ORIGINAL ARTICLE

EFFICACY OF ORAL VORICONAZOLE VERSUS ORAL ITRACONAZOLE, IN THE TREATMENT OF DERMATOPHYTE INFECTIONS

Maira Ali, Najia Ahmed, Seemab Khan, Afshan Kiran
Department of Dermatology, PNS Shifa, Karachi-Pakistan

Background: Dermatophyte infections are common in tropical areas with a humid climate. In recent times, it is getting extremely challenging to treat these infections because of resistance that has occurred to the conventional antifungals, which is attributed to changes in the fungal strains. Keeping in view this issue, more advanced drugs have come into being. Voriconazole is a potential such drug with promising results. **Methods:** A total of 76 patients participated in the study, they were divided into two groups, with 38 participants in each group. Group A was treated with voriconazole and group B was treated with itraconazole, for 2 weeks in patients who achieved a complete response, and 4 weeks for patients who achieved a partial response. Baseline complete blood count, Liver function tests, renal function tests, blood sugar levels, and KOH microscopy was done for every patient, and was repeated after completion of treatment. Clinical response was assessed on the basis of clearance of the lesion and negativity on KOH microscopy. **Results:** After completion of treatment with voriconazole, 32 (84.2)% of the patients achieved a complete clearance of the lesion, while 6(15.8%) of the participants achieved partial response to the treatment. Among the patients who received oral itraconazole,6 (15.7%) showed a complete response ,16 (42.1%) participants achieved a partial cure, while 16 (42.2%) patients did not show any improvement after the treatment. **Conclusion:** It is safe to conclude, that voriconazole shows better efficacy and results in treating resistant dermatophyte infections.

Keywords: Voriconazole; Dermatophytes; Itraconazole; Tinea; Resistant; Antifungal; Aropical; Response; Efficacy.

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INTRODUCTION

Superficial fungal infections are one of the most common skin infections, with an incidence of around 20–25% worldwide[1], more in negroes than Caucasians, more in rural, than in urban areas[2] predominantly caused by filamentous fungi, called “Dermatophytes”. Their mode of transmission is via direct or indirect contact with lesions of the infected people. They act by secreting keratinases, meant to degrade the keratin layer and thus, invading the superficial skin, along with structures like the hair and nails. Dermatophytes have three genres, that are; microsporium, Epidermophyton, and trichophyton.[3] Usually, these infections affect superficially, but, in some cases, they may invade deeper, especially when occurring with other bacterial infections. They are also called "ringworm infections", due to their characteristic ring like appearance. Tinea is also a term coined for these infections, and is differentiated based on the part of the body affected, for example, Tinea capitis, Tinea faceii, Tinea manuum, Tinea corporis, Tinea pedis etc. Dermatophytosis are more common in areas of greater humidity and are more common in summer than in winters, hence, being an issue of mostly the tropical regions. Another predilection to these infections, is poor hygiene and living conditions, due to overcrowding, excessive sweating and occlusive footwear.

Since years, several treatment options have been used for dermatophytosis, the commonly used ones include, oral terbinafine[4,5] and oral itraconazole[6,7]. Terbinafine acts by directly inhibiting the cytochrome P-450 enzyme, which is vital for ergosterol synthesis, an important component of the fungal cell membrane, putting a halt to the fungal activity, hence, having a fungistatic activity.[8] Itraconazole is a triazole antimycotic that inhibits 14 alpha demethylase, required for sterol synthesis, used in the synthesis of the fungal cell wall.[9] Although, the above-mentioned drugs have been successful in eradicating the infections, but still relapses were reported in patients after completion of the treatment.[10,11] With time, there have been environmental and genetic changes in the pathogens, that has led to the resistance to the first line drugs.[12,13] Hence, there was a need of the drug with a broader spectrum of the antifungal activity. Voriconazole is a potential second-generation drug.[14] that acts by inhibiting the cell membrane production by inhibiting the ergosterol synthesis, and it is

the synthesis of the ergosterol synthesis that has caught resistance.

Only one study, held in Egypt has compared the efficacy of voriconazole with itraconazole[15] which indicates a paucity of research work, with respect to this topic, especially in this region, and, Karachi, being a coastal area, is vulnerable to dermatophyte infections, which is attributed to the humid climate, demands more work in this regard. The fact that we are experiencing a resistance to the first line antifungals, resulting in poor response or relapse of the infection after completion of treatment, became the basis of our work.

In this study, we aim to compare the efficacy of two oral antifungals, namely, Itraconazole and voriconazole, for chronic and recurrent dermatophyte infections.

MATERIAL AND METHODS

This randomized control trial was registered under IRCT (ID 20210823052264N3) and trial ID (69692), after approval from the local ethical review committee (ERC/2023/DERMA/14) given on 27th April 2023. It was conducted for a period of six months, from April 2023 to September 2023, and was held at the dermatology department of the PNS Shifa hospital, Karachi.

A total of 76 patients participated in the study, inclusion criteria consisted of patients that were aged between 15 to 80 years, with recurrent and chronic dermatophyte infections, all over the body, except the who have not responded to conventional antifungals, taken for almost 4 weeks. Chronic infection is defined that has been present for more than 6 months, with proper treatment been taken. Recurrent infections are the ones in which symptoms reappear within 6 weeks of clinical cure or stopping of the treatment.

Patients of age less than 15 or greater than 80 years, with infections on the scalp, i.e., Tinea capitis and involving the nails, i.e., tinea unguum, with deranged lipid profile, liver functions or renal function tests, pregnant females, or breastfeeding mothers have been excluded from the study. A written informed consent was taken from all the participants of the study.

The patients were divided into two groups, with randomization by lottery method, into Group A, (38 patients) who were treated with oral voriconazole 200mg twice daily and Group B, (38 patients) who were treated with oral itraconazole 100mg twice daily. The patient as well as the treating physician were kept unaware of the treatment given, only the assessing physician was aware of the drug given to each patient. They were given a treatment for a period of 4 weeks, or earlier, in patients if complete response was achieved. They were called for follow-up at 2 weeks, 4 weeks, and 4 weeks after completion of the treatment, which means, after 6 weeks in patients who achieved complete response in two weeks and eight weeks, in patients who were treated for 4 weeks.

Baseline complete blood count, lipid profile, liver function and renal function tests were done, photographs were captured, and skin scrapings for KOH (Potassium hydroxide) microscopy were taken before the commencement of the treatment, and four weeks after the completion of the course. The patients were called for follow up after 4 weeks from the completion of the treatment. Clinical response was noted at the follow-up visits and the efficacy was classified as complete response, with 100% cure, which means that all the lesions healed completely and microscopy showed negative results, partial response, in which there was a cure in >50% or more than half of the total lesions, and, no response, in which the cure was only seen in one of the lesions present and microscopy was still positive.

Data was entered and analyzed by the Statistical analysis for Special Sciences 28. The qualitative variables were represented as frequencies and percentages, while the quantitative variables were presented as mean ±SD.

With a reported clinical cure in 53% of patients treated with itraconazole and 83% in patients treated with voriconazole, for recurrent dermatophytosis. The sample size was calculated using OpenEpi, Version 3, open-source calculator—SSCohort[16], with 95% confidence interval and 80% power, the sample size was calculated using the Kelsey method[17] was 76. Ratio of sample size was 1 and 38 patients were recruited in each group.

RESULTS

In this study, 76 individuals were recruited. Among these, 38 (50%) individuals were included in each of the two groups. The demographic characteristics of all the patients who are presented in table 1.

Outcome was assessed on the basis of clinical and mycological terms at the end of treatment. Treatment duration was two weeks for 58 (71.1%) and four weeks for 18 (28.9%) participants. As shown in table 2, significant improvement was seen in all domains among patients treated with voriconazole.

Overall response was assessed for all study participants. Complete cure was achieved in 47.4% of the patients being treated with voriconazole, however no patient treated with itraconazole was completely cured, and many of them did not show any response. The differences are statistically significant (p=0.00), as shown in table 3. Participants in our study reported adverse effects of raised alanine transaminases, dizziness, light headedness, mild photophobia and flashes of light, and hypoglycaemia. A comparison of both the drugs, in terms of adverse effects, as seen in our patients, is shown in table no 4.

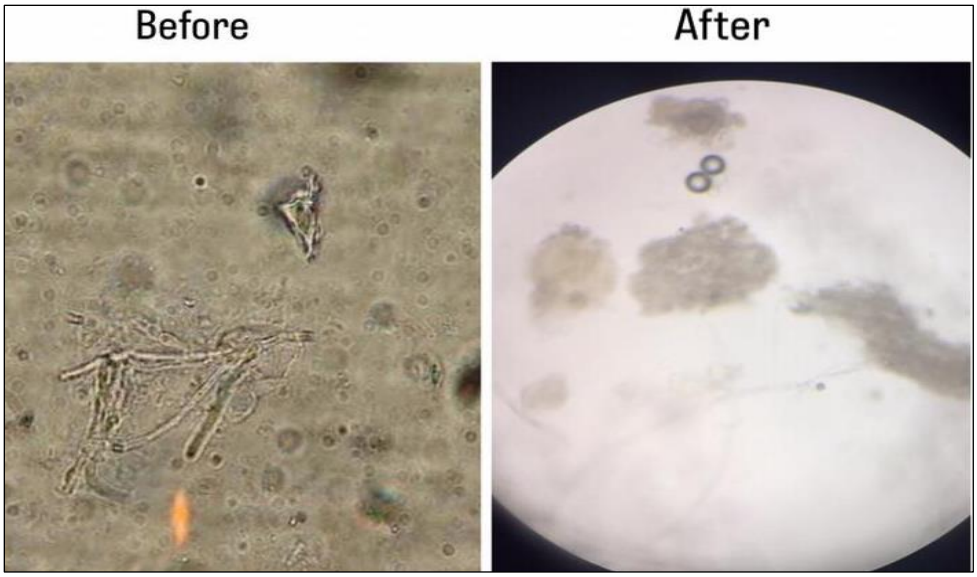

Figure-1: KOH mount in a patient, before and after treatment.

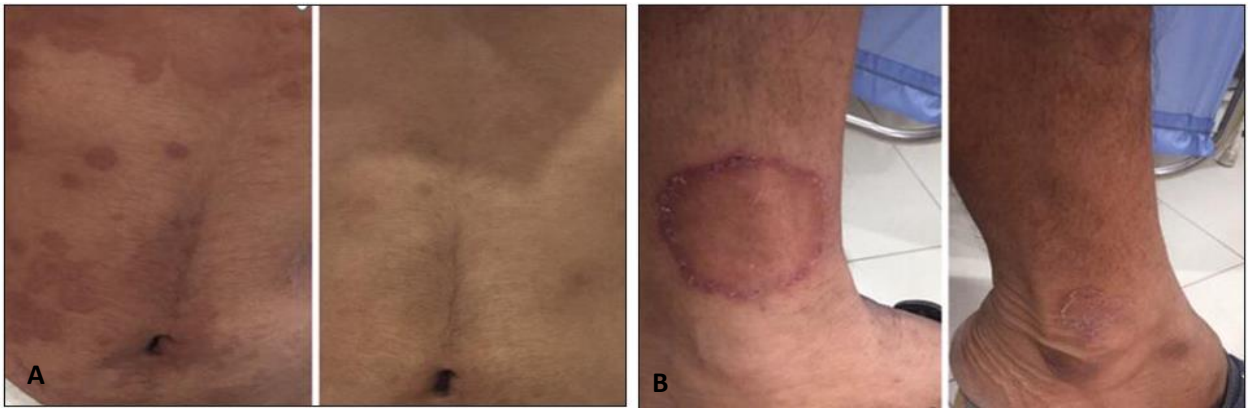

Figure-2: A before and after treatment with voriconazole, 2: B before and after treatment with itraconazole

Table-1: Demographic profile of study participants (N=76)

Demographic variables		Frequency (%)		
		Total	Voriconazole	Itraconazole
Gender	Male	39 (51.3)	17(44.7)	22(57.9)
	Female	37 (48.7)	21(55.3)	16(42.1)
Residence	Urban	46 (60.5)	28(73.7)	18(47.4)
	Rural	30 (39.5)	10(26.3)	20(52.6)
Marital status	Married	46 (56.6)	24(63.2)	19(50)
	Unmarried	33 (43.4)	14(36.8)	19(50)
Age (mean ± SD) in years		37.24 ± 13.67	36.26 ±13.10	38.21 ± 14.33

Table-2: Comparison of treatment outcome in voriconazole and itraconazole groups as calculated by SPSS

Outcome variable		Frequency (%)			P value
		Total	Voriconazole	Itraconazole	
Erythema	Improved	41 (53.9)	38 (100)	3 (7.9)	0.000
	Not improved	35 (46.1)	0	35 (92.1)	
Pruritus	Improved	47 (61.8)	38 (100)	9 (23.7)	0.000
	Not improved	29 (38.2)	0	29 (76.3)	
Lesion cleared	Yes	38 (50)	38(100)	0	0.000
	No	38 (50)	0	38 (100)	
KOH Mount cleared	Yes	39 (51.3)	38(100)	1(2.6)	0.000
	No	37 (48.7)	0	37 (97.4)	
Duration of treatment	2 weeks	58 (76.3%)	34(89.4%)	24 (63.1%)	0.000
	4 weeks	18 (23.6%)	4(10.5%)	14 (36.84%)	

Table-3: Comparison of treatment response with voriconazole and itraconazole groups

Response	Frequency (%)			P value
	Total	Voriconazole	Itraconazole	
Complete cure	38(50.0)	32(84.2)	6(15.7)	0.000
Partial response	22(28.9)	6(15.8)	16(42.1)	
No response	16(21.0)	0	16(42.2)	

Table-4 shows frequency of adverse effects in patients from both the drug groups.

Adverse effect	Voriconazole	Itraconazole
Raised ALT	8 (10%)	4 (5%)
Light headedness and dizziness	4 (5%)	1 (1.3)%
Headache	4 (5%)	0%
Mild photophobia and flashes of light	18 (24.9%)	0%
Hypoglycaemia	1(1.3%)	0%
Brownish curvy streaks along the horizontal axis of the nail bed	1 (1.3%)	0%

DISCUSSION

In recent times, it is getting extremely difficult to treat dermatophyte infections due to increased resistance against the conventional antifungals. Despite longer durations of treatment, complete and satisfactorily results could not be achieved, and hence, the use of second line antifungals have become mandatory. Voriconazole is the future in treatment of dermatophytosis with promising results, clinically and mycologicaly.[18]

Voriconazole showed complete improvement in 32 (84.2%) of the patients, which is almost similar to Chandrashekher and Poojitha *et al*[19], who reported a cure in 36 (90%) of the patients, with the same duration of treatment as ours. Additionally, Khurram *et al*[20] showed response in 181 (90%) of the patients, moreover, Lubna *et al*[21], showed complete clinical response in 55 (67.7%) of the patients. Work from other researchers have also supported our current results with voriconazole like Shawkat *et al*[22], in which complete clinical cure was observed in 82% of the patients, with a mycological improvement in 12%. Kafi *et al*[23], reported that 85% of the patients were completely cured with voriconazole, and 15% of the patients showed partial response to the drug, which is similar to our study, where 6 (15.8%) patients reported a partial cure. Itraconazole showed complete response in 6(15.7%) and partial response was seen in 16 (42.1%) patients, which is in contrary to Kousidou *et al*[24], who reported a complete response in 33 (83.3%) patients. This extreme difference in the response might be due to increased resistance to itraconazole, in recent times[25], Khattab *et al*, who conducted his study in Egypt concluded that complete clinical cure was observed in 53.3% of the itraconazole group, and 83.3% of the voriconazole group which is much better than our study. Ideally culture and sensitivity should be performed in chronic and recurrent infections. Mycological improvement was also seen in the best of the percentages in 100% of our patients, which is similar to Lubna *et.al*, which showed complete clinical response in 80(98.8%) patients, and much better than Kousidou *et.al*, which stated that response was seen in only 27 (66.7%) patients. Patients treated with voriconazole, showed improvement in all respects, like erythema, pruritis, and clearance of lesion, while the patients treated with itraconazole showed improvement in erythema in 3 (7.9%), pruritis in 9 (23.7%), and complete clearance of lesion was not achieved in any of the patients, which makes the situation alarming because it indicates how the efficacy of the conventional antifungals have reduced with time as the resistance has emerged among the fungal strains. During the course of their treatment, 10% of our patients reported raised ALT, which is a documented adverse effect, as reported by Levin *et.al.*[26] 19 (25%) patients in our study experienced mild photophobia, and 4 (5%) patients complained of headache, which was reported by Lubna *et al* and Kafi *et al*. as well.

Only one of our patients reported a rare adverse effect, not reported by any of the studies done earlier, in which a hyperpigmented curvy line was seen along the horizontal axis of the nail bed of both the thumbs of the hands, while being treated with voriconazole, which started to regress after stopping the treatment. Another patient, who was diabetic, reported hypoglycaemia, with oral voriconazole. It was confirmed with his daily blood sugar monitoring chart, that showed decreased blood sugar levels, after commencement of treatment with voriconazole. A diabetologist was taken on board, who advised a decrease in the dose of his anti-diabetics and regular monitoring of fasting and random blood sugar levels, thrice a day, during the treatment. The levels became normal after stopping of treatment and the dose was again increased as advised by the diabetologist.

Patients treated with itraconazole reported a raise in the serum ALT in 4 (5%), and light-headedness with dizziness in 1 (1.3%) of the patients. The lesser adverse effects might be attributed to the lesser duration of treatment in our patients. Despite some adverse effects, that were seen with the treatment, the frequency was much lesser than the high success rate in the response to treatment that the patients received after treatment with voriconazole.

CONSLUSION

We can safely conclude that voriconazole will be the drug of choice in the treatment of dermatophytosis, due to its

higher efficacy and better results concerning the clearance of the lesion clinically and negative results on KOH mount mycologically, with a lesser duration of treatment than that was needed with the conventional antifungals. Due to better efficacy and results achieved with voriconazole, it is important that we use the drug judiciously so that the resistance does not occur, and it keeps on giving the same result in the coming years. More work is required in this regard worldwide.

AUTHORS' CONTRIBUTION

MA: Literature search, conceptualization of study design, data collection, data analysis and interpretation, article writing. NA, SK, AK: Literature search, conceptualization of study design, data collection, data analysis and interpretation, proof reading.

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Address for Correpondence:

Maira Ali, House No R-14, The Comfort Homes, FB Area, Block-8, Karachi-Pakistan
Cell: +92 332 367 6671
Email: mairasmuian2012@gmail.com