

Original Article

Comparison of efficacy of continuous terbinafine versus intermittent itraconazole in the treatment of toenail onychomycosis

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Abstract *Objective* To compare efficacy of continuous terbinafine versus intermittent itraconazole in the treatment of onychomycosis.

Methods This randomized controlled trial was conducted in the Department of Dermatology Nishtar Medical College and Hospital Multan from 20-05-2018 to 20-11-20. A total of 64 patients meeting inclusion criteria were randomly allocated in to two groups by lottery method. Group A, having 32 patients, was treated with 250 mg terbinafine, given orally once daily for 12 weeks while group B, having 32 patients, was treated with itraconazole 400 mg per day (orally twice a day as 200 mg per dose), given intermittently for one week per month followed by a 3 week drug free period for a total duration of 12 weeks. Patients were called for follow up at 16 week and efficacy was documented.

Results Of these 64 study cases, 39 (60.9 %) were male patients while 25 (39.1 %) were female patients. Mean age of our study cases was 52.67±9.09 years. Our study results have indicated that majority of our study cases i.e. 39 (60.9 %) were aged more than 50 years. Mean disease duration was 4.45±2.53 years and 57 (89.1 %) had duration of illness more than 1 year. Efficacy was noted in 33 (51.6%) of our study cases, it was 23 (71.9%) in group A while efficacy was noted in 10 (31.2%) in group B patients ($p=0.002$).

Conclusion Our study results support the use of oral terbinafine in the treatment of toenail onychomycosis as compared with intermittent itraconazole as oral terbinafine was significantly highly efficacious.

Key words

Toenail onychomycosis, terbinafine, itraconazole.

Introduction

Nail abnormalities are prevalent worldwide. Onychomycosis is the most common cause of

toenail deformations in adults, accounting for up to 50% of all nail disorders.^{1,2} Onychomycosis has worldwide distribution and is estimated to affect approximately 2-10% of the general adult population in developed countries.³⁻⁵ Predisposition factors are numerous and include increasing age, humidity, occlusive footwear, repeated nail trauma, genetic predisposition, and concurrent disease, such as tinea pedis, diabetes mellitus, poor peripheral circulation and

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immunosuppression.⁴

Often a silent and overlooked fungal infection, onychomycosis is a cause of morbidity when associated with wounds and bacterial infectious complications, particularly in individuals with a compromised health status. In addition, it can be a cause of psychosocial stress. These facts often prompt treatment with antifungals, without previous mycological evaluation. Still, not all dystrophic nails are onychomycosis, while inadvertent antifungal treatment has economic costs and is associated with side effects. In most cases, the fungal pathogen, usually a dermatophyte of *Trichophyton spp.* that is present within adjacent periungual skin of the toes, gains access to the nail unit distally by invading past the hyponychium into the nail bed and the adjacent ventral surface of the nail plate.⁶ The large toenails are most commonly affected clinically; however, other toenails commonly exhibit visible changes characteristic of onychomycosis. Concomitant tinea pedis is often present as a source of the fungal pathogen; however, it may be subtle and considered by the patient or a clinician to be dry skin.⁷ Unlike many superficial infections involving glabrous skin, onychomycosis is well known as a disorder that is difficult to treat effectively due to the slow growth of the nail plate and the physical characteristics of the nail unit that impede drug penetration and access to the site of infection. In addition, host factors are recognized that can markedly influence therapeutic outcomes when treating onychomycosis. These include age, individual nail growth rate, overall health status, immune status, underlying medical disorders, pre-existing trauma-induced nail changes, and genetic predisposition to carriage of *Trichophyton rubrum* on pedal skin.⁸

Systemic treatments for onychomycosis now include terbinafine, an allylamine that is primarily fungicidal, and itraconazole, a triazole

that is primarily fungistatic; both represent a major therapeutic advance over griseofulvin in the treatment of this condition. For toenail infections terbinafine is usually taken continuously for 12 weeks, whereas itraconazole is taken either continuously for the same period or intermittently- that is, 1 week in 4 weeks for 12 or 16 weeks. Cure rate is 75.7% with terbinafine while 38.3% with intermittent itraconazole in treatment of toenail onychomycosis.⁹

Methods

This randomized controlled trial was conducted in the Department of Dermatology Nishtar Medical College and Hospital Multan from 20-05-2018 to 20-11-20. Patients were selected via Non-probability consecutive sampling. A total of 64 patients were enrolled meeting the inclusion criteria. Patients of both genders, aged ≥ 30 and ≤ 70 years, having onychomycosis for more than 1 month were included in the study. Patients who had taken topical antifungal treatment in 4 weeks, known cases of psoriasis, mucocutaneous candidiasis, or immunodeficiency, pregnant females or those taking oral contraceptives for more than 6 months, patients having poor compliance with therapy and lost to follow up were excluded. Total sample was divided in two equal groups. Group A, having 32 patients, was treated with 250 mg terbinafine given orally once daily for 12 weeks while group B, having 32 patients, were treated with itraconazole 400 mg per day (orally twice a day as 200 mg per dose), given intermittently for one week per month followed by a 3 week drug free period for a total duration of 12 weeks. Patients were called for follow up at 16 week and efficacy was documented.

Results

Our study comprised of a total of 64 patients



Figure 1 Onychomycosis.

Table 1 Distribution of efficacy among study cases.

<i>Efficacy (n=64)</i>	<i>Group A Frequency (%age)</i>	<i>Group B Frequency (%age)</i>
Yes n = 33 (51.6 %)	23 (71.9)	10 (31.2)
No n= 31 (48.4 %)	09 (28.1)	22 (68.8)
Total	32 (100)	32 (100)

*p = 0.002

meeting inclusion criteria. Of these 64 study cases, 39 (60.9%) were male patients while 25 (39.1%) were female patients. Mean age of our study cases was 52.67 ± 9.09 years (with

minimum age of our study cases was 35 years while maximum age was 67 years). Mean age of the male patients was noted to be 54.74 ± 8.73 years while that female patients was 49.44 ± 8.85 years ($p=0.022$). Our study results have indicated that majority of our study cases i.e. 39 (60.9%) were aged more than 50 years. Of these 64 study cases, 33 (51.6%) belonged to rural areas and 31 (48.4%) belonged to urban areas. Diabetes was present in 19 (29.7%) of our study cases. Hypertension was present in 33 (51.6%) of our study cases. Mean body mass index of our study cases was 26.14 ± 1.49 kg/m² and obesity was present in 17 (26.6%) of our study cases. Mean disease duration was 4.45 ± 2.53 years and 57 (89.1%) had duration of illness more than 1 year. Of these 64 study cases, 41 (64.1%) were illiterate and 23 (35.9%) were literate.

Efficacy was noted in 33 (51.6%) of our study cases, it was 23 (71.9%) in group A while efficacy was noted in 10 (31.2%) in group B patients ($p=0.002$) (**Table 1**). Efficacy is stratified with regards to gender, age, residential status, diabetes, hypertension, obesity, disease duration and literacy in **Table 2**.

Table 2 Stratification of efficacy with regards to gender, age, residential status, diabetes, hypertension, obesity, disease duration and literacy.

<i>With respect to</i>		<i>Group A</i>		<i>Group B</i>		<i>P value</i>
		<i>Yes</i>	<i>No</i>	<i>Yes</i>	<i>No</i>	
Gender	For male	12	08	05	14	0.054
	For female	11	01	05	08	0.011
Age	Up to 50 years	11	02	03	09	0.005
	>50 years	12	07	07	13	0.113
Residential status	Rural	10	06	05	12	0.084
	Urban	13	03	05	10	0.011
Diabetes	Yes	03	06	02	08	0.628
	No	20	03	8	14	0.001
Hypertension	Yes	09	07	05	12	0.166
	No	14	02	05	10	0.003
Obesity	Obese	07	02	00	08	0.002
	Non-obese	16	07	10	14	0.080
Duration of disease	Up to 12 months	03	00	01	03	0.143
	>12 months	20	09	9	19	0.008
Literacy	Illiterate	16	05	4	16	0.001
	Literate	07	04	06	06	0.680

Discussion

Treatment of onychomycosis includes chemical or surgical removal of the infected nail, systemic or topical drugs, pulse therapy, or a combination thereof. The treatment of onychomycosis has improved considerably over the past several decades, following the introduction of the oral antifungals terbinafine and itraconazole. However, these drugs may have side effects such as liver damage or drug interactions, which are particularly relevant in the elderly population. Further, nail infections caused by non-dermatophyte organisms, such as *Fusarium*, are especially difficult to treat.¹⁰

Our study comprised of a total of 64 patients meeting inclusion criteria of our study. Of these 64 study cases, 39 (60.9%) were male patients while 25 (39.1%) were female patients. A study conducted by Evans *et al.*⁹ has also reported 58 % male gender predominance which is close to our study results. Shemer *et al.*¹¹ from Israel also reported 59.3% male gender predominance which is close to our study results. A study conducted by Gupta *et al.*¹² from Canada has reported slight female gender preponderance which is different from our findings.

Mean age of our study cases was 52.67 ± 9.09 years (with minimum age of our study cases was 35 years while maximum age was 67 years). Mean age of the male patients was noted to be 54.74 ± 8.73 years while that female patients was 49.44 ± 8.85 years ($p=0.022$). Our study results have indicated that majority of our study cases i.e. 39 (60.9%) were aged more than 50 years. Shemer *et al.*¹¹ from Israel also reported 43.9 ± 9.8 years mean age which is similar to that of our study results. A study conducted by Evans *et al.*⁹ has also reported 50.1 ± 12.8 years mean age which is close to our study results. A study conducted by Gupta *et al.*¹² from Canada has reported 60.67 ± 1.52 years mean age which

follows our study results.

Of these 64 study cases, 33 (51.6%) belonged to rural areas and 31 (48.4%) belonged to urban areas. Diabetes was present in 19 (29.7%) of our study cases. Efficacy was seen in 5 (26.3%) of these patients. Out of these, 3 patients belonged to group A and 2 patients from B. Hypertension was present in 33 (51.6%) of our study cases. Mean body mass index of our study cases was 26.14 ± 1.49 kg/m² and obesity was present in 17 (26.6%) of our study cases. Efficacy was seen in 7 (41.1%) of these patients. All these patients belonged to group A while no efficacy was seen in any patient from group B. A study conducted by Gupta *et al.*¹² from Canada has reported similar results.

Mean disease duration was 4.45 ± 2.53 years and 57 (89.1%) had duration of illness more than 1 year. Of these 64 study cases, 41 (64.1%) were illiterate and 23 (35.9%) were literate. Shemer *et al.*¹¹ from Israel reported disease duration <10 years in 17.6% of the patients and >10 years in 82.5% of the patients.

Efficacy was noted in 33 (51.6%) of our study cases, it was 23 (71.9%) in group A while efficacy was noted in 10 (31.2%) in group B patients ($p=0.002$). Shemer *et al.*¹¹ from Israel also reported terbinafine to be highly effective in treatment of toenail onychomycosis which is following our study results. In the study conducted by Evans *et al.*⁹ patients were randomly allocated to one of four groups: terbinafine 250 mg a day for 12 weeks (T₁₂) or 16 weeks (T₁₆) or itraconazole 400 mg (four capsules of 100 mg) a day taken for 1 week in every 4 weeks for either 12 weeks (I₃) or 16 weeks (I₄). They reported cure rate of 75.7% in T₁₂ group and 80.8% in T₁₆ group, whereas a cure rate of 38.3% in I₃ group and 49.1% in I₄ group was seen. They concluded that continuous terbinafine is significantly more effective than

intermittent itraconazole in treatment of toenail onychomycosis. These findings are in compliance with our study results. A study conducted by Gupta *et al.*¹² from Canada has reported efficacy of both these drugs was comparable to each other which is different from our study results.

Conclusion

Our study results support the use of oral terbinafine in the treatment of toenail onychomycosis as compared with intermittent itraconazole as oral terbinafine was significantly highly efficacious. All clinicians treating such patients should employ oral terbinafine to attain desired clinical outcome.

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