Evaluation of Treatment of Tinea Corporis and Tinea Cruris with Oral Terbinafine Using Direct Microscopic Examination with Special Stains

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Abstract

Terbinafine is a fungicidal allylamine drug and was considered a drug of choice to treat dermatophyte infection. However recently there wasan increase in the incidence of clinical failure and relapses with terbinafine.

Aims and Objectives: This study was undertaken to assess the effectiveness and safety of oral terbinafine 250 mg given in patients suffering from tinea cruris and tinea corporis for 6 weeks.

Materials and Method: In a prospective, open-label randomized controlled comparative trial 40 patients suffering from tinea cruris and tinea corporis were recruited. Only patients with tinea cruris and tinea corporis, confirmed through positive microscopy before the start of treatment were eligible for inclusion in the trial. The patients were distributed into two groups and randomly allocated into group A and group B of 20 patients each. Both groups received the same treatment i.e., oral Terbinafine 250mg once daily for 6 weeks. Patients of both groups were followed up at weeks 2, 4, 6 during treatment and at the end of 8 weeks. Mycological control test for group A and group B patients were done by KOH mount at baseline and each visit. Patients of group B underwent mycological control testing in the form of KOH mount with the concurrent use of DMSO and CSB at baseline and each visit. By the end of treatment clinical and mycological cure were evaluated.

Results: In group A (mycological testing with only KOH was done), fungal elements were detected in 100%, 40%, 20%, 0% and 0% of baseline patients, 2 weeks, 4 weeks, 6 weeks and 8 weeks respectively. In group B (mycological testing with KOH and DMSO+CSB was done), fungal elements were detected in 100%, 75%, 50%, 10% and 15% of baseline patients, 2 weeks, 4 weeks, 6 weeks and 8 weeks respectively. Even after 2 weeks of completion of oral terbinafine 250 mg for 6 weeks,the clinical cure was not seen in 40% and 35% patients in groupA and group B.

Conclusion: Although mycological cure was achieved in more than 90% of patients in group A and group B after 8 weeks clinical cure was achieved in only 60% and 65 % patients in group A and group B respectively. Implying that we need to continue oral terbinafine for a longer period to achieve mycological as well as a clinical cure.

Keywords: *Tinea cruris, tinea corporis, dermatophytosis, terbinafine 250 mg, relapse.*

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Introduction

Dermatophytes are hyaline fungi of genera, Trichophyton, Microsporum and Epidermophyton which infect keratinized tissues such as skin, hair and nails.[1]

In tropical and subtropical countries dermatophytosis is common.[2] The superficial mycotic infections are the most frequent form of infection seen in clinical practice nowadays, which affects more than 20–25% population of the world.[3-6] Tinea corporis (contributing 36-59%) and tinea cruris (contributing 12-27%) are the most common type of dermatophytosis in India.[7] Directmicroscopic examination, culture and molecular studies are used to diagnose superficial dermatophytosis. The most common test employed to diagnose dermatophytosis is potassium hydroxide (KOH) wet mounts. Although rapid, direct microscopic examination with the KOH wet mount lacks a contrasting color and needs considerable interpretative ability. To increase the accuracy of KOH wet mount different stains are used. Chicago sky blue (CSB) stain is a rapidand reliable diagnostic method for diagnosingdermatophytosis.[8] Terbinafine is the orally available allylamine antifungal having fungicidal activity against dermatophytes. Oral terbinafine was considered to be a drug of choice for the treatment of tinea cruris and corporis.Terbinafine inhibitsthe synthesis of ergosterol, which disintegratesthe fungalcell wall.[9,10]. Oral terbinafine 250 mg/day is effective in treating tinea cruris, tinea corporis,andpedis, typically achieving mycological cure in 80 to 90 percent of patients treated for two weeks.[11]

However, resistance to common antifungal agents used in the treatment of patients with tinea infections is being reported with an increase in the incidence of clinical failure and relapses with terbinafine.[12,13,14]

Both clinical and microbiologic resistance, either occurring singly or in tandem, as well as primary and secondary resistance to antifungal agents have been reported.[15]

Terbinafine resistance frequency from patients with tinea pedis or tinea unguium having T. rubrum and T. interdigitale infection is alarmingly high, about 1%. Increased antifungal drug exposure favors the development of resistant strains.[16] The key reasons for this may include low plasma concentration and incomplete cure which are very frequent after 2 weeks of Terbinafine therapy with 250 mg/day.

The increased use, improper prescription and counter sale ofantifungal drugs have also created resistance to these drugs. Therefore different approaches were required when using terbinafine. We conducted this analysis to assess the effectiveness of terbinafine 250 mg given over 6 weeks.

Materials and Method

A prospective, open-label randomized controlled comparative research was carried out in patients sufferingfromtinea corporis and tinea cruris. On the first visit, informed written consent was taken. Demographic data along with clinical history was taken, followed by clinical examination.

The study was done in the dermatology OPD of a tertiary care hospital in central India. Patients between the age of 18 to 70 years suffering fromtinea corporis with or without tineacruris on clinical examination were taken up for the study. The number and body sites involved were recorded and the worst affected area was chosen for specific measurement and observation. The study included only KOH smear-positive patients and KOH smear-negative patients were excluded from thestudy. Patients who had taken topical or oral therapy in the past 1 month for dermatophytosis, patients withthe previous history of intolerance to the terbinafine,had any abnormality in the laboratory investigation, patients unwilling to participate in the study or who were pregnant or lactating, immunocompromised were omitted from the study.

Forty patients who attended the dermatology OPD of tertiary care hospital in central India and fulfilled the inclusion criteria and the clinically evaluable exclusion criteria underwent laboratory evaluation to rule out other exclusion criteria and then were recruited for the analysis.

The samples were collected from the worst affected area and two approaches tested for the presence of fungal elements first by 10% Potassium hydroxide mount (KOH) only and another approach by using 10% Potassium hydroxide (KOH) with Chicago sky blue (CSB) stain and Dimethyl Sulfoxide Mount (DMSO). Only tinea corporis and tinea cruris patients confirmed by positive microscopy before the start of treatment were eligible for inclusion in the trial. The patients were divided randomly into two groups of 20 each (groups A and B) based on a random allocation sequence generated by the software.

Pretreatment evaluation and advice: On the first visit, an informed written consent will be taken. Clinical history will be taken, followed by clinical examination, as per the proforma. Baseline laboratory investigations viz. Complete blood count,renal function test,and liver function test were done.

Treatment Protocol: Patients were split into 2 groups at random with, A and B having 20 patients in each group. Both groups received the same treatment i.e., oral Terbinafine 250mg once daily for 6 weeks. Patients of both groups were followed up at weeks 2, 4, 6 during treatment and at the end of 8 weeks. Mycological control tests were done at each visit for each patient of both groups. Mycological control test for patients of group A was done in the form of KOH mount at baseline and each visit. Patients of group B underwent mycological control testing in the form of KOH mount with the concurrent use of DMSO and CSB at baseline and each visit.

Efficacy Evaluation: The clinical and mycological cure were evaluated after completion of treatment.

Based on the improvement in pruritus, erythema and scaling grading of clinical response was done and categorized into 4 groups (Grade I - was very good response with>75% improvement,Grade II - was good response with 51 to 75% improvement Grade III - was poor response with 26% to 50% improvement Grade IV - response ≤25%improvement). The patients were declared clinically cured if clinical improvement was more than 75%. and if potassium hydroxide (KOH) with and without DMSO/CSB examination is negative patients were considered as mycologically cured. All adverse events (AEs) were assessed for severity and relationship to Terbinafine at each visit. Multiple occurrences of the same adverse effects were only counted once for each patient. Laboratory measurements such as liver function tests were also included for safety evaluation.

Statistical Test and software used: Statistical analysis was performed using descriptive statistics and inferential statistics by using the chi-square test and software used in the study were SPSS 24.0 version and GraphPad Prism 7.0 version and p-value <0.05 is considered as the degree of significance.

Results

A total of 40 patients (20 patients in each group) were included in this study. Both groups were matched for age and sex and were thus, comparable. The disease was found to be more common in males, with a male: female ratio of 1.67 (25 males and 15 females). The mean age of the patients was 30.04 ± 11.24 years (18-63 years). The majority of patients (64.78%) were in the age group of 20-30 years. The most common clinical type seen was tinea cruris et corporis (39.7%), followed by tinea cruris (31.88%) and tinea corporis (28.42%). Other infectionsonychomycosis (0.75%), tinea barbae (0.5%), tinea manuum (0.5%). The commonly involved sites were the inguinal region, waist, axillae and the inframammary areas (in females). In group A (mycological testing with onlyKOH was done), fungal elements were detected in 100%, 40%,20%, 0% and 0% patients at baseline, 2 weeks, 4 weeks, 6 weeks and 8 weeks respectively. In group B (mycological testing with KOH and DMSO+CSB was done), fungal elements were detected in 100%, 75%, 50%, 10% and 15% patients at baseline, 2 weeks, 4 weeks, 6 weeks and 8 weeks respectively.

Table 1: Demographic data

Total number of patients	40	
Males	25	
Females	15	
M:F	1.67:1	
Mean age	30.04 ± 11.24 years	
Clinical types	Tinea cruris et corporis Tinea cruris Tinea corporis	39.7% 31.88% 28.42%
Other infections	Onychomycosis (0.75%), tinea barbae (0.5%), tinea manuum (0.5%)	
Sites	Inguinal region Waist Axillae Inframammary areas (in females)	
The average number of body sites involved	2	

Table 2: Mycological testing at baseline and at follow up visits

		Baseline	2 Weeks	4 Weeks	6 Weeks	8 Weeks
Positive Results	Group A	20(100%)	8(40%)	4(20%)	0(0%)	0(0%)
	Group B	20(100%)	15(75%)	10(50%)	2(10%)	3(15%)

Table 3: Group A

	Baseline	2 Weeks	4 Weeks	6 Weeks	8 Weeks
Mycological detection	20 (100%)	8(40%)	4(20%)	0(0%)	0(0%)
Patients not having clinical cure	20(0%)	20(0%)	18(90%)	7(35%)	8 (40%)

Table 4: Group B

	Baseline	2 Weeks	4 Weeks	6 Weeks	8 Weeks
Mycological detection	20(100%)	15(75%)	10(50%)	2(10%)	3(15%)
Patients not having clinical cure	20(100%)	20(100%)	18(90%)	6(30%)	7 (35%)

Discussion

The most common superficial mycoses worldwide are dermatophytosis. A variety of antifungal drugs have been developed to treat this condition and more are underway. Terbinafine is one of the most widely used antifungal medications used in the treatment of superficial fungal infections because of its broad-spectrum fungicidal activity. The drug has shown consistent efficacy against dermatophytes achieving more than 90% cure rates when prescribed daily 250mg for 2 weeks. However, recently, clinical relapses and failure in patients with tinea infections with an increased incidence of terbinafine resistance have been identified with terbinafine. Although terbinafine resistance in dermatophytosis is not usual in clinical practice, it has been reported in clinical isolates by few authors. Mukherjee et al. published the first documented evidence of resistance to terbinafine in dermatophytes in 2003. In their study, Majid et al. reported that there were only 43 cases at the end of 12 weeks out of the total 100 cases enrolled, who maintained a long-term clinical and mycological cure after two weeks of oral terbinafine therapy. The authors concluded that incomplete mycological cure, as well as relapse,were very frequent in patients with tinea cruris and tinea corporis after standard terbinafine therapy (2 weeks). (5) In our study incomplete mycological cure was seen in 4 out of 20 patients in group A and 10 out of 20 patients in group B even after 1 month of terbinafine therapy which was statistically significant (p value = 0.023).

One of the principal mechanisms of antifungal resistance is a decrease in effective drug concentration, which in the case of Terbinafine is quite a known feature following standard dosing regimen of 250 mg daily because of substantial skin and adipose tissue build up.This clearly shows that the current standard terbinafine therapy with 250 mg/day dose is not sufficient in the current scenario where fungal resistance is further aggravated by increased use, unsuitable prescription and counter sale of antifungal drugs.

Even though there is no clear proof as to which strategy to use to best avoid resistance, the most commonly suggested measures in the past include rational use of antifungal agents and adequate dosing with particular focus on avoiding low antifungal dosage treatment and for the inadequate duration.

We conducted this survey to find out the safety and efficacy of terbinafine 250 mg/day in patients suffering from dermatophytosis. In our study, 65% of patients in group A, 70% group B patients,achieved clinical cure after 6 weeks of terbinafine 250mg (The clinical cure was described as Grade I response in improvement). Mycological cure was 100% in patients of group A and 90% in patients of group B after 6 weeks of daily terbinafine 250mg. In this survey, Terbinafine was well tolerated by the patients with only 12% of patients reporting the adverse effects. All the adverse effects were of mild to moderate severity and due to any incident, none of the patients interrupted treatment. Adherence to the medication was good across all the groups.

Limitations: Studies with more sample size to resolve the deficiencies of the present study are needed. The probability of observer bias due to the methodology and nature of study while interpreting the results cannot be ruled out.

Conclusions

While terbinafine resistance is uncommon in clinical practice, its occurrence is on the increase.

Relapses and incomplete cure and are usually seen with standard terbinafine therapy. Our analysis indicates that Terbinafine 250 mg/day should be given for more than 6 weeks for clinical and mycological cure or till complete clearing of lesions. Concurrent use of DSMO + CSB with KOH is more sensitive than KOH alone for determining the presence of fungal elements.

Ethical Clearance: Taken from institutional ethics committee.

Source of Funding: Self.

Conflict of Interest: Nil.

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