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Comparison of Efficacy and Safety of Oral Use of Terbinafine and Itraconazole for the treatment of Tinea paedis: A Randomized Controlled Parallel Group Open Labeled Trial with Clinico-Mycological Correlation

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Abstract

Treatment of tinea paedis is very crucial with the different antifungal drugs. The purpose of the present study was to compare the efficacy and safety of oral use of terbinafine and itraconazole for the treatment of tinea paedis. This study was a double-blind, randomized, single-center clinical trial. The patients were randomly allocated to receive a daily dose of terbinafine 500 mg daily for 4 weeks (Group I) or 200 mg of itraconazole for 4 weeks daily (Group II). The primary efficacy criterion was mycological cure, defined as negative results on microscopy and culture at the end of follow-up and no requirement of second intervention treatment. Secondary efficacy criteria included clinical cure without second intervention treatment and mycological and clinical relapse rates. A total of 50 patients were included in this study, it was observed that majority patients were age belonged to 31-40 years in both groups. Regarding gender distribution of the study patients, it was observed that male were predominant in both groups, which was 20(80.0%) in group A and 19(76.0%) in group B. All hyperkeratotic patients were shown 100.0% cases of clinical response. However, interdigital lesion were recovered in 7(100.0%) cases in group A and 6(85.7%) cases in group B. In conclusion, tinea paedis is significantly improved by both drugs, without significant difference after 8 weeks follow-up.

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Introduction

Tinea pedis is a common superficial fungal infection of the foot.[1] Causes include *Tricophyton rubrum*, *Tricophyton mentagrophytes* and *E floccosum*. Although tinea pedis often spreads among household members, it is uncommon in young children.[2-3] Individuals with Trisomy 21 or immune compromise have an increased susceptibility to dermatophyte infections. Onychomycosis fungal infections of fingernails and toenails may be caused by dermatophytes and less likely by non-dermatophytes.[4]

Many topical antifungals are effective against tinea pedis.[5] Drying agents, such as Burow's solution, may be a useful adjunct for macerated or vesicular lesions. Recurrence of the infection can be prevented with good foot hygiene. For infections involving the toenails (onychomycosis), topical antifungal lacquers are an effective first-line therapy. However, oral therapy with terbinafine is indicated for refractory cases.[6] A prolonged course of oral therapy of at least 6 weeks for fingernail infections and 12 weeks for toenail infections is needed for cases where the nail matrix is involved. Treatment may sometimes be required for months to a year. Terbinafine has excellent action against dermatophytes, but is less effective for *Candida onychomycosis*, and these cases are best treated with azoles.[7]

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Nail clippings sent for culture allow differentiation between dermatophyte and non-dermatophytic fungal nail infections. In difficult-to-clear infections, referral to an infectious diseases specialist is highly recommended. There are no established paediatric dosing guidelines for oral itraconazole to manage superficial mycoses.[8-9]

The purpose of the present study was to compare the efficacy and safety of oral use of terbinafine and itraconazole for the treatment of tinea paedis. There has been an increase in the incidence of terbinafine resistance with increasing numbers of clinical failures and relapses.[10] One of the principal mechanisms of antifungal resistance is a decrease in effective drug concentration.[11] Terbinafine was reported to be efficacious and safe in dermatophytosis with fewer failure rates at higher doses of 500 mg/day.[12]

Itraconazole is another antifungal drug which acts by inhibiting cytochrome P450-dependent enzyme, hence interfering with the demethylation of lanosterol to ergosterol. It has shown good results in the treatment of dermatophytosis at doses of 100 mg once a day for 2 weeks and 200 mg once a day for 7 days.[11,13] Because of frequent relapses at short intervals, some physicians have used it in doses of 200 mg once a day for prolonged periods.[14] It has been observed that there has been widespread resistance to various antifungal agents used in conventional doses with an increase in relapse rates prompting a need to find an effective first-line antifungal drug and appropriate dosage and duration schedule to achieve maximum results with fewer relapses. Hence, the present study was conducted to compare the efficacy of oral terbinafine versus itraconazole in the treatment of tinea corporis and tinea cruris.

Methodology

Study Design and Settings: This randomized control trial was performed in patients of both genders aged 18 years and above with clinical diagnosis of tinea pedis confirmed by potassium hydroxide (KOH) test. We excluded pregnant and lactating women and patients with preexisting renal and hepatic diseases, cardiac failure, or a history of hypersensitivity to the study medications from our study. Patients receiving treatment with systemic immunosuppressive drugs during the study or in the past 2 weeks before enrolling in the study were also excluded from the study.

Randomization and Allocation: The patients were randomly allocated to receive a daily dose of terbinafine 500 mg daily for 4 weeks (Group I) or 200 mg of itraconazole for 4 weeks daily (Group II). Patients were followed up after 2 weeks and 4 weeks of the study period. At each visit, clinical response was noted including pruritus, erythema, and scaling. These were rated as clinical scores 0–3, 0 – absent, 1 – mild, 2 – moderate, and 3 – severe.

Follow Up and Outcomes Measures: Global clinical evaluation was done, and the response was noted accordingly as healed, marked improvement, considerable residual lesions (more than 50%), no change, or worse. KOH examination was done at the time of enrolling the patient and at the end of the 4th week. Liver function tests were done at the start of therapy and after 2 weeks of therapy. Monitoring of signs and symptoms for any adverse cardiac event was done at each visit, especially for high-risk patients (diabetics and hypertensive) on itraconazole. Patients were considered cured when there was

an absence of scaling, erythema, and pruritus, and KOH was also negative. Post-inflammatory pigmentary changes were not taken into consideration.

Statistical Analysis: Statistical analysis was performed by Windows based software named Statistical Package for Social Science (SPSS), version 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Continuous data were expressed as mean, standard deviation, minimum and maximum. Categorical data were summarized in terms of frequency counts and percentages. The Chi-square test was used for the comparison of categorical variables and the Student t-test was applied for continuous variables. Every effort was made to obtain missing data. A two-sided P value of less than 0.05 was considered to indicate statistical significance. Differences between the case and control were tested.

Ethical Clearance: The study was approved by the Institutional Ethics Committee, and informed consent was taken from all patients before recruiting.

Results

A total of 50 patients were included in this study, it was observed that the majority of patients were aged belonged to 31-40 years in both groups. Regarding the gender distribution of the study patients, it was observed that males were predominant in both groups, which were 20(80.0%) in group A and 19(76.0%) in group B (Table 1). Chronic Hyperkeratotic type was the same in both groups which were 32.0% cases in group A and 32.0% cases in group B (Table 2).

Table 1: Distribution of the patients by age (n-50)

Variables	Group A (n=25)	Group B (n=25)	P value
Age Group			
Less Than 20 Years	0(0.0%)	1(4.0%)	0.423
21 to 30 Years	5(20.0%)	4(16.0%)	
31 to 40 Years	11(44.0%)	14(56.0%)	
41 to 50 Years	9(36.0%)	5(20.0%)	
More Than 50 Years	0(0.0%)	1(4.0%)	
Gender			
Male	20(80.0%)	19(76.0%)	
Female	5(20.0%)	6(24.0%)	

Group A: Patients treated with Terbinafine; Group B: Patients treated with Itraconazole

Table 2: Distribution of Clinical Type of Tinea Pedis (n=50)

Clinical type	Group A	Group B	P value
Chronic Hyperkeratotic	8(32.0%)	8(32.0%)	1.00
Chronic Interdigital	7(28.0%)	7(28.0%)	
Vesico-bullous	6(24.0%)	6(24.0%)	
Mixed type	4(16.0%)	4(16.0%)	
Total	**25(100.0%)**	**25(100.0%)**	

All hyperkeratotic patients were shown 100.0% cases of clinical response. However, interdigital lesion were recovered in 7(100.0%) cases in group A and 6(85.7%) cases in group B (Table 3).

Table 3: Clinical Response in among Study Population

Clinical Pattern	Group A	Group B
Hyperkeratotic	8(100.0%)	8(100.0%)
Interdigital	7(100.0%)	6(85.7%)
Vesico-bullous	5(83.3%)	5(83.3%)
Mixed type	3 (75.0%)	2(50.0%)
Total	**23(92.0%)**	**21(84.0%)**

Considering the side effects of the patients, it was observed that in group A, the majority of 5(20.0%) patients had nausea and in group B it was 7(28.0%) patients (Table 4).

Table 4: Distribution of the patients by side effects (n=50)

Side effects	Group A	Group B
Nausea	5(20.0%)	7(28.0%)
Diarrhoea	2(8.0%)	7(4.0%)
Abdominal Cramp	2(8.0%)	0(0.0%)
Fatigue	0(0.0%)	1(4.0%)
Headache/Tinnitus	0(0.0%)	0(0.0%)
Elevated liver enzyme	0(0.0%)	1(4.0%)

Discussion

Tinea pedis is the most common fungal infection.[3] It may last for a long time and may come back after treatment. The affected areas are usually itchy, painful or asymptomatic.[14] It ranges from mild to severe. They may persist or recur but they generally respond to treatment. Long term medication and preventive measures may be needed. Several systemic antifungal drugs have been used to treat Tinea pedis. Many of these agents have considerable adverse effects on the GIT, and hepatic system but Terbinafine has a little side effect on the GIT and hepatic systems'. This prospective study was carried out with an aim to compare the efficacy and safety of Terbinafine over Itraconazole in the treatment of Tinea pedis and to monitor the adverse effects encountered during therapy followed by treatment outcome. A total of 50 patients having tinea pedis patients attended the department of Dermatology & Venereology, OPD, Combined Military Hospital Dhaka Cantonment, from January 2013 to July 2013, were included in this study. About 25 patients were treated with Terbinafine and rest 25 patients were treated with Itraconazole considered as group A and group B respectively. Age below 18 years or above 60 years, pregnant and lactating mothers, patients taking other anti-fungal systemic drugs, patients suffering from liver and kidney diseases and patients/attendants unwilling to give informed consent to take part in the study were excluded from the study. The present study findings were discussed and compared with previously published relevant studies. The majority of patients belonged between 31 to 40 years age in both groups which is differing from other studies.[15] In this current series it was observed that married patients were predominant in both groups, which were 88.0% and 100.0% in group A and group B respectively.

In the present study, a total of 50 patients were involved. Males 39(78.0%) were more predominant in the study than females 11 (22%) which is consistent with other studies.[16] In this study it was observed that Tinea pedis were more common in male subjects, which was 80.0% in group A and 76.0% in group B. In another study has shown 40.0% of cases and 55.6% of cases were males in Terbinafine and Itraconazole group respectively. Sex distribution was observed more in males (70.0%) than in female (30.0%) by another study.[17] In each study group, male and female ratio was equally observed in other studies.[18-20] In Bangladesh less female predominance may be due to the fact that female patients report less frequently because of a lack of health consciousness and religious bindings.

In this study, most common clinical variant was found chronic hyperkeratotic 16 (32%) followed by chronic interdigital 14(28%) which is also

different from another study, where they found chronic interdigital type was most common. Two groups of people were group A with terbinafine 250 mg daily and group B with itraconazole 200 mg daily for 14 days. We evaluated weekly during treatment and 2 weeks after cessation of therapy and finally at 8 week to see the clinical improvement and adverse effects. The clinical response was rated as marked improvement (>75%), significant improvement (over 50% and <75%) and moderate improvement (<50%) and no change or mild improvement. The clinical response was found in chronic hyperkeratotic (08/08, 08/08); chronic intertriginous type (07/07, 07/06); vesiculobullous type (06/05, 06/05); mixed type (04/03, 03/02) in group A and group B respectively.

On average 92% clinical improvement was found in group A and 84% in group B. In a study[21] it was compared 2 weeks of terbinafine at 250 mg/day to 2 weeks of itraconazole at 100 mg/day in tinea pedis, they found terbinafine superior to itraconazole for clinical cure (94% vs 72.4%). Takinchi *et al*[21] studied and found 89.3% improvement in tinea pedis with 1 week treatment with 250 mg terbinafine. A study was done by Barnatson *et al*[22] and found 72% improvement with 250 mg of terbinafine for 1 week in tinea pedis. Hay *et al*[23] compared 2 weeks of oral terbinafine (250mg/day) with 4 weeks of oral itraconazole (100mg/ day) and the cure of the terbinafine group was 78% in tinea pedis. Using a similar regimen, Wahab *et al*[24] treated tinea pedis and found 86% improvement. In another study[15] it has found 63% improvement with 400mg/day for 1 week with Itraconazole and 75% in 100mg/day with itraconazole for 1 month at the end of 6 weeks follow up period. In a study[17] it has found 81% improvement of tinea pedis with 400mg/day for 1 week and 75% with 100mg/ day for 4 weeks with itraconazole at the end of 6 weeks follow up period. E. So comparing the other studies with our study revealed some of the studies are almost consistent with our result and some of the studies are slightly differing from the cur study.

In this present series, it was observed that the majority of patients had nausea (20.0%) followed by 8% diarrhoea in group A. On the other hand, in group B, most of the patients had nausea (28.0%), followed by 4.0% fatigue, and 4.0% diarrhoea and only 01 patient found elevated liver enzyme but does not exceed the upper limit. The side-effects were mild and tolerable in terbinafine group. Eighty percent of patients in the terbinafine group had transient, mild to moderate nausea. None of the patients in any group discontinued the treatment because of the drugs adverse effects. It is significantly important to mention that side effects were minimum in both groups of patients observed by other studies.[21,23]

There are some limitations of the study. The study population was selected from one selected hospital in Dhaka city, so that the results of the study may not reflect the exact picture of the country. The present study was conducted in a very short period of time. The small sample size was also a limitation of the present study. Therefore, in the future further study may be under taken with a large sample size.

Conclusion

In conclusion, tinea paedis is significantly improved by both drugs. Both drugs are well tolerated in the short courses of treatment. Terbinafine may represent a good alternative in the treatment of Tinea pedis in those patients unable to take Itraconazole or other available

drugs due to contraindication or toxicity. More studies with a larger population size are required to confirm these results.

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