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Original Article

Comparison of Efficacy of Double Dose Oral Terbinafine versus Itraconazole in the Treatment of Dermatophyte Infections of Skin

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ABSTRACT

Objective: To compare the efficacy of double-dose oral Terbinafine and Itraconazole in treating dermatophytic infections.
Study Design: Randomized controlled trial (ClinicalTrials.gov: NCT04880980).
Setting and Duration of Study: Department of Dermatology, Pak Emirates Military Hospital, Rawalpindi Pakistan, from Mar 2021 to Mar 2022.
Methodology: One hundred and twenty patients with dermatophyte infections of the skin (i.e., *tinea corporis and cruris*) diagnosed by clinical presentation and KOH mount were included in this study. After randomization, patients were divided into two groups. Group-A was managed with double-dose oral Terbinafine, while Group-B was managed with double-dose oral Itraconazole. Clinical response and side effects were seen and recorded initially at two weeks and then at four weeks. Efficacy and adverse effects were compared in both groups at the end of four weeks.
Results: Out of 120 patients with dermatophyte infections of the skin included in the study, 59(49.2%) took double-dose oral Terbinafine while 61(50.8%) took double-dose oral Itraconazole after randomization. It was revealed that Itraconazole was more efficacious in achieving cure at the end of 4-weeks as compared to double dose Terbinafine (p-value=0.001), while adverse effects studied were not statistically significant or different in both the groups (p-value>0.005).
Conclusion: This randomized controlled trial showed that double dose oral Itraconazole was more efficacious in treating dermatophyte infections of the skin (i.e., *Tinea corporis and cruris*) compared to double dose oral Terbinafine. Adverse effects were minimal in both groups and were not specially related to any of these medications.

Keywords: Dermatophyte infections, Double dose, Itraconazole, Terbinafine.

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INTRODUCTION

Fungal infections are one of the most commonly encountered infections in the clinical practice of physicians from various specialities.[1] Multiple modalities have been used to manage fungal infections involving the skin of various body parts. Topical treatment usually remains the treatment of choice in most cases, but some patients require systemic therapy.[2,3] Oral antifungal medications of various classes remain a priority for systemic treatment.[4] Parenteral treatment is usually reserved for severe or high-risk cases or patients who cannot take oral medications.[5,6]

Various treatment options remain in practice for dermatophyte infections. Kaul *et al*. concluded that topical azoles and allylamines should be preferred for treatment in pregnancy as well as at both extremes of age. Oral Itraconazole was also a preferred therapy in the elderly and children.[7] Bhatia *et al.* in concluded that Itraconazole had a higher cure rate than Terbinafine for treating *tinea corporis and cruris*.[8] Sahoo *et al.* highlighted that both options were equally effective in managing dermatophyte skin infections.[9]

Local weather and many other factors predispose our population to fungal infections of various parts of the skin. Therefore, the treating team may weigh systemic treatment options according to efficacy and safety before they can be used on a particular patient. Haroon *et al.* summarized the epidemiological findings related to dermatophyte infections in Pakistan.[10] Limited local data has been generated regarding the safety and efficacy of oral antifungal agents. In addition, there is an emerging trend of resistant dermatophyte infections not responding to conventional doses of available systemic antifungal therapies. Therefore, we planned this study to compare the efficacy and safety of double-dose oral Terbinafine versus double-dose oral Itraconazole in treating dermatophyte skin infections at the dermatology department of our tertiary care hospital in Rawalpindi, Pakistan.

METHODOLOGY

The randomized controlled trial (Clinical Trials. gov, having ID: NCT04880980) was conducted at the

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Department of Dermatology, Pak Emirates Military Hospital, Rawalpindi Pakistan, from March 2021 to March 2022. Ethical approval (letter no: A/28/EC/258/2021 dated 25/02/2021) was sought from the Ethical Committee. The sample size was calculated by WHO Sample Size Calculator with the response to Itraconazole and Terbinafine as 16.7% and 29.6%.[8] Non-probability consecutive sampling technique was used to gather the sample for this trial.

Inclusion Criteria: Patients of either gender, aged 15 to 50 years, with dermatophyte infections diagnosed by clinical presentation and Potassium hydroxide (KOH) mount were included in the study.

Exclusion Criteria: Patients with uncontrolled diabetes mellitus or hypertension, individuals having two or more co-morbidities or known cases of chronic liver disease were excluded. Those who had known allergies to any one of the medications used in the trial were also excluded. Women who were either pregnant or breastfeeding babies were excluded. Patients who stopped medication without any obvious reason or lost to follow-up were not included in the final analysis.

Written informed consent was also taken from all the study participants after a complete description. *Tinea corporis* and *cruris* were diagnosed by clinical presentation and KOH mount. To ensure randomization, the lottery method was used to allocate the patients to study groups. Group-A was managed by a double dose of oral Terbinafine (250mg twice daily for 2 to 4 weeks, depending upon response)13 while Group-B was managed by a double dose of oral Itraconazole (100mg twice daily for 2-4 weeks, depending upon response).[11,12] Response of treatment was recorded at 2 and 4 weeks in terms of both clinical (resolution of erythema, pruritus and scaling) and mycological (negative KOH mount test) cure. Liver Function Tests were checked at the start and two and four weeks. Common side effects studied were nausea, vomiting and deranged liver function tests.

All statistical analysis was performed using Statistics Package for Social Sciences version 24.0 (SPSS-24.0). Characteristics of participants and the distribution of the patients in two treatment groups were described by using descriptive statistics. The chi-square test was applied to look for the difference in efficacy and side effects in both groups. Differences between groups were considered significant if the *p*-values were less than or equal to 0.05.

RESULTS

One hundred and twenty patients were recruited for the study. Out of 120 patients with dermatophyte infections of the skin included in the study, 59(49.2%) took double-dose oral Terbinafine, while 61(50.8%) took double-dose oral Itraconazole after the randomization. In addition, 28(23.3%) patients were females, while 92(76.7%) were males (Table-I).

Table-I: Characteristics of Study Participants with Tinea Corporis and Cruris (n=120)

Study Parameters	n (%)
Age (years)	
Mean±SD	29.74±8.82 years
Range (min-max)	18 years - 50 years
Gender	
Male	92(76.7%)
Female	28(23.3%)
Treatment Received	
Double dose oral Terbinafine	59(49.2%)
Double dose oral Itraconazole	61(50.8%)
Response at two weeks	
Cure	85(70.8%)
No cure	35(29.2%)
Response at 4 Weeks	
Cure	102(85.0%)
No cure	18(15.0%)
Common Side Effects	
Nausea	16(13.3%)
Vomiting	05(4.1%)
Deranged Liver function tests	04(3.3%)
Others	02(1.6%)

It was revealed that double dose oral Itraconazole was more effica-cious in achieving cure at the end of 4 weeks with a cure rate of 95.1%(n=58) as compared to double dose oral Terbinafine having a cure rate of 74.6%(n=44) respectively (*p*-value=0.001), while adverse effects studied were not statistically significantly different in both the groups (*p*-value>0.005) (Table-II).

Table-II: Differences in Efficacy and Adverse Effects at Four Weeks of Treatment in Both Groups (n=120)

Factors Studied	Terbinafine Group (n=59)	Itraconazole Group (n=61)	*p*-value
Complete Cure at 4 weeks			
Yes	44(74.6%)	58(95.1%)	0.001
No	15(25.4%)	03(4.9%)	
Nausea			
Yes	10(16.9%)	06(9.8%)	
No	49(83.1%)	55(90.2%)	0.250
Vomiting			
Yes	01(1.7%)	04(6.6%)	0.168
No	58(98.3%)	57(93.4%)	
Deranged Liver Function Tests			
Yes	01(1.7%)	03(4.9%)	0.024
No	58(98.3%)	58(95.1%)	

Figure showed the clinical response to treatment in both groups at the end of 4 weeks.

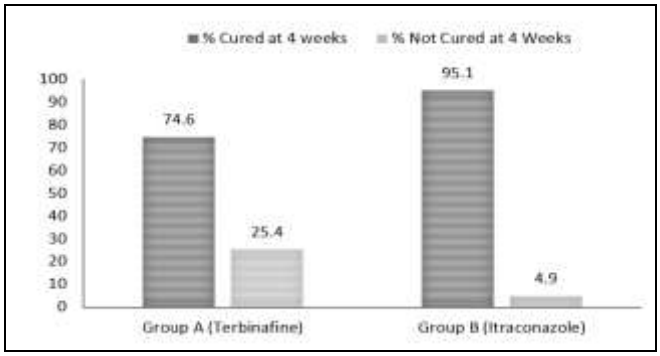

Figure: Clinical Response to Treatment between Group-A (n=59) and Group-B (n=61)

DISCUSSION

Itraconazole was a better treatment option among the two drugs used in our trial in terms of efficacy in treating Tinea corporis and cruris. However, four patients' liver function tests were deranged in total, so the comparison was not up to mark. Fungal infections can occur in patients of all age groups. If the patient is not immuno-compromised or the clinical situation is usually simple, topical treatment works in most cases. Nevertheless, in cases of severe Tinea corporis or cruris, oral treatment usually remains the mainstay in many patients. Multiple antifungal medications from various groups have been in practice.[13,14] Still, no single medication outclasses others completely in terms of efficacy and/or safety.[15] Rising trends in resistance to treatment by conventionally used antifungal agents in conventional dosages are of great concern for clinicians. The use of double-dose commercially available oral antifungal medication not only improves the cure rate in the face of emerging antifungal resistance but also shortens the duration of therapy, providing improved efficacy and economy simultaneously. Therefore, we tried to gather data in our population and conducted this trial to compare double-dose oral Terbinafine versus double-dose oral Itraconazole in the treatment of dermatophyte infections of the skin.

Bhatia *et al.* compared the efficacy of some medications we used to treat dermatophyte skin infections in our study. They used a double dose of both Terbinafine and Itraconazole.[8] Comprehensive review of their data set concluded that though Itraconazole was slightly expensive cure rate was better. In addition, the treatment duration was short, making it superior to Terbinafine for managing dermatophyte infections. Our results supported their results that Itraconazole was more efficacious than Terbinafine. Sharma *et al.* concluded that both clinical and mycological parameters were better in patients who took a combination therapy. In addition, Itraconazole was superior to Terbinafine but inferior to combination treatment.[16] We did not study the effect of combination therapy, but out of two medications, Itraconazole was superior in curing patients with dermatophytosis. Bell-Syer *et al.* revealed that Terbinafine was more effective than griseofulvin, and Terbinafine and Itraconazole were more effective than no treatment.[17] We only compared double-dose oral Terbinafine and double-dose oral Itraconazole and found that Itraconazole was more effective than the two in treating tinea corporis or cruris. Comparing more options and conducting large multicenter trials would be a better option.

Singh *et al.* showed that Itraconazole was more effective than Terbinafine.[18] Higher doses and combination treatment of the two had added advantages as a prolonged duration of treatment was required with conventional dosage for a complete cure. Our results support the results of Singh *et al.* as Itraconazole was more effective, and more patients achieved cures after four weeks of treatment.

CONCLUSION

This randomized controlled trial showed that double-dose oral Itraconazole was more efficacious in treating dermatophyte infections (i.e. *tinea corporis and cruris*) than double-dose oral Terbinafine. Adverse effects were minimal in both groups and were not specially related to any of these medications.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

UAA & NI: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

NAM & JH: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

UB & MWS: Critical review, concept, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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