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Research Article

A PROSPECTIVE RANDOMIZED OPEN-LABELED PARALLEL GROUP STUDY TO COMPARE THE EFFICACY OF ORAL TERBINAFINE VERSUS ORAL TERBINAFINE PLUS ORAL FLUCONAZOLE IN DERMATOPHYTE INFECTIONS

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ABSTRACT

Objectives: The objectives of this study were to assess the efficacy of oral monotherapy (Terbinafine) as compared to combination of oral drugs (Terbinafine and fluconazole) in treatment of dermatophyte infections.

Methods: Patients of clinically diagnosed, potassium hydroxide (KOH) confirmed dermatophyte infections (n=235), were recruited as per inclusion criteria and randomized into Group A (Tab. Terbinafine 6 mg/kg body weight daily) and Group B (Tab. Terbinafine 6 mg/kg daily+Tab Fluconazole 3 mg/kg twice per week) treatment for 2 weeks. Assessment was done in beginning, after week 1 and after week 2 using visual analog scale (VAS) and global physician assessment (GPA). At the end of 4 weeks, they were again called back to assess the residual disease activity.

Results: VAS scoring at week 1 and week 2 showed a significant reduction of scores in both the groups as compared to basal score of 0 week. Inter-group comparison showed decrease in mean-VAS itch scores in Group B as compared to Group A. Week 1 reduction in the Group B was statistically significant ($p<0.001$). GPA reflected a gradual but significant improvement in GPA scores end of week 1 and week 2 in both groups. The improvement seemed robust in Group B reflecting the stronger clinical response. The inter-group comparison showed statistically significant improvement in Group B over Group A in both 1stweek ($p<0.001$) and 2nd week ($p=0.021$).

Conclusion: Dermatophyte infections treated with either terbinafine alone or terbinafine and fluconazole combination is clinically effective. Combination therapy is better than single drug therapy in terms of treatment response.

Keywords: Dermatophytes, KOH preparation, Visual analogue scale, Global physician assessment, Terbinafine, Fluconazole.

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INTRODUCTION

Worldwide, large number of populations, suffers with superficial fungal infections including dermatophytosis. Many predisposing factors such as hot, humid environment in tropical and subtropical region, tight clothing, close contacts, diabetes, and drug resistance contribute to its persistence and recurrence.

Incidence and prevalence of mycotic infections are increasing in the past three decades due to growing number of immunocompromised state and susceptible individuals [1]. In developed countries, it is due to underlying immunocompromised conditions as compared to developing countries where majority of infections due to low hygienic practices and environment [2]. These infections become an important public health problem due to frequent recurrences of the infection, leading to prolonged treatment and relapsing nature leads to the problem of constant supervision. Antifungal drug consumption and public health expenditure has increased worldwide [3].

For many years, griseofulvin was the only approved systemic anti-dermatophyte agent [4]. However, today, it is not widely used due to griseofulvin-resistant isolates of dermatophytes and existence of strains with elevated MIC levels to griseofulvin [5,6]. However, currently, many other newer antifungal agents are available for the treatment of dermatophytosis, such as allylamines and triazoles with more efficacy and less side effects.

The fungal infections are not completely cured with antifungal drugs. The treatment is less successful than that of bacterial infections because the fungal cells are eukaryotic and much more similar to human than the bacteria [7]. Many drugs that inhibit or kill fungi are therefore quite toxic for humans also. Moreover, the fungal cells are equipped with a detoxifying system, which is able to modify many antifungals; probably by hydroxylation [8]. Hence, the antifungals used to treat the fungal infection will remain fungistatic for a period of time and repeated usage of antifungals which are advised.

An important aspect to be considered in the susceptibility to antimycotics *in vivo* is the formation of biofilms. Biofilms are differentiated masses of microbes that adhere to surfaces and are surrounded by a matrix of extracellular polymers, increasing resistance to standard antimicrobials [9]. The concept of biofilm for dermatophyte was introduced to explain dermatophytomas, a form of onychomycosis refractory to standard antifungal therapies. Dermatophytomas are characterized by a dense white mass of fungus tenaciously adherent to the surrounding nail plate, which may require surgical removal [10].

Historically, the clinical resistance of microbes has been defined as the persistence or progression of an infection despite appropriate antimicrobial therapy. *In vivo*, resistance is also correlated with antifungal misuse because patients often fail to finish the full course of treatment. Thus, the inadequate use or dosage of drugs contributes to the failure in eliminating the disease agent completely, encouraging growth of the most resistant strains, which may lead to hard-to-treat fungal infections [11]. Many newer antifungals are coming day by day and are under clinical trials to detect sensitivity, efficacy, and adverse effect profile, resistance pattern.

Combination therapy may be an alternative to monotherapy for widespread lesions and for those who fail to respond to monotherapy. Combination

therapy of an azole agent and terbinafine has shown synergistic effects against yeast and molds [12]. With this background, the present study intends to assess the efficacy of oral monotherapy as compared to combination of oral drugs in treatment of dermatophyte infections.

METHODS

The study was conducted in patients with dermatophyte infection attending the dermatology outpatient department of Sri Ram Murti Smarak Institute of Medical Sciences Hospital.

Study design

It is a prospective randomized open-label parallel group study designed to study the effect of oral terbinafine versus oral terbinafine plus oral fluconazole in dermatophyte infections.

Study period/duration

This study was 2 weeks of drug intervention with assessment at the beginning, week 1 and week 2. Follow-up at the end of 4 weeks to assess residual disease activity.

Study source

All the patients visiting the outpatient department of Sri Ram MurtiSmarak Institute of Medical Sciences who were KOH positive and were ready to come on a regular basis and allowed their photographs to be taken after the due consent were included in the study.

Study population

Most of the patients consisted of people coming from villages or neighboring talukas near Bareilly or Bareilly. Of this, majority were male, illiterate (n=235).

Selection criteria of patients

Inclusion criteria

The following criteria were included in the study:

1. Clinically diagnosed case of dermatophyte infection having tinea cruris or tinea corporis
2. Patients not on any antifungal medication from the past 1 month
3. Age ≥18 years
4. Patients should be willing for investigation, treatment, and regular follow-up
5. Only KOH positive cases to be selected.

Exclusion criteria

The following criteria were excluded from the study:

1. Pregnant or lactating women
2. Patient unsure about attending treatment schedule regularly
3. Patients who fail to come for follow-up after initiation of therapy
4. Past/present history of any type of malignancy
5. Patients having hepatic abnormalities
6. Patients having hypertension, diabetes mellitus, bronchial asthma, and tuberculosis.

Ethical approval, randomization, and treatment allocation

1. The study was approved by the Institutional Ethics Committee; further, patients were included in the study after taking an informed consent
2. All KOH positive and/or culture positive samples were included for further data analysis

   Patients were allocated randomly to two parallel groups, A and B based on a computer-generated randomized number sequence.
3. Patients from both the groups were asked to discontinue their antifungal medicines after the 2nd week and were advised a checkup at the end of 4th week to know the residual activity of disease and thus find out the efficacy of Group A versus Group B.

Assessment parameters

1. KOH was done at the beginning of therapy
2. Visual analog scale (VAS) score for itching was assessed at the start and weekly for 2 weeks
3. Global physician assessment (GPA) based on single observer was done on the patient at the start and in each weekly visit for 2 weeks.

Data collection

Data were collected in a predesigned format. It included patient's identification number, sex, age, occupation, history, and clinical presentation.

For patient with visible and sufficient scales on the lesion, the following protocol was followed:

Specimen collection

Skin specimens were collected as per standard techniques.

The involved site was cleaned with 70% alcohol and the specimen was obtained by scraping the edge of the affected area with sterile blade.

Microscopic examination with KOH

The direct microscopy with potassium hydroxide (KOH) preparation is done and fungal filaments observed.

Statistical analysis

The analysis was carried out by SPSS version 28.0.1.1. The data included both qualitative and quantitative characteristics; therefore, data were summarized numerically in the form of percent for both qualitative as well as for categories of quantitative characteristics. Mean and standard deviations were given where ever necessary in case of quantitative characteristics. Further, difference of means between the two groups was tested by student's t-test. Statistical significance was seen at $p \leq 0.05$.

RESULTS

In this study, total sample size was 235 out of which 35 did not qualify for the inclusion criteria. Total 200 patients were evaluated, 100 each was randomly assigned into Group A (which consisted of Oral Terbinafine 6 mg/kg body weight daily) and 100 into Group B (which consisted of Oral Terbinafine 6 mg/kg body weight daily Plus Fluconazole 3 mg/kg body weight twice per week).

Demographic profile of patients

Out of these 200, maximum 138 (69%) patients were in the age group of 18–30 years with 73 (73.0%) patients in Group A and 65 (65.0%) patients in Group B, followed by age group 31–40 years and least in age group of 41–50 years, thus indicating the prevalence of fungal infection correlated to increased sweat production in younger individuals. The mean age for Group A was 27.41±11.86 years, whereas it was 26.79±9.54 years in Group B (Table 2).

Table 1: Drugs prescribed

Groups	Prescription (for 2 weeks)
Group A	Tab. Terbinafine 6 mg/kg body weight daily (along with Tab. levocetirizine 5 mg daily and Tab. hydroxyzine hydrochloride 25 mg daily)
Group B	Tab. Terbinafine 6 mg/kg body weight daily+Tab. Fluconazole 3 mg/kg body weight twice per week (along with Tab. levocetirizine 5 mg daily and Tab. hydroxyzine hydrochloride 25 mg daily)

Table 2: Age distribution between the two Groups A and B

Age group	Group A (%)	Group B (%)	Total (%)
18–30 years	73 (73.0)	65 (65.0)	138 (69.0)
31–40 years	17 (17.0)	20 (20.0)	37 (18.5)
41–50 years	10 (10.0)	15 (15.0)	25 (12.5)
Mean±SD	27.41±11.86	26.79±9.54	p=0.684

SD: Standard deviation

The study population reflected a strong male to female predisposition with males (81% and 72%) and females (19% and 28%) in Groups A and B, respectively, thus achieving a ratio of approximately 3:1 of males-to-females (Fig. 1).

Maximum numbers of the patients were illiterate comprising 40 patients in Group A and 39 patients in Group B (total 79), this is followed by graduation, higher secondary and secondary education in both groups. Most patients were students (59), followed by laborers, housewives, servicemen, unemployed, and businessman in both groups.

Weekly assessment of VAS score for itching

At the beginning, patients from both the group experienced severe itching which was reflected from VAS. Group A and Group B showed mean score of VAS as 7.90±0.644 and 7.80±0.71, respectively, before starting treatment. Repeated VAS for itching was analyzed at the end of 1st week and 2nd weeks which showed a significant reduction in both the groups 6.57±0.655 and 4.35±0.672 in Group A; and 5.95±0.716 and 4.16±0.735 in Group B as compared to basal score of 0 week (Table 3).

Inter-group comparison showed the decrease in mean-VAS itch scores in Group B as compared to Group A. Week 1 reduction in the Group B was statistically significant with p<0.001* (Table 4 and Fig. 2). The 2nd week comparison, however, did not show any statistically significant difference.

Weekly GPA

GPA scale was used in which every week patient was assessed for improvement in lesions. It was seen that there was gradual but significant improvement in GPA score with 2.76±0.571 and 3.01±0.482 in Groups A and B, respectively, in the 1st week and 2.79±0.729 and 3.02±0.66 in Group A and B, respectively, in 2nd week (Table 5).

The inter-group comparison showed significant improvement in Group B over Group A in both 1st and 2nd week (Table 6 and Fig. 3).

Follow-up for the assessment of residual disease activity

Follow-up at the end of 4 weeks showed poor compliance; despite of calling by telephonic reminders and requests only 40 patients out of 100 in Group A, while 25 patients out of 100 patients turned up for follow-up at the end of 4th week. Almost all patients in both groups (36 in Group A and 23 in Group B) were found to be disease free at follow-up visit.

DISCUSSION

According to the WHO, approximately 20–25% of world population is suffering from tinea infection [13]. Morbidities of tinea infection are not only due to its high occurrence but also its chronicity, relapse, recurrence, and increasing resistance to antifungal drugs and these factors are becoming main concern of practicing dermatologists and patients too. Hence, in this study, clinicomycological pattern was seen to look for current situation. First systemic antifungal used was griseofulvin, later on azoles like ketoconazole, fluconazole, and itraconazole came. However dermatophytes long back have started showing the resistance to griseofulvin [14]. Fluconazole for dermatophytes is not as effective as for *Candida* species. Ketoconazole has broad spectrum of antifungal sensitivity, but due to its hepatotoxicity, drug interactions and antiandrogenic properties its use in tinea infection for long term are limited. Itraconazole has activity similar to ketoconazole and it is not hepatotoxic. Terbinafine is a widely used fungicidal drug, very effective against dermatophytes has low MIC as compared to others. Its resistance is first notified in 2003 in a study by Mukherjee *et al.* [15]. In current scenario, we observed many patients in our OPD, who do not or incompletely respond to terbinafine.

In the present study, 235 patients were included with tinea infection involving the glabrous skin, attending the dermatology outpatient department. Out of 235 patients, 35 patients did not meet inclusion criteria and 200 patients underwent clinical examination and KOH examination. Further were randomized and treatment allocated into two groups followed by visual analog scoring and GPA at starting, 1 week and 2 week of assigned treatment.

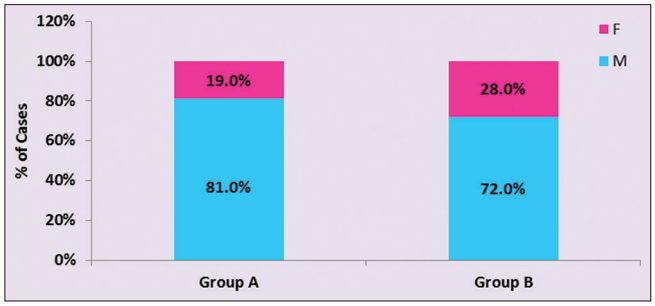

Fig. 1: Sex distribution between the two Groups A and B

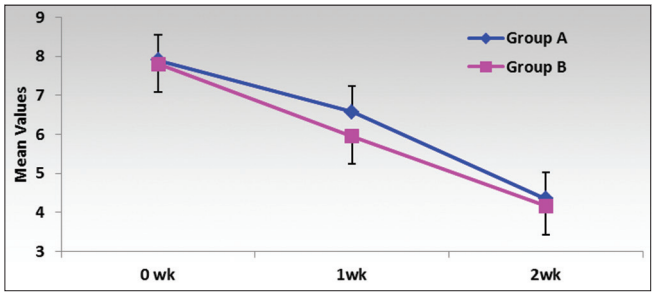

Fig. 2: Visual analog scale between the two Groups A and B

Table 3: Comparison of visual analog scale itching at different time points in Groups A and B

VAS for itching	Group A			
	n	Mean±SD	Mean diff from O wk±SD	Student (paired) t-test p-value*
0 week	100	7.90±0.644		
1 week	100	6.57±0.655	1.330±0.514	<0.001*
2 week	100	4.35±0.672	3.550±0.626	<0.001*
	Group B			
	n	Mean±SD	Mean diff from O wk±SD	p-value*
0 week	100	7.80±0.711		
1 week	100	5.95±0.716	1.850±0.50	<0.001*
2 week	100	4.16±0.735	3.640±0.659	<0.001*

SD: Standard deviation, VAS: Visual analog scale

Table 4: Comparison of visual analog scale for itching between the Groups A and B

VAS for itching	Group A	Group B	Student t-test p-value*
	Mean±SD	Mean±SD	
0 week	7.90±0.644	7.80±0.71	0.298*
1 week	6.57±0.655	5.95±0716	<0.001*
2 week	4.35±0.672	4.16±0.735	0.058

SD: Standard deviation, VAS: Visual analog scale

Tinea infection can occur at any age. In the present study, most common age group involved was 18–30 years (69%), with mean of 27 years in Group A and 26 years in Group B. This observation is coincided with the study done by Aggarwal *et al.* [16]. Out of 200 patients, 153 were male (76.5%) and 47 were female (23.5%). Male: Female ratio was 3.25:1. This may be attributed to the fact that males are more involved

Table 5: Comparison of GPA at different time points in group A and B

GPA	Group A			
	n	Mean±SD	Mean difference from 0 week±SD	Student (paired) t-test p value*
0 week	100	2.52±0.659		
1 week	100	2.76±0.571	0.240±0.82	0.004*
2 week	100	2.79±0.729	0.270±0.89	0.003*
	Group B			
	n	**Mean±SD**	**Mean Difference from 0 week±SD**	**Student (paired) t-test p value***
0 week	100	2.42±0.622		
1 week	100	3.01±0.482	0.59±0.621	<0.001*
2 week	100	3.02±0.666	0.60±0.603	<0.001*

SD: Standard deviation, GPA: Global physician assessment

Table 6: Comparison of GPA between two Groups A and B

GPA	Group A	Group B	p-value*
	Mean±SD	Mean±SD	
0 week	2.52±0.659	2.42±0.622	0.271*
1 week	2.76±0.571	3.01±0.482	<0.001*
2 week	2.79±0.729	3.02±0.666	0.021*

SD: Standard deviation, GPA: Global physician assessment

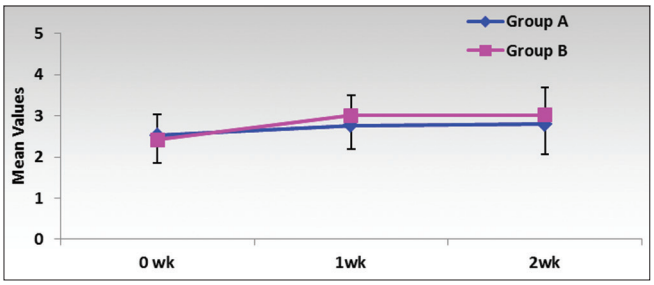

Fig. 3: Global physician assessment at different time points in Groups A and B

in outdoor physical activities, which leads to excessive sweating making a favorable environment for the fungal infections. This finding of male predominance is similar to other previous studies, in which M:F ratio varied from 2 to 4:1 [17,18]. However, the literature shows certain studies in the past exhibiting female predominance, which were mainly had T. pedis and manuum and onychomycosis due to kitchen and household work, their most common clinical variant [19,20].

Distributions of lesions of tinea infection in the present study were noted on groin and buttocks 86.8% of patients among both sexes. This can be explained by the fact that occlusive dressing of vest initiates fungal growth, which later on spread to other part of body by direct contact. Less aeration due to tight clothing, maceration, and high rate of sweating in groin and waist region make this site more vulnerable to dermatophytosis [21].

Visual analog score is an arbitrary scale used to measure itching based on the patient's comprehension. Similar study has been done by Kirck [22], in which he showed that implication of VAS based on itching is that successful elimination of the inflammatory symptoms of tinea pedis, such as pruritus, may promote adherence to therapy. Furthermore, early and rapid relief of symptoms, as seen in his study, may encourage patients to continue therapy for the full recommended period of 4–6 weeks, thereby reducing the risk for relapse which leads to chronic disease.

In this study, we found that after giving treatment, there was a reduction in visual analog score based on itching at the end of 1st week and 2nd week in both the groups as compared to beginning of the therapy. In between groups, the mean reduction showed statistical significance at week 1 but not at the end of 2nd week. This might be due to early response of dual therapy as a result of synergistic effect, but this effect tends to get alleviated with continuation of treatment. Further, extension study duration may confirm this explanation. There are few recent studies which considered VAS as mainstay evaluation tool in assessment of treatment efficacy of antifungal drugs in treatment of tinea [23,24].

A recent study evaluated comparative efficacy of terbinafine versus itraconazole in treatment of tinea cruris, even though this study had limitation of small sample size (n=60), the authors concluded that both drugs are highly effective in therapy response [25].

Global physical assessment has been used to assess the improvement in overall patient's condition in diseases such as acne and psoriasis using the GPA in a clinical setting to measure and track patient outcomes and validate practice guidelines, but it has not been used to track the improvement in dermatophyte infections [26]. Literature shows studies using GPA as mainstay tool for comparative efficacy and safety assessment in dermatophytoses [27]. One comparative study assessing the efficacy and safety of tea tree oil in a cream base against clotrimazole 1% cream for the treatment of tinea corporis or cruris concluded both are safe and effective [28].

In our study, the GPA scores significantly increased in both groups during the therapy as compared to beginning, reflecting the well-being, and improvement of the patient condition. This increase was notably more within Group B indicating the stronger therapy response for combination therapy. This was further clarified during intergroup comparison showing statistical significance in Group B as compared to Group A in both end of week 1 and week 2 of treatment. Our findings thus establish a distinct efficacy advantage of combination oral therapy as compared to monotherapy in terms of strength of response, and alleviation of symptoms with general improvement. A recent randomized open-labeled parallel group study comparing efficacy and safety of topical terbinafine versus miconazole in patients with tinea corporis employed GPA to establish miconazole has better clinical efficacy as compared to terbinafine, with both having similar safety profile [29].

The follow-up of residual disease activity could not be well assessed in this study as less number (only 1/3rd) of patients in both groups turned out despite of repeated requests. This reflects the notion of patient behavior considering fungal infections of skin as non-serious medical problem; this general perception is reflected by other authors previously [30]. Our study also has inherent limitations regarding study period and lesser sample size. Due the brevity of time, we also did not asses case to case adverse drug reactions, thus omitting the analysis of safety aspect of both therapy arms. Much larger studies are warranted along with robust follow-up and safety data to establish stronger evidence in this regard. Nevertheless, this study succeeds to assess clinical effectiveness of dual therapy versus monotherapy.

CONCLUSION

Two weeks' treatment of dermatophyte infections with either terbinafine alone or terbinafine and fluconazole combination is clinically effective. Combination therapy (Terbinafine plus fluconazole) is better than single drug therapy (Terbinafine alone) in terms of treatment response. Considerable improvement is noticed in symptomatic relief with overall patient's condition at the end of 2 weeks when a combination therapy is used. Follow-up in dermatophyte infections is poor as people do not consider it as a serious problem.

AUTHORS' CONTRIBUTIONS

1. Dr. Amit Shekar accomplished the research conduct of the study
2. Dr. Geetika Mittal conceived the concept and design of the study

3. Dr. Umesh Devappa Suranagi performed the compilation of data and assessment of results
4. Dr. Rakhamaji Dattarao Chandane contributed toward statistical analysis of data.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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