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Comparison between oral voriconazole and terbinafine in treatment of relapse or resistant tinea corporis and cruris

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Abstract

Background: Dermatophytosis is a worldwide health-related problem. A number of antifungal agents have been introduced to treat dermatophytosis. Once it was very easy to treat with either topical or systemic antifungal agents but now become a challenge for dermatologists because of increasing resistance against conventional antifungals fluconazole, itraconazole, and terbinafine with standard dosages and duration for the last few years. So, search for an effective new oral antifungal agent now become essential.

Materials & methods: This cross-sectional comparative study was conducted in Department of Dermatology and Venereology, Dhaka Medical College Hospital, Dhaka and Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh to observe the efficacy of voriconazole and oral terbinafine in the treatment of relapse or resistant tinea corporis & cruris. Out of total tinea infected patients selected only those patients who didn't respond to routine treatment, relapsed soon after stoppage of treatment or those having persistent dermatophytic infection. A total number of 100 patients was selected and they were allocated into two groups (group-A and group-B), each of which included 50 patients. Group A was received Voriconazole (200 mg) twice daily for 4 weeks and group B patients given double dose of Terbinafine (250 mg) twice daily for 4 weeks. Patients were followed up on 2nd week (1st follow up) and 4th week (2nd follow up) to see clinical improvement and adverse effects.

Results: Mean age was found 32.4±5.7 years in group A and 31.9±5.9 years in group B. Out of 50 cases, 54.0% cases were male in group A and 56.0% in group B. Large number of respondents hailing from urban area. Socioeconomically middle class (42.0%) comprising the major percentage of the patients. Majority of patients (52%) had a duration of tinea between 6 months to < 2 years (27%). All patient (100%) had tinea corporis and tinea cruris was present in 72.0% patients. Complete cure was seen in 82% of patient in group A and 64.0% patients in group B. The difference was statistically significant, means voriconazole is highly effective antifungal agent than terbinafine.

Conclusions: Present study concluded that voriconazole is a highly effective and safe oral antifungal agent that can be used in the treatment of relapse and resistant cases of dermatophytosis.

Keywords: Dermatophytes; Terbinafine; Voriconazole; Tinea corporis; Tinea cruris

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1. Introduction

Dermatophytoses are one of the most common skin diseases. Dermatophytes invade and multiply within keratinized tissues (skin, hair, and nails) causing infection. Based upon their genera, dermatophytes can be classified into three groups: Trichophyton (which causes infections on skin, hair, and nails), epidermophyton (which causes infections on skin and nails), and Microsporum (which causes infections on skin and hair). Based upon the affected site, these have been classified clinically into tinea capitis (head), tinea faciei (face), tinea barbae (beard), tinea corporis (body), tinea manus (hand), tinea cruris (groin), tinea pedis (foot), and tinea unguium (nail).[1] The estimated lifetime risk of acquiring a dermatophyte infection is between 10 and 20 percent. Dermatophytes manifest in humans in different forms and most commonly Tinea corporis and Tinea cruris that disrupts keratin in the stratum corneum (epidermis of skin).[2] Epidemiological study reported that among 587 cases, 151 patients had Tinea corporis infection and 138 had Tinea cruris infection.[3] Recognition and appropriate treatment of these infections reduces both morbidity and discomfort and lessens the possibility of transmission. Fungal transmission occurs through direct contact with infected persons, animals, soil or fomites. Infection is the result of the host's reaction to the enzymes released by the fungus during its digestive process. So far about 30 species of dermatophyte have been identified responsible for human infection. The most common dermatophytes that cause cutaneous infection are Trichophyton rubrum, Trichophyton mentagrophyte, Trichophyton tonsurans, and Microsporum canis.[1,2] Overpopulation and poor hygienic living conditions also contribute to dermatophyte infection. The Hot and humid climate of Bangladesh makes tinea a very common superficial fungal infection of the skin. Recent developments in understanding the pathophysiology of dermatophytosis have confirmed the central role of cell-mediated immunity in countering these infections. Hence, a lack of delayed hypersensitivity reaction in presence of a positive immediate hypersensitivity (IH) response to trichophytin antigen points toward the chronicity of disease.[1] The factors which predispose to such an infection are underlying diseases such as diabetes mellitus, lymphomas, immunocompromised status, or Cushing's syndrome, older age, which could produce severe, widespread, or recalcitrant dermatophytosis. Some areas of the body are more susceptible to the development of dermatophyte infections such as intertriginous areas (web spaces and groins) where excess sweating, maceration, and alkaline pH favor the growth of the fungus. After inoculation into the host skin, suitable condition favor the infection to progress through adherence followed by penetration mediated by proteases, serine-subtilisins, and fungolysin, which causes digestion of keratin network into oligopeptide or aminoacid and also act as a potent immunogenic stimuli. In addition, the mannans produced by T. rubrum lead to inhibition of lymphocytes. Impaired function of Th17 cells leading decreased production of interleukin-17 (IL-17), IL-22 (key cytokine in clearing mucocutaneous fungal infection) results in persistence of infection.[4]

Once Dermatophytosis was very easy to treat with either topical or systemic antifungal agents but now a days it become a challenge for dermatologists. Resistant to anti-fungal or refractory and treatment failure cases are observed increasing over the last few years against commonly used oral antifungal agents such as fluconazole, itraconazole and terbinafine with standard doses and duration.[5,6] Studies conducted show that resistance among dermatophytes is not an uncommon and incomplete mycological cure as well as relapse is very common after standard (2-week) terbinafine therapy in patients of tinea cruris/corporis.[7] Some investigators reported that the disease pattern of fungal infections varies among the different countries and different areas within the same country. Due to high temperature and increased humidity, there are increased cases of dermatophytosis and other fungal infections. There was increased incidence of drug resistance observed over a period of time to the antimycotic drugs commonly used for the treatment. It's time demand to search for an effective oral agent against fungal infections. Widespread resistance to conventional and higher doses and standard and extended durations warrant a search for an effective oral anti-fungal drug that brings about a rapid clinical cure. Currently, synthetic drugs with antifungal activity are under scientific research. These drugs show action against new cellular targets, as they inhibit different metabolic pathways from those previously described, including pathways for the gly-oxylate cycle, pyrimidine and heme biosynthesis, cytochrome P450, and iron metabolism. Voriconazole is a new broad spectrum antifungal agent that was discovered in the late 1980s and belongs to the triazole class of drugs with a spectrum of activity beyond that of fluconazole. Voriconazole selectively inhibits the fungal cytochrome P450-dependent enzyme 14 ά- sterol dimethylase, thereby interrupting an essential step in ergosterol biosynthesis. The terminal half-life of voriconazole is dose-dependent and the drug is rapidly and almost completely absorbed following oral administration with maximum plasma concentration being achieved 1- 2 hour after dosing. The oral bioavailability of voriconazole is estimated to be 96%.[8]

Voriconazole is found to be sensitive against fluconazole and terbinafine-resistant cases.[9] One study included 500 patients with dermatophytosis to find out antifungal resistance pattern and efficacy of drugs. Resistance against fluconazole and terbinafine was most common, 85.33% and 58% respectively. No resistance against voriconazole was observed. Resistance against fluconazole was noted among all species of dermatophytes, followed by terbinafine. Among 500 patients 88% was fully cured and rest of 12% were partially cured with Voriconazole.[10] Another study also found no resistance against voriconazole.[11] Common adverse events of voriconazole are abnormal vision, photophobia,

photosensitivity, nausea, headache, abdominal pain, skin rash, and diarrhea.[7-11] Voriconazole is a newer second-generation triazole antifungal agent available as oral and intravenous formulations with broad-spectrum antifungal activity, approved by the US Food and Drug Administration for the treatment of invasive fungal infections.[12] British Association of Dermatologists recommended voriconazole as an alternative treatment option for Dermatophytosis refractory to other regimens and in exceptional circumstances.[13] To date, literatures are very limited in studying the clinical efficacy and safety of oral Voriconazole in the treatment of dermatophytosis. Therefore, this study was carried out to find out the efficacy of Voriconazole to superficial fungal infection.

2. Material and methods

This cross-sectional comparative study was conducted in Department of Dermatology & Venereology, Dhaka Medical College Hospital, Dhaka and Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. Patients with relapse and treatment resistant tinea infection were enrolled for study. Inclusion criteria were long-standing, extensive (involvement of multiple anatomical sites) relapse and recurrent dermatophytosis not adequately responding or complete failure with conventional oral antifungal agent's and patient agreed to participate and apparently healthy. Diagnosis was confirmed by patient's statement of previous treatment, medical records and examination findings. Exclusion criteria were patients age below 15 years, pregnant and lactating women, women on oral contraceptive, patient with history of Photosensitivity and known allergy to azoles drugs, patient presenting with other dermatological diseases with tinea, patient with pre-existing hepatic, renal and cardiac disease. Consecutive type non-probability sampling technique was followed in this study. Then clinical conditions of the patient were recorded along with hematological and biochemical profile. A total number of 100 patients were selected and they were allocated into two groups (group-A and group-B), each of which included 50 patients. Group A patients received Tab voriconazole (200 mg) twice daily for 4 weeks and group B patients given Double dose of Terbinafine (250 mg) twice daily for 4 weeks. Patients were followed up on 2nd week (1st follow up) and 4th week (2nd follow up) to see clinical improvement and adverse effects. During the screening visit, detailed history including previous treatment details, age at onset, duration, site of lesions, etc were recorded in a predesigned questionnaire form. Thorough cutaneous examination was performed in each patient and various clinical sign and symptoms such pruritus, scaling and erythema were rated. Efficacy was determined clinically by complete remission of disease leaving behind postinflammatory pigmentation or absence of any visible erythema or scaling (clinical cure). Patients were assessed for severe side effects for safety assessment at each appointment. The data was recorded on preformed Proforma for each patient. Frequencies and percentages were calculated for qualitative variables. Effect modifiers like age, gender and site of disease were controlled by stratification. Post stratification chi-square test was applied to see the effect of this on outcome. P value equal or less than 0.05 was considered as significant.

3. Results

It was observed that majority of patients (52.0%) in group A and 23(46.0%) patients in group B were age group 30-45 years. The mean age was found 32.4±5.7 years in group A and 31.9±5.9 years in group B. The mean age difference was not statistically significant (p>0.05) between two groups. Out of 50 cases, 54.0% cases were male in group A and 56.0% in group B. Large number of respondents hailing from urban area (Table I). Socioeconomically middle class (42.0%) comprising the major percentage of the patients (Figure I). Majority of patients (52%) had a duration of tinea between 6 months to < 2 years (27%). All patient (100%) had tinea corporis and tinea cruris was present in 72.0% patients (Table II). Complete cure was seen in 82% of patient in group A and 64.0% patients in group B. The difference was statistically significant, means voriconazole is highly effective antifungal agent than terbinafine. Failure to treatment (no or minimal improvement of clinical sign and symptom with positive KOH microscopic examination) was seen in 6% of the patients in group A and 16.0% patients in group B (Table III). Adverse events from both treatments were similar, no significant differences were observed. Common adverse effects were visual disturbances, headache, skin rash, nausea etc (Table: IV)

Table 1 Demographic characteristics of the respondents (n=100)

Variables	**Group A (n=50)**		**Group B (n=50)**		**P-value**
	n	%	n	%	
Age (In year)					
15-29	15	30.0	17	34.0	

30-45	26	52.0	23	46.0	
45-60	9	18.0	10	20.0	
Mean±SD	32.4	±5.7	31.9	±5.9	0.781
Gender					
Male	27	54.0	28	56.0	0.943
Female	23	46.0	22	44.0	
Residence					
Rural	15	30.0	14	28.0	0.705
Urban	35	70.0	36	72.0	

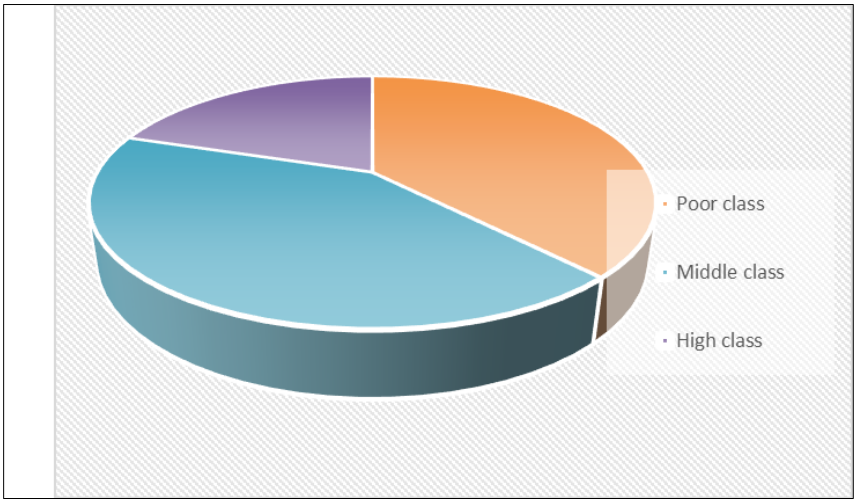

Figure 1 Socioeconomic status of the study population (n=100)

Table 2 Clinical characteristics of the respondents (n=100)

Variables	**Group A (n=50)**		**Group B (n=50)**		**Total**
	n	%	n	%	
Duration in lesion					
<6 months	8	16.0	6	12.0	14
6-12 months	27	54.0	25	50.0	52
1-2 years	12	24.0	15	30.0	27
>2 years	3	6.0	4	8.0	7
Site of lesion*					
Tinea cruris (groin)	50	100.0	50	100.0	100
Tinea corporis (body)	37	74.0	35	84.0	72

*Multiple respondents

Table 3 Evaluation of response of therapy at the end of follow up (n=100)

Outcome	Group A (n=50)		Group B (n=50)		P-value
	n	%	n	%	
Complete recovery (Fully cure)	41	82.0	32	64.0	0.043
Moderately cure	6	12.0	10	20.0	0.277
Failure/ persistent lesion	3	6.0	8	16.0	0.111

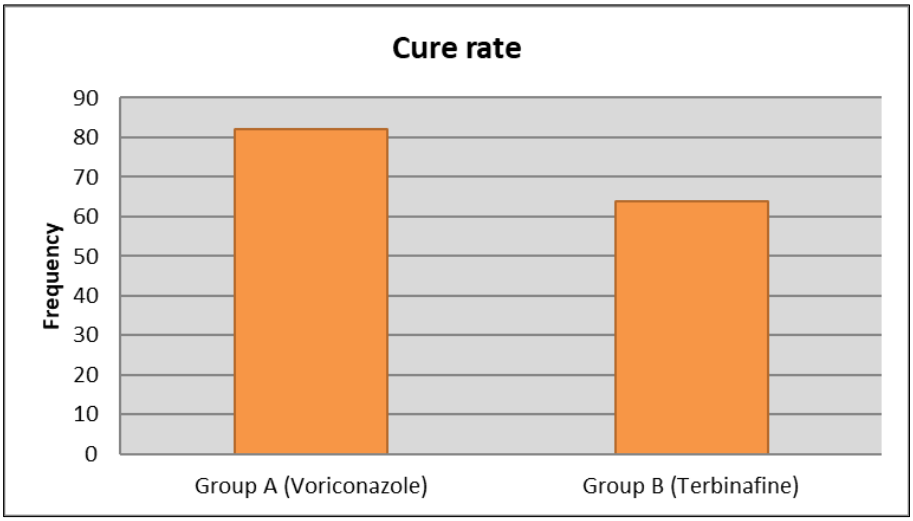

Figure 2 Cure rate in between group (n=100)

Table 4 Distribution of patients by side effects (n=100)

Side effects	Group A* (n=50)		Group B* (n=50)		P-value
	n	%	n	%	
Visual disturbance	4	8.0	3	6.0	
Headache	5	10.0	7	14.0	
Diarrhea	2	4.0	2	4.0	
Nausea	4	8.0	5	10.0	0.832
Jaundice	2	4.0	3	6.0	
Skin rash	3	6.0	2	4.0	
Fever	3	6.0	2	4.0	
Total	16	32.0	17	34.0	

*Multiple respondents

4. Discussion

This cross-sectional comparative study was conducted to observe the efficacy of voriconazole and oral terbinafine in treatment of relapse or resistant tinea corporis & cruris. Total 100 patients with treatment failure or relapse tinea infection were enrolled for study. It was observed that majority of patients (52.0%) in group A and 23(46.0%) patients in group B were age group 30-45 years. The mean age was found 32.4±5.7 years in group A and 31.9±5.9 years in group B. Out of 50 cases, 54.0% cases were male in group A and 56.0% in group B. The mean age & sex difference was not statistically significant (p>0.05) between two groups. Findings consistent with result of previous study. Ahmed et al reported that among 100 patients 52% were males and 48% were females. Patient in the age group 15-25 years was (34%), 26-35 years was (24%), 36-45 years was (20%), and (16%) and (6%) were between (46-55) and (56-65) years respectively.[9] Hoq et al shows that 31-40 years age group was 58%, 20-30 years was 31%- and 41-50-years age group was 11%, regarding sex, (58%) males and (42%) females between 20-50 years aged patients with tinea infections.[10]

Present study shows that complete cure was seen in 82% of patient in group A and 64.0% patients in group B. The difference was statistically significant, means voriconazole is highly effective antifungal agent than terbinafine. Failure to treatment (no or minimal improvement of clinical sign and symptom with positive KOH microscopic examination) was seen in 6% of the patients in group A and 16.0% patients in group B. Ahmed et al reported that complete cure (clinical cure + mycological cure) was seen in (82%) of patient, failure to treatment was seen in (6%) of the patients.[9] Another study reported that 88.4% participants with tinea infections were fully cured and 11.6% were moderately cured.[10] Khondker et al reported clinical cure in 55(67.9%) patients, improvement in 25(30.9%) patients and failure in 1(1.2%) patient and mycological response was eradicated in 80(98.8%) patients and persistent in only 1(1.2%) patient.[14]

Majid et al reported that at the end of oral terbinafine therapy, only 70 cases out of 100 were clinically cured while the rest (30/100) had signs of persistent infection at the treated site (persisters). On repeat fungal culture, five cases out of the seventy clinically cured patients had a positive culture with the same organism that was grown initially. Thus, out of a total of 100 cases enrolled, only 65% could achieve both clinical and mycological cure after 2-week terbinafine therapy (cured).[7] Khatri et al., reported resistance against fluconazole and terbinafine was 61.33% and 48% respectively but resistance against Voriconazole was not observed in his study.[15] Majid et al., found a cure rate of 43% with oral terbinafine 250mg/ day for 2 weeks while Sharma et al., found a cure rate of 35% with the same dose given for 3 weeks for tinea corporis and cruris.[7, 16]

Common adverse effects were visual disturbances, headache, skin rash, nausea etc. Adverse events from both treatments were similar, no significant differences were observed. Findings consistent with result of study of Ahmed et al. Adverse events from treatment with Voriconazole was found in (40%) of patients with visual disturbances such as blurred vision, colour change, photophobia was present in (27%) patient, followed by headache in (5%), skin rash in (3%), others being nausea and abdominal pain 2% each.[9] In the study of Khondker et al about 12(14.8%) developed side effects and among them disturbance of vision (photophobia, blurred vision, visual hallucination) was found in 4(33.2%) cases, followed by perioral stickiness 3(25%) cases and diarrhoea, abdominal pain, general weakness, headache and skin rash in 1(8.3%) case for each respectively.[14]

Widespread resistance to conventional and higher doses and standard and extended durations warrant a search for an effective oral anti-fungal drug that brings about a rapid clinical cure. As there were no new oral antifungal agents available right now in Bangladesh to treat therapy-resistant dermatophytosis, Voriconazole can be used routinely in treatment of tinea infection.

5. Conclusion

This study concluded that Voriconazole a new oral antifungal agent is highly effective and well tolerated by patients and can be considered a treatment option for relapse and recurrent cases in the treatment of tinea corporis and cruris.

Compliance with ethical standards

Disclosure of conflict of interest

All authors of the manuscript have no conflict of interests to declare.

Statement of ethical approval

This study was approved by Institutional Review Board (IRB), Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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