



ORIGINAL RESEARCH PAPER

Medical Science

AN OPEN, RANDOMIZED CLINICAL COMPARATIVE STUDY DETERMINING THE EFFICACY AND SAFETY OF ITRACONAZOLE VERSUS TERBINAFINE IN THE TREATMENT OF ONYCHOMYCOSIS.

KEY WORDS:

Onychomycosis, Itraconazole, Terbinafine

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ABSTRACT

Background: Onychomycosis, also known as tinea unguium, is a fungal infection of nail unit. **Objective:** To compare the efficacy and safety of itraconazole versus terbinafine in the treatment of onychomycosis. **Study Design:** An open, randomized, prospective clinical comparative study was done on 70 patients of onychomycosis attending skin OPD of SNMC Agra UP during the period from august 2019 to march 2021. 35 patients were randomly assigned to receive oral itraconazole 200mg once a day for 12weeks in group A and other 35 patients received oral terbinafine 250mg once a day for 12weeks in group B. The patients were evaluated at the start of the therapy and thereafter at 4,8,12,24 weeks. **Results:** In group A (Itraconazole), 62.85% of patients showed mycological cure and 51.43% of patients showed clinical cure. In group B (Terbinafine), 74.28% of patients showed mycological cure and 62.86% of patients showed clinical cure. The difference in cure rates between two groups was not statistically significant (p>0.05). Adverse effects were seen in 17.14% of patients in group A and 20% of patients in group B. None of these effects was significant enough to discontinue therapy. The difference in adverse effects between two groups was not statistically significant (p>0.05). **Conclusion:** Both itraconazole and terbinafine were equally effective and safe in the treatment of onychomycosis. Both drugs were well tolerated and were relatively free of major adverse effects.

INTRODUCTION

Onychomycosis is a fungal infection of nail unit caused by dermatophytes, yeast and nondermatophyte moulds, which gradually destroys the nail plate.^[1]

It is a frequent nail disease that causes various complications such as physical and occupational limitations due to loss of part or all of a nail bed, prolonged standing and walking are impaired in toenail onychomycosis, infected nails serve as a chronic reservoir of fungal infection, can promote to secondary bacterial infection and significantly impair health-related quality of life.^[2]

Management of onychomycosis include topical or systemic antifungal therapy, surgical interference and nail debridement.^[3] Patients are advised for proper general care of their nails. The aim of treatment is to eradicate the organism as demonstrated by microscopy and culture, this is primary end-point. Clinical improvement and clinical cure are secondary end-points. Main goals are to reduce morbidity and to prevent complications.^[4]

The reported prevalence of onychomycosis varies from 0.5% to 5% in India^[5] and from 2% to 8% worldwide.^[6]

Treatment of onychomycosis is mainly based on systemic therapy. Antimycotics used earlier griseofulvin and ketoconazole had their limitation because of side effects such as nausea, headache, skin rash, hypersensitivity, drug interaction, hepatotoxicity, longer duration of treatment and frequent relapse after the cessation therapy. Newer antifungal agents like terbinafine and itraconazole are in use for the treatment onychomycosis because of their better pharmacokinetic profile like fast penetration into nail and persist there for many months even after stopping the therapy as these drugs have high affinity for keratin. Terbinafine, an allylamine is primarily fungicidal and Itraconazole, a triazole is primarily fungistatic. Itraconazole (200mg) and Terbinafine (250mg) form the mainstay of treatment in onychomycosis but limited data is available comparing the two. Hence this study has been done to evaluate the efficacy and safety of itraconazole and terbinafine in a comparative manner to know which one is more effective and safe.

MATERIAL AND METHODS

This prospective, open label, randomized, clinical

comparative study was conducted in the Department of Clinical Pharmacology and Therapeutics in collaboration with Department of Dermatology at S.N. Medical College and Associated Hospital, Agra (U.P.), during the period from august 2019 to march 2021. The study was approved by Institutional ethics committee and informed consent was taken from all patients before recruiting.

Inclusion Criteria

All clinically diagnosed cases of onychomycosis (e.g. nail discoloration, nail thickening, crumbling of nail plate or subungual debris) in the age group 18-70 years attending dermatology OPD, SNMC, Agra, confirmed by direct microscopic examination of nail material under potassium hydroxide (KOH) and culture in sabouraud's dextrose agar (SDA) were included in the study.

Exclusion Criteria

Patients who had applied topical antifungal medication in the previous 1 month or had used oral antifungal medication in previous 3 months, pregnant and lactating females, history of hypersensitivity to itraconazole and terbinafine, patients with nail abnormalities due to associated skin disease or any systemic disease like psoriasis, contact dermatitis, congenital nail dystrophy, lichen planus, malnutrition etc. were excluded from the study. A baseline liver function test was done in all of them and those with hepatic dysfunction in the form of jaundice and/or elevated hepatic enzymes more than twice the normal values were also excluded from the study.

Study Procedure

A total of 100 patients were screened, 30 of whom were excluded from the study because of negative results on mycological examination, withdrawal of consent or irregular follow up. Hence, a total of 70 patients were enrolled in the final study. The patients were clearly explained about the nature of the study and a written consent was taken for their participation in the study. All patients were assigned individual identification numbers and were divided randomly and equally into two groups (A and B) using a table of random numbers. 35 patients were assigned to receive oral itraconazole 200mg once a day for 12weeks in group A and other 35 patients received oral terbinafine 250mg once a day for 12weeks in group B. The patients were evaluated at the start of the therapy and thereafter at 4,8,12,24 weeks. During these visits, they were assessed for growth of normal and healthy appearing nail plate and asked for any adverse

effects of the drugs. In addition, microscopic examination of nail material under KOH and culture of nail material in SDA was also done. Laboratory investigations including complete blood count, liver and kidney function tests were done in all patients, at the onset and at the completion of study.

- Evaluation of efficacy is done by mycological cure and clinical cure.
- Mycological cure (M.C.) – It is defined as negative microscopy under potassium hydroxide(KOH) and negative culture in Sabouraud's Dextrose Agar(SDA).
- Clinical cure(C.C.) – It is defined as completely normal appearing nail.
- Evaluation of safety is done clinically and adverse event reported.

Statistical Analysis

At the end of the study, the results were compiled, tabulated and analyzed using suitable statistics like percentages and chi-square tests. A $p < 0.05$ was taken as significant.

RESULTS

Table-1, Figure-1 shows the age wise distribution of cases in both groups. Maximum no. of cases (28.57%) were in age group 31-40 years in group-A and 41-50 years in group-B. In our study, disease was more common in females (57.14%) as compared to males (42.86%) [Table-2, Figure-2]. In this study, fingernails were more common being involved in 71.43% of patients while toenails were involved in 28.57% of patients [Table-3, Figure-3]. In group A, 62.85% of patients showed mycological cure and 51.43% of patients showed clinical cure. In group B, 74.28% of patients showed mycological cure and 62.86% of patients showed clinical cure [Table-4a, 4b; Figure-4a, 4b]. The difference in cure rates between two groups was not statistically significant ($p > 0.05$). Table-5, Figure-5 shows adverse effects seen in 17.14% of patients in group A (gastric upset-4, altered taste-1, headache-1) and 20% of patients in group B (gastric upset-4, altered taste-2, headache-1). None of these effects was significant enough to discontinue therapy. The difference in adverse effects between two groups was not statistically significant ($p > 0.05$).

Table 1: Age Wise Distribution Of Patients In Both Groups

Age groups (yrs.)	Group A (Itraconazole)		Group B (Terbinafine)		Overall	
	No.	%	No.	%	No.	%
18-30	9	25.71	5	14.29	14	20.00
31-40	10	28.57	9	25.71	19	27.14
41-50	6	17.14	10	28.57	16	22.86
51-60	2	5.71	9	25.71	11	15.71
61-70	8	22.86	2	5.71	10	14.29
Total	35	100.00	35	100.00	70	100.00

Chi-square value=2.018
p-value= 0.732 NOT SIGNIFICANT

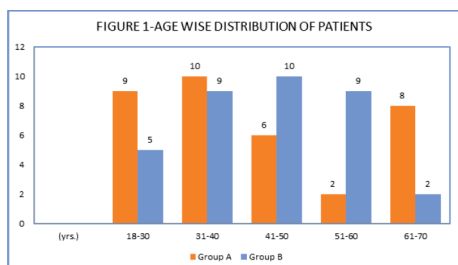


Table 2: Sex Wise Distribution Of Patients In Both Groups

Sex	Group A (Itraconazole)		Group B (Terbinafine)		Overall	
	No.	%	No.	%	No.	%
Female	15	42.86	25	71.43	40	57.14
Male	20	57.14	10	28.57	30	42.86

Total	35	100.00	35	100.00	70	100.00
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Chi-square value=5.833
p-value= 0.0157 SIGNIFICANT

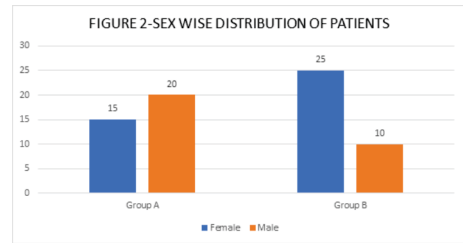


Table 3: Nail Affected Of The Patients In Both Groups

Nail affected	Group A (Itraconazole)		Group B (Terbinafine)		Overall	
	No.	%	No.	%	No.	%
Finger nails	30	85.71	20	57.14	50	71.43
Toe-nails	5	14.29	15	42.86	20	28.57
Total	35	100.00	35	100.00	70	100.00

Chi-square value=7.00
p-value= 0.0081 SIGNIFICANT

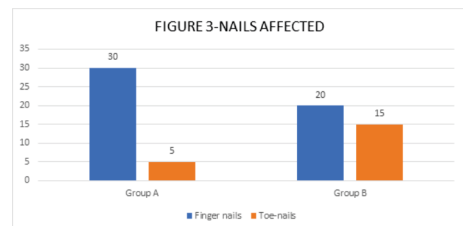


Table 4: Evaluation Schedules Of The Patients In Both Groups

Table 4 (a): Mycological Cure (MC) Analysis

Weeks of follow-up	Group A (Itraconazole)		Group B (Terbinafine)	
	No.	%	No.	%
4 weeks	0	0	0	0
8 weeks	0	0	0	0
12 weeks	12	34.29	14	40.00
24 weeks	22	62.86	26	74.29

Chi-square value=0.0007
p-value= 0.979 NOT SIGNIFICANT

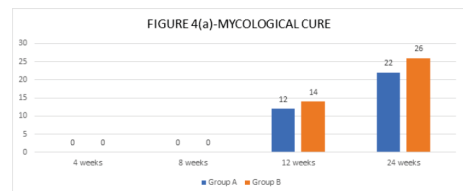


Table 4 (b): Clinical Cure (CC) Analysis

Weeks of follow-up	Group A (Itraconazole)		Group B (Terbinafine)	
	No.	%	No.	%
4 weeks	0	0	0	0
8 weeks	0	0	0	0
12 weeks	10	28.57	12	34.29
24 weeks	18	51.43	22	62.86

Chi-square value=0.0012
p-value= 0.972 NOT SIGNIFICANT

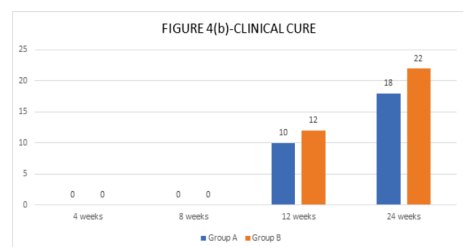
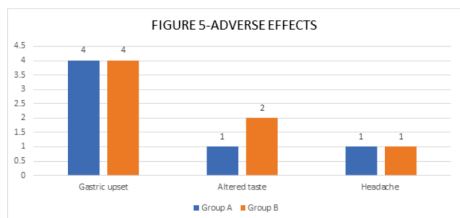


Table 5: Adverse Effects In Both The Groups

Adverse effects	Group A (Itraconazole)		Group B (Terbinafine)	
	No.	%	No.	%
Gastric upset	4	11.43	4	11.43
Altered taste	1	2.86	2	5.71
Headache	1	2.86	1	2.86
Total Patients	6	17.14	7	20

Chi-square value=0.258
p-value= 0.879 NOT SIGNIFICANT



DISCUSSION

Successful treatment of onychomycosis is still challenging. Traditional agents like griseofulvin has narrow spectrum, high relapse rate and require longer duration of therapy.^[7] Ketoconazole carries risk of hepatotoxicity. Newer anti-fungal agents such as itraconazole and terbinafine are in use for the treatment of onychomycosis now a days because these drugs have better pharmacokinetic profile like prompt penetration of the nail and nail bed, persistence in the nail for months even after stopping therapy and fewer adverse effects.^[8] Itraconazole is in the triazole family of medication, it inhibits the fungal-mediated synthesis of ergosterol, via inhibition of lanosterol 14 α -demethylase. Terbinafine is an allylamine antifungal agent, it acts by inhibition of squalene epoxidase synthesis so inhibiting ergosterol formation that makes it fungicidal.

Mycological cure and clinical cure findings in our study is in accordance with reports by Arenas R. et al and Tosti A. et al^[9,10] but contrast with the finding by other authors.^[11,12]

Clinicians need to be well informed about current treatment options, their success rate and limitations and the uncertainty of individual outcomes defined. The management of the patient with onychomycosis is time-consuming, requiring medical assessment, detailed explanation with counseling and reassurance and continued supervision of any medical treatment.

Limitations of our study include its small sample size and short duration of follow ups. Due to short duration of follow ups, we could not evaluate patients relapse rates. This study was conducted at a single centre, hence these findings cannot be generalized. For this purpose, further multicenter studies with larger sample size are required.

CONCLUSION

In this comparative study, it is concluded that both itraconazole and terbinafine are equally effective and safe in the treatment of onychomycosis. Both drugs were well tolerated and adverse events reported or observed were within the known safety profile of each drug.

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None

Conflicts Of Interest

None

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