythema in patients.

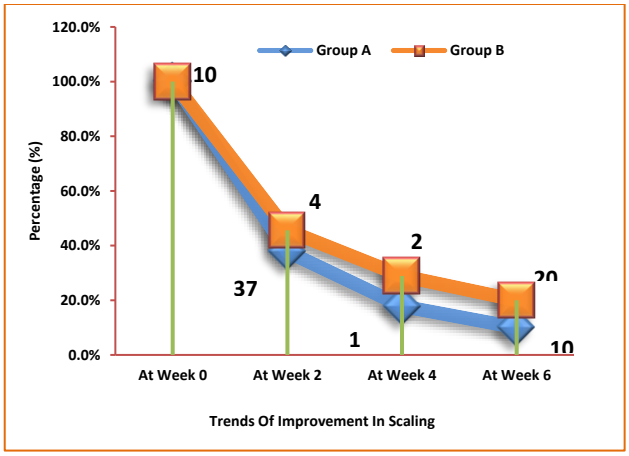

Figure 3: Trends of improvement in scaling in patients.

These patients were then segregated into two groups, that is group A and group b with N=90 in each group. There were eleven dropouts (5 patients from Group A and 6 patients from Group B), so 169 patients completed the study. Patients in the age range of the 18-65 years were included in the study with 103 (57.2%) males and 77 (42.8%) females.

Table 1: Basic epidemiologic parameters of the patients.

Parameters		Group A (N=90) Frequency (%)		Group B (N=90) Frequency (%)		P value
Age (years)	<20	13	14.4	11	12.1	0.57
	21-30	41	45.6	41	45.6	
	31-40	12	13.3	26	28.9	
	41-50	19	21.1	11	12.2	
	>50	5	5.6	1	1.1	
Mean age: 31.5±10.1 years						
Sex	Female	35	38.9	42	46.7	0.32
	Male	55	61.1	48	53.3	
Occupational Profile	Farmer	13	14.4	14	15.6	0.96
	Homemaker	27	30.0	24	26.7	
	Labourer	16	17.8	19	21.1	
	Service class	7	7.8	6	6.7	
	Student	23	25.8	21	23.3	
	Others	4	4.4	6	6.7	

Table 2: Comparison of clinical, microscopy and culture characteristics in patients.

Parameters		Group A (N=90) Frequency (%)		Group B (N=90) Frequency (%)		P value
Types of *Tinea*	*Tinea cruris*	18	20.0	20	22.2	0.57
	Tinea corporis	15	16.7	16	17.8	
	Tinea corporis et cruris	30	33.3	32	35.5	
	Tinea faciei	15	16.7	11	12.3	
	Tinea manuum	7	7.8	6	6.7	
	Tinea pedis	5	5.5	5	5.5	
KOH examination before therapy	Positive	80	88.9	75	83.3	0.38
	Negative	10	11.1	15	16.7	
KOH examination after therapy	Positive	1	1.1	3	3.3	0.06
	Negative	89	98.9	87	96.7	
Culture	*T. rubrum*	70	77.8	74	82.2	0.83
	T. mentagrophytes	16	17.8	15	16.7	
	T. tonsurans	2	2.2	1	1.1	
	E. floccosum	1	1.1	0	0.0	
	M. gypseum	1	1.1	1	1.1	

The mean age of the patients was calculated to be 31.5±10.1years. Majority of patients seeking treatment in this study were homemakers (28.3%) followed by students (24.4%) and labourers (19.4%). The basic epidemiologic parameters of the patients in the study have been summarised in (Table 1). Most common type of tinea observed in the study was Tinea corporis et cruris (34.5%) followed by Tinea cruris (21.1%) and Tinea corporis (17.2%). Microscopy by KOH was positive in 86.1% of the study population at the start of study. Microscopy by KOH was negative in 97.8% of the study population at the end of study. Most common species isolated in both the groups was *T. rubrum* (80.0%) followed by *T. mentagrophytes* (17.2%) (Table 2).

At baseline all patients in both the groups had pruritus (100% in group A and B). Improvement in pruritus was seen from the first follow-up at 2 weeks itself. At the end of 2 weeks, pruritus was present in 31 (34.4%) patients in group A and 45 (50%) in group B. On follow up at 4 weeks, pruritus was present in 17 (18.9%) patients in group A and 24 (26.7%) in group B. At the end of 6 weeks, pruritus was present in only 7 (7.8%) patients in Group A compared to 17 (18.9%) patients in Group B. (p value <0.0001) (Figure 1). At baseline all patients in both the

groups had erythema (100% in group A and B). On follow up at 2 weeks, erythema was present in 28 (31.1%) patients in group A and 37 (41.1) in group B. On follow up at 4 weeks, erythema was present in 14 (15.6%) patients in group A and 25 (27.8%) in group B.

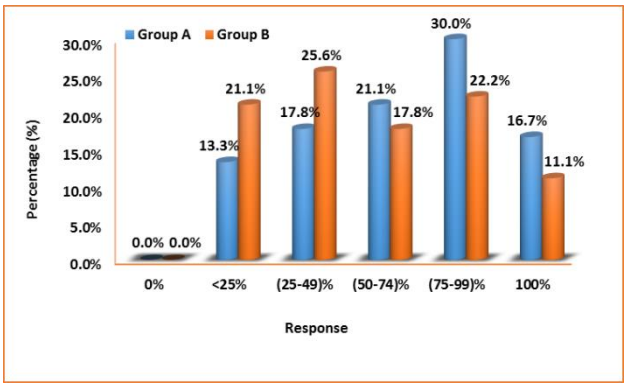

Figure 4: Comparison of therapeutic response at the end of 2 weeks.

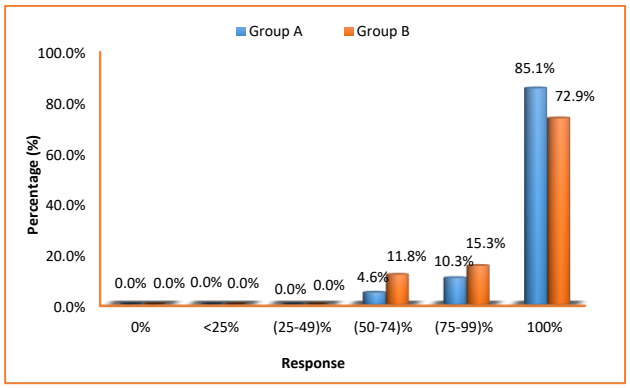

Figure 5: Comparison of therapeutic response at the end of 4 weeks.

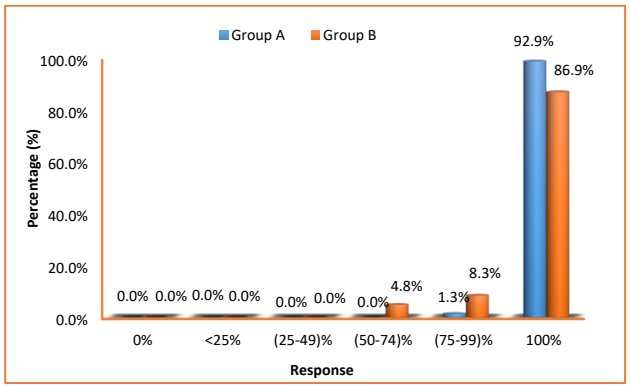

Figure 6: Comparison of therapeutic response at the end of 6 weeks.

At final follow up at 6 weeks, erythema was present in only 8 (8.9%) patients in Group A compared to 13 (14.4%) patients in Group B (p value <0.0001) (Figure 2). At baseline all patients in both the groups had scaling (100% in group A and B). On follow up at 2 weeks, scaling was present in 34 (37.8%) patients in group A and 41 (45.6%) in group B. On follow up at 4 weeks, scaling was present in 16 (17.8%) patients in group A and 26 (28.9%) in group B. At final follow up at 6 weeks scaling was present in only 9 (10.0%) patients in Group A compared to 18 (20.0%) patients in Group B. (p value <0.0001) (Figure 3). At 2 weeks about 30.3% of patients of Group A showed (75-99) % improvement as compared to 22.7% in Group B. Clinical response was hundred percent in 16.9% of patients from group A and 11.4% of patients from group B, however the result was not statistically significant (p=0.24) (Figure 4). At 4 weeks, about 85.1 percent of patients of Group A showed 100 % improvement as compared to 72.9 percent in Group B. However, the result was not statistically significant (p value=0.19) (Figure 5). At the end of 6 weeks, 100% clearance of dermatophytic infection was observed in 92.9% of patients in Group A as compared to 86.9% in Group B. The result was statistically significant (p-value = 0.01) (Figure 6). With respect to patient satisfaction, Group A patients showed significantly better results compared to Group B (p value=0.04). Most common adverse effect noted in this study was gastrointestinal complaints (21.7%) followed by headache and dizziness (7.8%).

DISCUSSION

Dermatophytosis is a common dermatological problem in India. Recent studies have reported an increase in the prevalence of the disease. The causes are expected to be much more diverse, ranging from the irrational use of antifungal drugs to topical steroid usage. Poor compliance to the prescribed medicines, changes in lifestyle and poor socioeconomic status of the population are other reported causes. These infections can cause a significant distress to the patients affecting them socially, physically, and financially. Management of dermatophytosis thus has become challenging for both dermatologists and patients due to their resistance to treatment and their refractory nature. There are various antifungal agents available for the treatment of dermatophytic infection.[24] In the current scenario the management of dermatophytic infection includes both oral and topical antifungals.[25]

In our study majority of patients belonged to the age group of 21-30 years. The mean age of patients calculated was 31.5±10.1 years (Mean±SD) (Table 1). Higher prevalence in this age group could be due to the fact that this population group takes part in maximum outdoor activities, which predisposes them to acquire infection from environmental exposure. This observation was consistent with the study conducted by Singh et al where they included patients in the age group of 18 to 50 years with mean age of 29.36±11.37 years. Similar observation was also seen in the study by Baveja et al[27]with a mean age of 34.00±10.03 years. Out of 180 patients in our study, there were 103 (57.2%) males and 77 (42.8%) females (Table 1). This observation was consistent with the study conducted by Bhatia et al and Singh et al where males outnumbered females (65.9% and 74.1% respectively).[26,28]

Low frequency in females may be due to under reporting, lack of education and gender discrimination prevailing in the society. Male outnumbered female patients in our study. (Male:Female=1.33:1). Most patients seeking treatment in our study were homemakers (28.3%) (Table 1). The reason for the predominance of dermatophytosis among homemakers could be best explained by their work in hot environment of kitchen which increases sweating conducive for the growth of dermatophytosis. Rudramurthy et al in their study also found homemakers as the most common affected group (25.1%).[29] Tinea corporis et cruris was the most common dermatophytic infection observed (30 patients in group A and 32 patients in group B) followed by Tinea cruris (18 patients in group A and 20 patients in group B) and Tinea corporis (15 patients in group A and 16 patients in group B) (Table 2). Similar observation was also seen in the study by Kumar et al with Tinea corporis et cruris (59 patients in group A and 48 patients in group B) as the 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).[30] In our study microscopy by KOH was found to be positive in 86.1% of the study population at the start of the study. Microscopy by KOH was found to be negative in about 97.8% of the study population at the end of the study. KOH was negative in 98.9% in group A and 96.7% in group B. Similar observation was seen in the study by Bhatia et al (28) where mycological cure was observed in 91.8% in group 1 (receiving oral terbinafine) and 74.3% in group 2 (receiving oral itraconazole). In our study Trichophyton rubrum was the predominant isolate comprising of (80.0%) cases followed by Trichophyton mentagrophytes (17.2%), Trichophyton tonsurans (1.7%), Epidermophyton floccosum (0.6%) and Microsporum gypsium (1.1%) (Table 2). This is consistent with the study conducted by Poluri et al, dermatophytic species isolated were *T. rubrum* (58.06%), *T. mentagrophytes* (22.58%), *Epidermophyton floccosum* (6.45%), *Trichophyton violaceum* (6.54%), *Trichophyton tonsurans* (3.22%) and *Trichophyton schoenleinii* (3.22%).[31]

In our study at baseline all patients in both the groups had pruritus (100% in group A and B). Improvement in pruritus was seen from the first follow-up at 2 weeks itself. At the end of 2 weeks, pruritus was present in 31 (34.4%) patients in group A and 45 (50%) in group B. On follow up at 4 weeks, pruritus was present in 17 (18.9%) patients in group A and 24 (26.7%) in group B. At the end of 6 weeks, pruritus was present in only 7 (7.8%) patients in Group A compared to 17 (18.9%) patients in Group B (p-value<0.001) (Figure 1). All patients in both the groups had erythema (100% in group A and B). On follow up at 2 weeks, erythema was present in 28 (31.1%) patients in group A and 37 (41.1) in group B. On follow up at 4 weeks, erythema was present in 14 (15.6%) patients in group A and 25 (27.8%) in group B. At final follow up at 6 weeks, erythema was present in only 8 (8.9%) patients in Group A compared to 13 (14.4%) patients in Group B (p value<0.001) (Figure 2). The relative improvement in pruritus and erythema was less in the study by Kumar et al.[30] It could be due to the use of only systemic antifungal therapy in contrast to the combined use of systemic and topical antifungal therapy which is the current treatment protocol. All patients in both the groups had scaling (100% in group A and B). On follow up at 2 weeks, scaling was present in 34 (37.8%) patients in group A and 41 (45.6%) in group B. On follow up at 4 weeks, scaling was present in 16 (17.8%) patients in group A and 26 (28.9%) in group B. At final follow up at 6 weeks scaling was present in only 9 (10.0%) patients in Group A compared to 18 (20.0%) patients in Group B (Figure 3). In our study at 2 weeks about 30.3% patients in group A showed up to (75-99) % improvement as compared to 22.7% group B. Clinical response was 100% in 16.9% of patients from group A and 11.4% of patients from group B (Figure 4). Group A patients showed greater percentage of clinical improvement; however, this difference was not statistically significant (p value=0.24). Bishwas et al in their study observed that clinical symptoms were improved in 60% of patients on itraconazole compared to 75% of patients on terbinafine at the end of 2 weeks.[32]

This response was better in patients on terbinafine at the end of 2 weeks but with a continuous regimen of 250 mg twice a day compared to our study where once daily dose of terbinafine 250 mg was used. Our study findings were comparable to study conducted by Sharma et al wherein they observed that both clinical and mycological cure rate was higher in itraconazole (50%) as compared to terbinafine (35%) at the end of 3 weeks.[33] However, the percentage improvement was less which could be due to the increased availability and irrational use of topical corticosteroids creams with a failure to respond to the standard doses of oral antifungals. In our study at four weeks, about 85.1% patients in group A showed 100% improvement as compared to 72.9% in group B (Figure 5). However, this difference was not statistically significant (p value=0.19). Bishwas et al in their study observed that 92% patients on itraconazole were cured compared to 75% of patients on terbinafine at the end of 4 weeks. Similar results were observed in the study by Bhatia et al wherein they observed mycological cure of 91.8% in patients on itraconazole compared to 74.3% in patients on terbinafine.28,32 Brigida et al in their study on efficacy of oral terbinafine and oral itraconazole in tinea corporis/ tinea cruris infection concluded that mycological cure was better in patients on itraconazole (88%) compared to patients on terbinafine (70%).[34] In our study at the end of 6 weeks, 100% clearance of dermatophytic infection was observed in 92.9% of patients in group A as compared to 86.9% in group B (Figure 6). This difference was statistically significant (p value =0.01). The response rate in our study was better than the study conducted by Kumar et al wherein they observed a cure rate of 72.5% in patients on itraconazole compared to 67.6% in patients on terbinafine at the end of 6 weeks and this difference was not statistically significant although the treatment response was better in itraconazole as compared to terbinafine.[30,34] Overall, most common adverse effect was gastrointestinal

complaints (21.7%) followed by headache and dizziness (7.8%) in our study.

Limitations

The limitations of the study were small sample size and use of fixed doses even though variation in the weights of subjects. Long follow-up for recurrences and relapse was also not done.

CONCLUSION

Dermatophytosis is a commonly encountered condition in dermatology out-patient department. It is caused by dermatophytes which are keratinophilic organisms with the ability to invade skin, hair and nails of the living host. Over the past few years, there has been an increase in the prevalence of dermatophytosis with an increase in the resistant and recalcitrant cases. This has made the management of dermatophytosis more challenging for both dermatologists and patients. There are various antifungal agents available for the treatment of dermatophytic infection. Oral and topical antifungals have shown promising results as monotherapy in the past. But resistance to different classes of antifungals is on the rise. Because of the increase in the number of resistant and recalcitrant cases in recent times, it is imperative to combine topical and systemic antifungal therapy for the management of dermatophytic infection. This study compared the efficacy and safety profile of oral Itraconazole with Sertaconazole 2% cream and oral Terbinafine with Sertaconazole 2% cream in treatment of dermatophytosis. When we compared Itraconazole with Sertaconazole 2% cream and Terbinafine with Sertaconazole 2% cream we observed that both were effective but Itraconazole with Sertaconazole 2% cream was more efficacious in terms of both clinical (pruritus, scaling, and erythema) and mycological cure. The study also showed earlier response in patients receiving Itraconazole with Sertaconazole 2% cream by early decrease in pruritus, erythema, and scaling. When we compared the side effect profile, gastrointestinal complaints were the most common side effect observed. None of the patients required discontinuation of therapy. Based on the results of our study we conclude that Itraconazole with Sertaconazole 2% cream is superior to Terbinafine with Sertaconazole 2% cream in the treatment of dermatophytosis. However more studies are needed to validate the results of combining oral and topical antifungals in the treatment of dermatophytosis.

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