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Original Article

Recurrence of dermatophytosis and therapeutic efficacy of systemic antifungals in recurrent dermatophytosis of adults– A randomized, assessor-blind controlled trial in a tertiary institution

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Abstract

Objective To validate the efficacy and safety of supra-pharmacological dose of Itraconazole in one arm and combination of Itraconazole and Terbinafine in another arm for successful treatment of recurrent dermatophytosis.

Methods The study was a single-center, randomized, assessor-blind, parallel-group, multi-arm, controlled trial on 155 patients with allocation ratio as 1:1:1. The control group (Group A) received conventional dose of oral Itraconazole and two experimental groups received supra-pharmacological dose of oral Itraconazole (400 mg for 2 weeks and 200 mg for another 2 weeks for Group B) and combination of oral Itraconazole (200 mg for 4 weeks) and Terbinafine (250 mg for 4 weeks in Group C) respectively. The clinical and mycological cure was noticed in every group. Statistical analysis was done with the help of Microsoft Excel and Med Calc. 12 software.

Results 41, 42 and 41 patients of respective three groups were completed their last follow-up visits. 78.57% and 73.18% of patients showed cure in Group B and C respectively whereas 4.88% cure in control group. So, both the experimental groups show better outcome compared to the conventional treatment ($p<0.001$). In the multiple regression model, it is clearly shown that the clinico-mycological cure is dependent on the treatment regime ($p = <0.0001$), not on the fungal species ($p = 0.0622$).

Conclusion Supra-pharmacological dose of oral Itraconazole or a combination of Itraconazole and Terbinafine can be given in recurrent tinea cases.

Conclusion Small sample size and single-centre study were some limitations.

Key words
Recurrent; Dermatophytosis; Itraconazole; Terbinafine; Randomized controlled trial.

Introduction

In recent times, dermatophytoses or tinea infections are occurring extensively in India and causing significant morbidities with negative impacts on the social, psychological, occupational, and financial states of patients. In India, the prevalence of tinea infection has been found to range from 36.6-78.4%.[1] Dermatologists of India are facing recurrent, chronic tinea infections frequently due to combinations of the host, agent, drug, and

environmental factors.[2,3] In most cases, the clinical manifestations of tinea cases are also atypical and unusual from the classical ones and they are rosecea-like, seborrhoeic dermatitis-like, psoriasis-like, erythema multiforme-like, dermatitis-like and so on.[4] The prevalence of this chronic, recurrent nature is about 5-10% of all new dermatological cases in a tertiary care center in North India.[2] The changing character of dermatophytosis has now become a potential therapeutic challenge to the treating physician. Most of us are treating these cases on the belief of our own opinions and knowledge with or without success. There is no concrete guideline to treat these cases in textbooks or journals.

With this background, the present study is undertaken to evaluate the effective treatment regime for recurrent tinea infections and the safety, tolerability, and relapse rate of the experimental drugs.

Materials and Methods

Trial design - The study was a single-center, randomized, assessor-blind, parallel-group, multi-arm, controlled trial. It was conducted in the departments of dermatology and microbiology of a tertiary institution in eastern India for the duration of about thirteen months from 20th Sep'17 to 5th Oct'18.

The study population was the patients with recurrent tinea infections attending our Dermatology Outpatient Department (OPD). The study sample was the study population that fulfilled the following inclusion criteria:

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Adult patients (15-60 years) with recurrent tinea corporis or cruris or faciei or combinations of any two or all three with positive fungal hyphae on KOH smear from skin scraping were included in the study. Recurrent dermatophytosis is to be defined as when there is re-occurrence of the disease (lesions) within few weeks (< 6 weeks) after completion of the treatment. (ECTODERM India)

The exclusion criteria of the study were:

1 Patients with Diabetes Mellitus, hepatic or renal diseases or other immunocompromised disorders.

2 Patients with H/O steroid or other immunosuppressant intake or application.

3 Pregnant or lactating mother.

4 Patients with other forms of tinea infections like tinea pedis, tinea manuum, tinea unguium etc.

5 Chronic tinea infections in other close family members.

The selected patients were sent to the hospital's central laboratory for complete blood count, blood sugar, liver function test (LFT), and renal function test from their random blood samples after taking proper written consent and lucid explanation about it. After that, they were sent to the Microbiology department for skin scraping aseptically for the fungal element by 10% KOH wet mount preparation and fungal culture in Sabouraud dextrose agar media. Further, fungal species identification was done later on by macroscopic and microscopic (Lactophenol cotton blue slide mount) features of the isolated colony. The patients with normal blood reports and fungal hyphae positivity on KOH smears were recruited for the study. Then the selected

patients were allocated to any of the groups through randomization. It has to be mentioned that the patients of negative culture reports/ contaminated culture were treated as "screen failure" and excluded from analysis. Thus, only those patients who showed positive fungal culture were included in analysis.

Interventions - The experiment was designed as an assessor-blind, parallel-group, three-arm trial. As described below, there were two experimental groups in excess of a control group that would receive the conventional treatment as described in many textbooks.[5,6]

The control group was: Group A- Cap Itraconazole 100 mg once daily after meals for two weeks (conventional Itraconazole).

And the two experimental groups were: Group B- Cap Itraconazole 200 mg (2 capsules of 100 mg) twice daily after meals for the first 2 weeks then 100 mg twice daily after meals for another 2 weeks. (Supra-pharmacological dose of Itraconazole)

Group C- Cap Itraconazole 100 mg twice daily after food along with Tab Terbinafine 250 mg once daily after food for 4 weeks. (Combination of Itraconazole and Terbinafine)

Study medications- Both the branded drugs were manufactured by two reputed Indian pharmaceutical companies ([1] Cap Canditral 100 mg, Manufacturer – Glenmark Pharmaceuticals Ltd., Expiry date – 09/2019, Batch no. - 05170610, [2] Tab Sebifin 250 mg, Manufacturer – Sun Pharmaceutical India Ltd., Expiry date – 03/2019, Batch number - 2864557). There was no scope for topical antifungal application in the present study and patients were advised to apply petrolatum over lesions to combat dryness if necessary. All patients were treated with Levocetirizine 5 mg tablet (Govt. hospital supply from Central Medical Store) at bedtime to alleviate symptomatic itching. They were categorically advised about general measures regarding personal hygiene with regard to avoidance of risk factors for tinea.

Visits and follow-ups - The selected patients were revisited regularly at Dermatology OPD on the 8th day (2nd visit), 15th day (3rd visit), and 29th day (4th visit) of the first month for the treatment of experimental groups and were followed up at the end of 2nd month (5th visit) and 3rd month (6th visit) to know the outcome and to overcome any complications. For the control group, the patients were revisited regularly on the 8th day (2nd visit), and 15th day (3rd visit) of the first month for treatment and were followed up after one month (4th visit) and two months (5th visit, test of cure visit) of treatment. At the end of the treatment period, all patients were examined carefully if there were any sustained clinical signs or symptoms or re-occurrence of fungal infections to be proved by KOH smear and/or culture. The persisters or recurrent tinea cases were diagnosed as failure cases of the specific treatment group and were treated on an alternative effective regimen. LFT was done in the 3rd and 4th visits for the experimental groups and in the 3rd visit for the control group.

Outcomes parameters- The primary outcome parameters of the study were clinically and mycologically cured at the end of the treatment and continued this outcome on follow up visits after treatment. Clinical cure was defined as the patient being clinically free from any symptoms (itching, burning) and signs (erythema, scaling) of superficial fungal infections. Secondary outcomes were set on safety profile, patients' tolerability of drugs, relapse rates, and also the treatment response on specific fungal species, body surface areas involvement.

Sample size - The sample size of each group was estimated by the following formula:

Sample size=c X $[\{\pi_1(1-\pi_1) +\pi_2(1-\pi_2)\}/(\pi_1-\pi_2)^2]$

Here π_1 represented the proportion of cure with the standard treatment with Cap. Itraconazole 100 mg which was about 70% [$\pi_1 = 0.7$] [7] and π_2 represented the expected proportion of cure in the experimental group and c is 7.9 for 80% power. However, the estimated cure rates in experimental groups in our pilot study, conducted in our department were found to be about 93% [$\pi_2 = 0.93$].

So, the calculated sample size was 41.08 per group. Because of the one-month treatment period, another two-month follow-up period and repeated investigations, it was assumed about 25% of dropout cases were discontinued during treatment or lost to follow-up. A few patients were also included in dropout cases due to contamination of the fungal cultures. So, the sample size per group was 51.35 after adding dropout cases and the total sample size was at least 51.35X3 patients or 154 patients.

Randomization The patients were allocated into three treatment groups as a 1:1:1 ratio by the process of simple randomization with the help of a random number table. One of the co-investigators was delegated to look after the randomization and allocation process of patients. Allocation concealment was done by sequentially numbered containers technique.

Blinding Physician blinding was ensured by having an independent assessor judging the clinical cure and a separate microbiologist assessing the mycological cure was blinded to the assigned treatment. Mycological cure was determined by the absence of fungal hyphae on the KOH mount and the absence of fungal growth on culture media.

Statistical analysis The data were tabulated in Microsoft Excel software. Med Calc 12 software was used for data analysis. All the probable hypothesis was tested with a suitable statistical test with an alpha set as 0.05 ($p<0.05$) and this value was taken as statistically significant. Multiple regressions were also performed to assess the influence of treatment arms, and types of dermatophyte species on the treatment outcome.

Results

The patients were enrolled as a study sample for the period of ten months from 20th September 2017 to the 1st week of July 2018. A total of 510 patients were selected for the study during the specified period. But 355 patients were excluded following the application of specific inclusion and exclusion criteria. Ultimately, a total of 155 patients with recurrent tinea corporis and/or tinea cruris and/or tinea faciei were included during this period. The study duration was continued for another three months for one-month treatment and another two-month follow-up period from the last enrolled date.

After the randomization and allocation process, the Control arm (Group A) obtained 52 patients, whereas Group B acquired 52 patients and Group C 51 patients. In Group A, Group B, and Group C, the following number of patients have not completed the study such as 11 patients, 10 patients, and 10 patients respectively due to several reasons (Figure 1). Thus, the final analysis was done on 41 patients in Group A, 42 patients in Group B, and 41 patients in Group C.

The participants' flowchart is depicted in **Figure 1**.

Baseline data - Group-wise baseline data with age, male, and female distribution, clinical types of tinea specified above, and body surface area

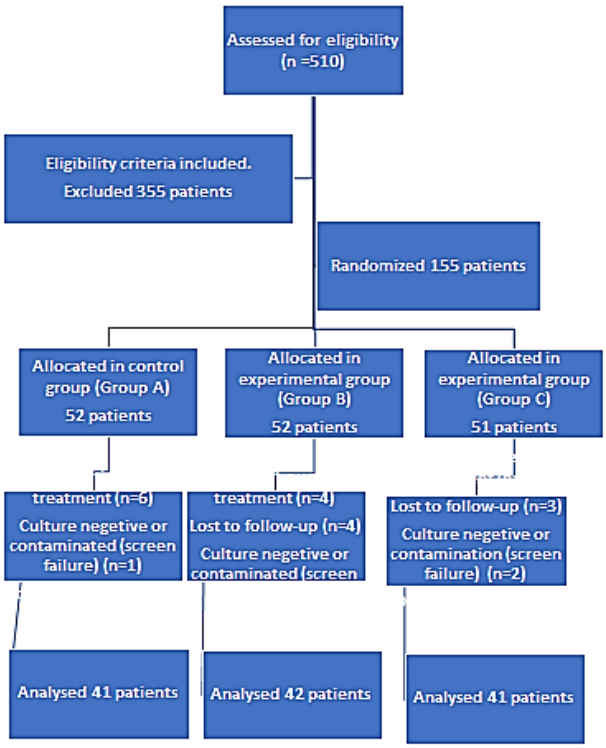

Figure 1 Participants' flowchart.

involvement are described in **Table 1**.

In all three groups, the majority of patients were young adults. In Group A, Group B, and Group C, the mean age was 30.2439 ± 9.9518 years, 30.1905 ± 10.189 years, and 29.6585 ± 9.5121 years respectively. In all groups, males outnumbered females very widely (90.3% males as a whole). The patients with 3-10% body surface area involvement were more predominant than the other two varieties in all three groups (47.6% of total patients). It was found that 65.3% of total patients suffered from the combination of any two clinical types of tinea followed by the combination of three types of tinea (21%).

It is noted that there was no statistical difference ($p>0.05$) among the treatment arms with regard to age, gender, or clinical types of tinea (one or combination of more than one type) affected or involved body surface area. Thus, these factors have unbiased equal distribution among the study groups. Outcomes and estimation – The primary outcome is tabulated in **Table 2**. In the control group, the clinical and mycological cure was estimated only in 4.88% of patients (2 patients) and sustained on follow-up visits. Cure was not obtained in 37 patients (90.24%) at any of the follow up visits and 2 patients relapsed

Table 1

	Group A (n = 41)	*Group B (n = 42)*	*Group C (n = 41)*	*Total (n = 124)*	*P value*
Age					
Mean±SD	30.2439 ± 9.9518	30.1905 ± 10.189	29.6585 ± 9.5121	30.0323 ± 9.8137	
Median	29	29.5	28	29	0.957
IQR	22 - 34.25	21 - 37	20.75 – 37.25	21.5 – 37	
95% CI of Mean	27.1027 to 33.3851	27.0153 to 33.3656	26.6561 to 32.6609	28.2878 to 31.7767	
Gender					
Male	38 (92.68%)	37 (88.10%)	37 (90.24%)	112 (90.3%)	0.7788
Female	3 (7.32%)	5 (11.90%)	4 (9.76%)	12 (9.7%)	
BSA					
Less than 3%	6 (14.63%)	6 (14.29%)	7 (17.07%)	19 (15.3%)	*0.8525*
3-10%	22 (53.66%)	18 (42.86%)	19 (46.34%)	59 (47.6%)	
More than 10%	13 (31.71%)	18 (42.86%)	15 (36.59%)	46 (37.1%)	
Clinical types					
Tinea corporis or Tinea cruris or Tinea faciei	6 (14.63%)	5 (11.90%)	6 (14.63%)	17 (13.7%)	
Combination of two clinical types	28 (68.29%)	27 (64.29%)	26 (63.41%)	81 (65.3%)	0.9497
Combination of all three specified clinical types	7 (17,07%)	10 (23.81%)	9 (21.95%)	26 (21%)	

Table 2

	Group A (n = 41)	*Group B (n = 42)*	*Group C (n = 41)*	*Total (n = 124)*	*P value*
Clinico-mycological cure					
Yes	2 (4.88%)	33 (78.57%)	30 (73.17%)		*< 0.0001*
No	39 (95.12%)	9 (21.43%)	11 (26.83%)		
Culture					
T. Rubrum	23 (56.09%)	14 (33.33%)	32 (78.05%)	69 (55.6%)	0.0002
T. Mentagrophyte	18 (43.90%)	28 (66.67%)	9 (21.95%)	55 (44.4%)	

Note: Fisher's Test between Group A and Clubbed Group B and C (in terms of Clinico-mycological cure) P value <0.0001; Fisher's Test between Group B and Group C (in terms of Clinico-mycological cure) P value =0.614.

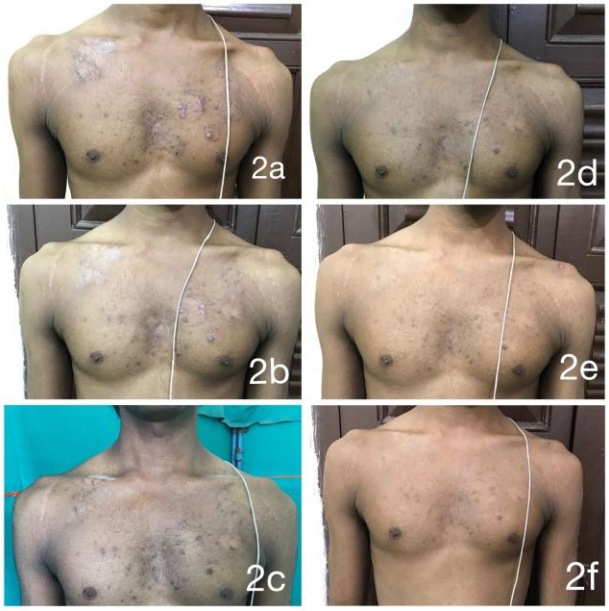

Figure 2 Patient of Group B in six consecutive visits.

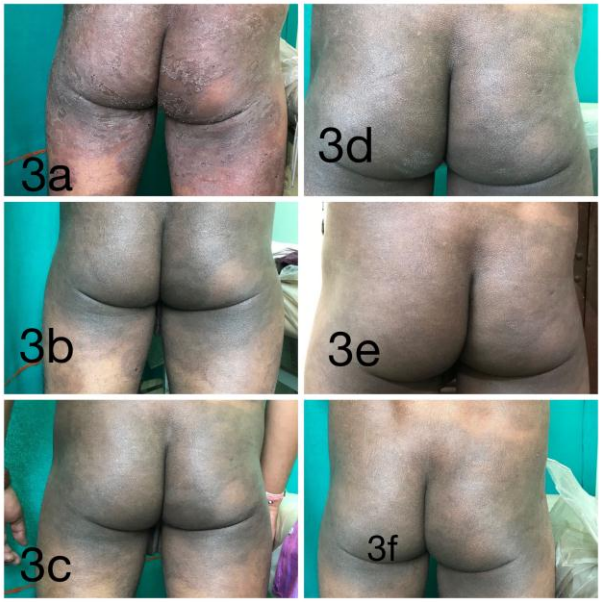

Figure 3 Patient of Group C in six consecutive visits.

during follow up at 1 month after achieving cure at 2 weeks (end-of-treatment visit). In Group B, the cure was obtained in 78.57% of patients (33 patients) **(Figure 2)** and sustained this effect till the last follow-up visit. Among the rest nine patients (21.43%), eight (19.05%) showed relapsed at follow up visit at test-of-cure visit (2 months after end-of-treatment) and one patient (2.38%) did not show any cure. In Group C, 73.18% of patients (30 patients) showed complete cure during treatment and continued this status during the follow-up period **(Figure 3)** and seven patients (17.07%) relapsed at test-of-cure visit (at 2 months after end-of-treatment visit) and four patients (9.76%) never achieved any cure.

Ancillary analysis – In **Table 2**, it is clearly seen that *Trichophyton rubrum* (69 patients, 55.6% of total) outnumbered *Trichophyton mentagrophytes* (55 patients, 44.4%) in a fungal culture which is statistically significant (p-value 0.0002). No other species were identified in this study. In Group A, B, and C, the *T. rubrum* was identified in 23 patients (56.09%), 14 patients (33.33%), and 32 patients (78.05%) respectively **(Figure 4)** whereas the *T. mentagrophytes* species were in 18 patients (43.90%), 28 patients (66.67%), and 9 patients (21.95%) respectively **(Figure 5)**.

Group-wise treatment outcome with regard to fungal culture is tabulated in **Table 3**. The clinico-mycological clearance was found to be more when the etiological agent as *T. rubrum* (85.5%) than with *T. mentagrophytes* (75%)

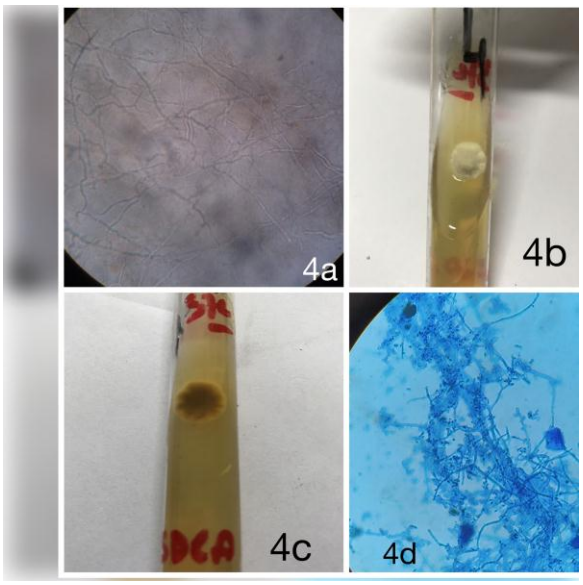

Figure 4 KOH smear (Fig 4a), Trichophyton Rubrum culture both sides (Fig 4b, 4c) Lactophenol cotton blue smear (Fig 4d).

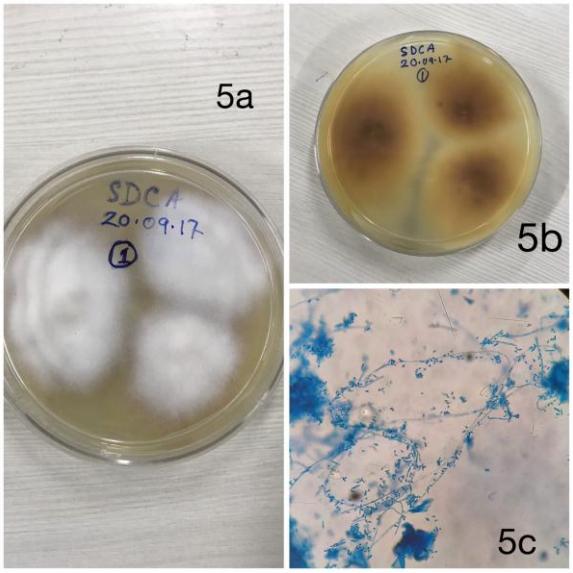

Figure 5 Trichophyton Mentagrophytes culture both sides (Fig 5a,5b), Lactophenol cotton blue smear (Fig 5c).

Table 3

Clinical and Mycological cure	*Group A (n = 41)*		*Group B (n = 42)*		*Group C (n = 41)*	
	T. Rubrum (n=23)	*T. Mentagro-phyte (n=18)*	*T. Rubrum (n=14)*	*T. Mentagro-phyte (n=28)*	*T. Rubrum (n=32)*	*T. Mentagro-phyte (n=9)*
Yes	1 (4.35%)	1 (5.56%)	12 (85.71%)	21 (75%)	22 (68.75%)	8 (88.89%)
No	22 (95.675%)	17 (94.44%)	2 (14.29%)	7 (25%)	10 (31.25%)	1 (11.11%)
P value (Chi-square)	0.581		0.690		0.436	

when Supra-pharmacological dose of Itraconazole (400 mg for 2 weeks and 200 mg for another 2 weeks) was used though not statistically significant (P=0.690). On the other hand, with a combination regime of Itraconazole and Terbinafine (Intraconazole 200mg and Terbinafine 250mg for 4 weeks) the reverse was observed with 88.89% of patients infected with *T. mentagrophytes* and 68.75% with *T. rubrum* showed a successful outcome, though the difference was not statistically significant (P = 0.436).

The Multiple regression with Clinico-mycological cure as the dependent variable and the Culture Characteristic and Drug regime as an independent variable is highlighted in **Table 4**. The statistical modeling reveals that the outcome is not influenced by the culture characteristics (P=0.062) but is definitely influenced by the treatment regime (P<0.0001).

Safety profile, tolerability, and relapse - Single patient was complicated with deranged hepatic function (Total bilirubin – 2.54mg%, Serum glutamic oxaloacetic transaminase (SGOT) – 118IU/L and Serum glutamic pyruvic transaminase (SGPT) – 125 IU/L) during treatment of group C on the third visit and put on appropriate therapy after discontinuation from the study. An increased level of SGPT (up to 65 IU/L) in three cases each from Group B and C was found after the completion of the second-week treatment (3rd visit). There were no serious adverse reactions in those patients with the continuation of further treatment. On the 4th visit, no further increment of SGPT level in Group B patients but the further increment of SGPT level (maximum 80 IU/ml) was found in said patients of Group C. Bilirubin levels of

Table 4 Multiple regression model with Clinico-mycological cure as Dependant variable Culture Characteristic and Drug regime as the independent variable

Independent variable	*Coefficient*	*Std. Error*	$r_{partial}$	*t*	*P*
Culture characteristic	0.1432	0.07611	0.1687	1.882	0.0622
Treatment regime	0.3572	0.04650	0.5726	7.682	<0.0001

Note: Adjusted-R^2 0.318, Multiple regression co-efficient 0.573, Analysis of Variance <0.001

Table 5

	Group A (n = 41)	*Group B (n = 42)*	*Group C (n = 41)*	*Total (n = 124)*	*P value*
Side effects					0.0375
Yes	0	6 (14.29%)*	6 (14.63%)**	12 (9.7%)	
No	41(100%)	36 (85.71%)	35 (85.37%)	112 (90.3%)	

* Side-effects of Treatment B: 3 cases of increased liver enzymes (up to 65 IU/L), 1 case each of pedal edema, puffiness of the face, and frequent spotting (vaginal bleeding).

** Side-effects of Treatment C: 3 cases of increased liver enzymes (up to 65 IU/L) in 3rd visit, another 2 patients of high SGPT (up to 70 IU/L) in 4th visit and 1 case of menorrhagia.

those patients were within normal limit. Another two patients of Group C had shown an increment of SGPT level (up to 70 IU/L) in their 4th visit. One female patient was suffering from mild puffiness of the face and another female from moderate pedal edema in Group B near the end of treatment (4th visit). Specific investigations were within the normal limit for those patients. Both the symptoms subsided on follow-up visits (5th visit). Another two females (one each from Group B and C) had experienced menstrual abnormality like frequent spotting from Group B and menorrhagia from Group C, though the symptoms subsided during the follow-up period. The above side effects are statistically significant with a p-value of 0.0375. A few patients complained of indigestion, belching, and acidity for the first few days of treatment and the symptoms decreased spontaneously even with the continuation of treatment. As per these gastrointestinal side effects, patients of Group B showed a comparatively higher side (40% of patients) than Group C (25% of patients). No other specific abnormality was detected in any participant. The patients tolerated well with the experimental drugs and were not in need of withdrawal from treatment except for the patient with hyperbilirubinemia. Most of the patients (about 40%) had post-treatment hyperpigmentation.

Discussion

Dermatologists in India in recent times have to resort to up-dosing the oral antifungal drug or adding another group of oral antifungals or prolonging the treatment duration to manage the menace of difficult-to-treat recurrent tinea cases.[8-11]

Itraconazole, a classically time-dependent drug, works better in twice-daily doses than in a higher once-daily dose.[12] In spite of the non-linear pharmacokinetics of Itraconazole, it has been proved in an ex-vivo study that 200mg Itraconazole in twice daily dose appeared to be more fungitoxic against *T. mentagrophytes* species than 250 mg Terbinafine per day or 200mg Itraconazole per day.[9,13] It is well-known fact that Itraconazole and Terbinafine act in two different steps for inhibition of ergosterol synthesis of the fungal cell wall for their antifungal activity.

Supra-pharmacological dose of Itraconazole regimen, used in this study, 400mg per day in divided doses for two weeks decreased the fungal load more effectively than the usual dose and then maintained its action with 200mg per day for another two weeks. This regime cured 78.57% of patients with recurrent tinea cases (Tinea corporis, cruris, faciei) without relapse.

In this group, 7 patients (25%) with *T. mentagrophyte* and 2 patients (14.3%) with *T. Rubrum* showed relapse or partially cured. Combination oral treatment of Itraconazole 200mg with Terbinafine 250mg per day for four weeks showed almost the same efficacious (73.18%) as the previous group. In this group, 10 patients (31.3%) of *T. Rubrum* and 1 patient (11.1%) of *T. mentagrophyte* noticed relapse or partially cured. In the multiple regression model, it is clearly shown that the clinico-mycological cure is dependent on the treatment regime ($p = <0.0001$), not on the fungal species ($p = 0.0622$). Though Centers for disease control and prevention (CDC) announces antimicrobial resistance cases due to *Trichophyton mentagrophytes* type VIII (*Trichophyton indotineae*) causing an epidemic of tinea in India apart from well-known Terbinafine-resistant *Trichophyton rubrum* in their fungal diseases chapter. This *Trichophyton indotineae*-induced resistant tinea has also been found in Europe and North America.[14-16] The present study reflects disparate findings and the results have highlighted the fact that both *T. rubrum* and *T. mentagrophytes* are indolent to treatment and we need to undertake multicentre, RCT studies required to know the more effective treatment with appropriate drugs and duration for specific fungal species.

Apart from the single patient with LFT abnormality, no other serious problem was noted in the study. So, as per the safety profile and tolerability of drugs, we can highly recommend these regimes with better efficacy.

As this is a single-center study, it is difficult to comment on the effectiveness of experimental drugs in other parts of the globe where the microbiological milieu can be different. It can definitely be commented that the experimental drugs of stated doses and durations are applicable in the study area and its surroundings. It is probably applicable in the whole of India due to the same disease activity and spectrum, the same quality of drug/s intake or application, and almost the same climatic conditions. Though several reports from India showed different dermatophyte species and in vitro antifungal drug sensitivity apart from this study, the given regimes were applied equally to both major Trichophyton species.[17]

Limitation

The study could have certain limitations like a single-centre study, and a small sample size. History of topical steroid application and proper family history might be altered by participants. The patients could not be followed up beyond 3 months due to operational reasons. Hygiene, quality of life, and overcrowding may also alter the effective results. The genetic sequencing and antifungal sensitivity testing facilities were not available during the study period. We humbly like to submit that due to infrastructural limitations we could not perform the genetic sequencing to find the prevalence of *T. indotineae* in our study population

Conclusion

The study shows that *T. rubrum* is still a prominent etiological agent for dermatophytosis (55.6%) though *T. mentagrophytes* is coming up as the second most common agent in eastern India. The clinico-mycological unresponsiveness which revolves around the hypothesis of *T. mentagrophytes* being responsible is refuted by the present study wherein it is established that the cultural profile of the fungus is not having any impact on the outcome. The study also reveals that the conventional regimen is not effective in the present scenario and newer regimes are required for recurrent tinea cases. Both the two regimes (supra-pharmacological dose of itraconazole and combination of

itraconazole with terbinafine) studied were found to be equally effective but the side-effect profile with the combination regime favours the use of Supra-pharmacological dose of Itraconazole (Cap Itraconazole 200 mg twice daily after meals for the first 2 weeks then 100 mg twice daily after meals for another 2 weeks.) as a preferred regimen.

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