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Efficacy and Safety of Oral Voriconazole in Refractory and Recurrent Cases of Dermatophytosis: A Prospective Study in a Tertiary Care Hospital in Bangladesh

Dr. Syed Shawkat Ahmed[1*], Dr. Syed Shair Ahmed[2], Prof. Dr. Md. Muzammal Haque[3], Dr. Fahmida Tabassum[4]

[1]Associate Professor, Department of Dermatology, Jahurul Islam Medical College, Bhagalpur, Bajitpur, kishoreganj, Bangladesh
[2]Assistant Registrar, Department of Dermatology, Z.H. Sikder Women's Medical College, Dhaka, Bangladesh
[3]Professor and Head, Department of Dermatology, Jahurul Islam Medical College, Bhagalpur, Bajitpur, Kishoreganj, Bangladesh
[4]Medical Officer, Department of Dermatology, Jahurul Islam Medical College, Bhagalpur, Bajitpur, Kishoreganj, Bangladesh

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***Corresponding author:** Dr. Syed Shawkat Ahmed
Associate Professor, Department of Dermatology, Jahurul Islam Medical College, Bhagalpur, Bajitpur, kishoreganj, Bangladesh
E-Mail ID: drshawkatahmed@gmail.com

Abstract

Background: Dermatophytosis is a worldwide health-related problem, affecting 20-25% population globally. 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 in Bangladesh. Search for an effective new oral antifungal agent now become essential. ***Aim of the Study:*** To evaluate the efficacy and safety of the new antifungal agent voriconazole in the treatment of refractory and recurrent cases of dermatophytosis. ***Methods:*** The study was conducted in the outdoor patient department of Jahurul Islam Medical College Hospital, a rural-based tertiary care teaching hospital on 100 patients with extensive, recurrent, treatment failure cases of dermatophytosis. The clinical diagnosis was confirmed by KOH microscopic examination. Patients were given oral voriconazole at a dose of 200mg twice daily one hour after food for 4 weeks. The patients were followed up at week 2 to assess clinical response and any adverse effects from the prescribed drug. The final efficacy assessment was made at the end of week 4 with the combined evaluation of mycological results and the sum of clinical scores according to a 4-point physician assessment scale of 0-3 (0-absent, 1- mild, 2-moderate, 3- severe). ***Results:*** A total of 100 patients completed the clinical trial. Among them 52% were male and 48% were female. The 15-25 year's age group was 34% and the 26-35 year's age group was 24%. Majority of patients 56% had a duration between 6 months to <1 year. Of all patients, 100% had tinea corporis and tinea cruris was present in 85%. Involvement with outdoor work was present in 60% of cases. A Complete cure was seen in 82%, mycological cure was seen in 12%, and failure to treatment was seen in 6% cases. Adverse effects were seen in 40% of patients with visual disturbances in 27%, followed by headache and skin rash in 5% and 3% respectively ***Conclusion:*** Based on the result, it can be concluded that voriconazole is a highly effective and safe oral antifungal agent that can be used in the treatment of recurrent therapy-resistant cases of dermatophytosis.

Keywords: Voriconazole, Refractory, Dermatophytosis.

INTRODUCTION

Dermatophytes are filamentous fungi that invade and multiply within keratinized tissues (skin, hair, and nail) causing infection [1]. Based on their genera dermatophytes are classified into three groups: Trichophyton, Epidermophyton, and Microsporum. Based on the mode of transmission divided into Anthrophophilic, Zoophilic, and Geophilic, and finally based on anatomical site, classified clinically into Tinea capitis (head), Tinea faciei (face), Tinea barbae (beard), Tinea corporis (body), Tinea cruris (groin), Tinea manuum (hand), Tinea pedis (foot), Tinea unguium (nail) [2]. Cutaneous mycoses caused by dermatophyte are called Dermatophytosis, Tinea, or Ringworm. It 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 as

causing human infection [3, 4]. The most common dermatophytes that cause cutaneous infection are Trichophyton rubrum, Trichophyton mentagrophyte, Trichophyton tonsurans, and Microsporum canis [5]. Dermatophyte infections are prevalent worldwide and it affects 20%-25% population globally. They are common in geographical areas with higher humidity. Overpopulation and poor hygienic living conditions also contribute to dermatophyte infection [6]. The Hot and humid climate of Bangladesh makes tinea a very common superficial fungal infection of the skin [7]. Dermatophytosis, once it was very easy to treat with either topical or systemic antifungal agents, now become a challenge for dermatologists. 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 in this subcontinent including Bangladesh [8, 9]. It's time demand to search for an effective oral agent against fungal infections. Voriconazole is found to be sensitive against fluconazole and terbinafine-resistant cases [10]. 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 [11]. British Association of Dermatologists recommended voriconazole as an alternative treatment option for Dermatophytosis refractory to other regimens and in exceptional circumstances [12]. To date, literatures are very limited in studying the clinical efficacy and safety of oral Voriconazole in the treatment of dermatophytosis. We conducted this current study with Voriconazole in our outdoor patient department at Jahurul Islam Medical College Hospital, a tertiary care rural-based teaching hospital, against 100 treatment-resistant cases of Dermatophytosis.

METHODOLOGY

The study was conducted in the department of dermatology and venereology, Jahurul Islam Medical College Hospital, a rural-based tertiary care teaching Hospital, in Bhagalpur, Bajitpur, Kishoreganj, Bangladesh from October 2021 to September 2022. A total of 100 patients of either sex and age range from 15-65 years suffering from clinically and mycologically (KOH microscopic examination) confirmed tinea infection was selected in the study with the following inclusion and exclusion criteria.

Inclusion Criteria

Patients with long-standing, extensive (involvement of multiple anatomical sites), recurrent dermatophytosis not adequately responding or complete failure with conventional oral antifungal agent's fluconazole, itraconazole, and terbinafine and patient agreed to participate and apparently healthy were included in the study.

Exclusion Criteria

Patients age below 15 years, weight below 40 Kg. 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 were excluded.

Study Procedures

During the screening visit, detailed history including previous treatment details, age at onset, duration, site of lesions, occupation, family history and marital status 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 according to a 4-point physician assessment scale of 0-3 (0=absent, 1= mild, 2=moderate, 3= severe). Blood was tested for haematological profile and biochemical tests such as liver function test and renal function test were performed for each patient. Ethical clearance was taken from the ethical review committee of the institution. All the data were analysed by software SPSS version 23.0.

RESULTS

A total of 100 Patients were recruited for a clinical trial. All had extensive tinea with more than 10% body surface area involvement, resistant to previous treatment. 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 (Table 1). Out of 100 tinea-infected patients, (76%) were married and (24%) were unmarried. Family history of tinea was positive in (33%) and negative in (67%). Regarding occupation (60%) of patients were outdoor workers and the rest (28% & 12%) were involved in indoor and other services respectively (Table: 2). Majority of patients (56%) had a duration of tinea between 6 months to <1year followed by 1year to< 2 years (27%) (Table: 3). All patient (100%) had tinea corporis and tinea cruris was present in (85%), tinea faciei and tinea manuum was in 23% and 10% respectively (Table: 4). Complete cure (clinical cure + mycological cure) was seen in (82%) of patient, mycological cure (clinical scores less than 2 with negative KOH microscopic examination) was seen in (12%) of patients, failure to treatment (no or minimal improvement of clinical sign and symptom with positive KOH microscopic examination) was seen in (6%) of the patients (Table: 5). 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 (Table: 6).

Table 1: Age and Sex Distribution of Patients (N=100)

Age in years	Male (%)	Female (%)	Total (%)
15-25 yrs.	24(46.15%)	10(20.83%)	34(34%)
26-35 yrs.	12(23.8%)	12(25.00%)	24(24%)
36-45 yrs.	7(13.46%)	13(27.08%)	20(20%)
46-55 yrs.	6(11.54%)	10(20.83%)	16(16%)
56-65 yrs.	3(5.77%)	3(6.25%)	6(6%)

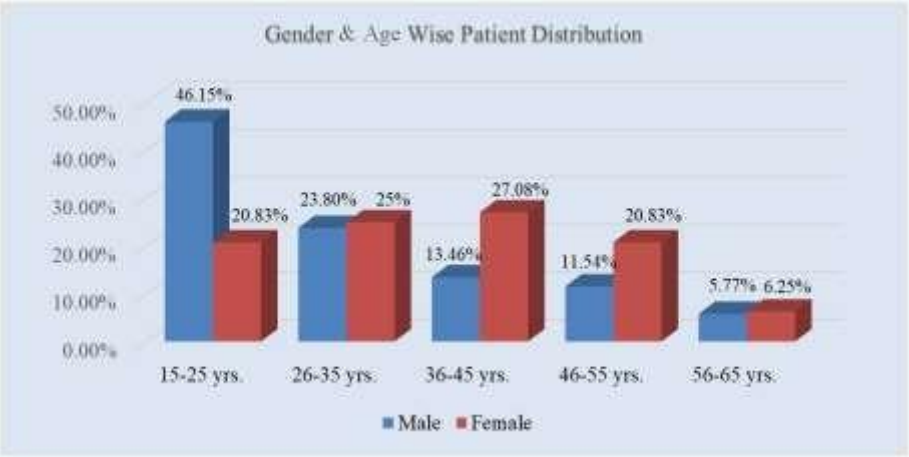

Figure I: Bar Chart Age & Sex wise Patients Distribution (N=100)

Table 2: Epidemiological Profile of Studied Patients (N=100)

Marital Status	Male (%)	Female (%)	Total (%)
Married	30(57.69%)	46(95.83%)	76(76%)
Unmarried	22(42.30%)	2(4.16%)	24(24%)
Family History			
Positive	17(32.69%)	16(33.33%)	33(33%)
Negative	35(67.30%)	32(66.66%)	67(67%)
Occupation			
Indoor	8(15.38%)	20(41.66%)	28(28%)
Outdoor	36(69.23%)	24(50%)	60(60%)
Others	8(15.38%)	4(8.33%)	12(12%)

Figure II: Bar Chart showed sex wise marital status distribution of Patients (N=100)

Table 3: Duration of Lesion in both gender (N=100)

Age	Male (%)	Female (%)	Total (%)
<6 month	7(13.46%)	8(16.66%)	15(15%)
6 month - < 1yr	32(61.53%)	24(50%)	56(56%)
1yr- < 2yr	13(25%)	14(29.16)	27(27%)
2yr ≥	0(0%)	2(4.16%)	2(2%)

Figure III: Bar Chart showed sex wise Lesion distribution of Patients (N=100)

Table 4: Distribution of Tinea Infection by Anatomical Site. (N=100)

Site of lesion	Male	Female	Total
Tinea corporis(body)	52 (52%)	48(48%)	100(100%)
Tinea cruris(groin)	48(48%)	37(37%)	85(85%)
Tinea faciei(face)	9(9%)	14(14%)	23(23%)
Tinea manuum(hand)	6(6%)	4(4%)	10(10%)

Table 5: Cure rate of Tinea with Voriconazole (N=100)

Result	Male	Female	Total
Complete cure	46(46%)	36(36%)	82(82%)
Mycological cure	5(5%)	7(7%)	12(12%)
Failure	2(2%)	4(4%)	6(6%)

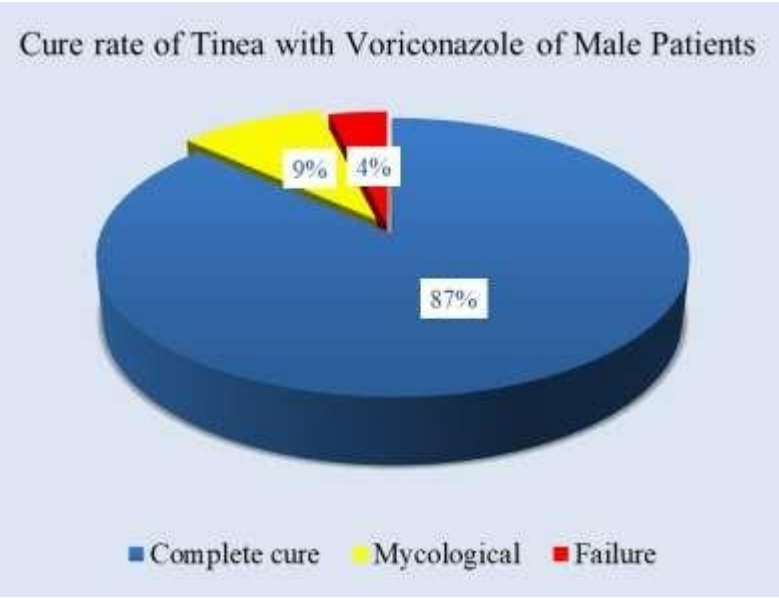

Figure IV: Pie Chart showed cure rate of Tinea with Voriconazole of Male Patients (N=100)

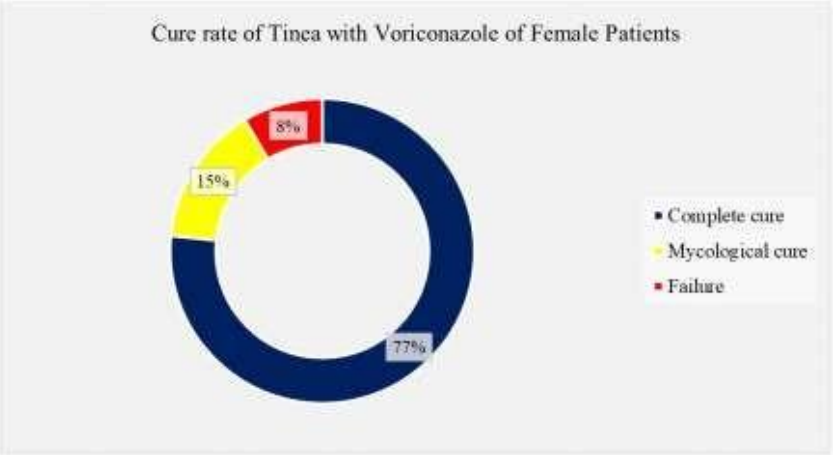

Figure V: Pie Chart showed cure rate of Tinea with Voriconazole of Female Patients (N=100)

Table 6: Distribution of patients by side effects (n=40)

Side effects	Male	Female	Total
Visual disturbance	14(28.57%)	13(32.5%)	27(67.5%)
Headache	2(5.0%)	3(7.5%)	5(12.5%)
Diarrhea	0(0.0%)	1(2.5%)	1(2.5%)
Nausea	1(2.5%)	1(2.5%)	2(5.0%)
Skin rash	1(2.5%)	2(5.0%)	3(7.5%)
Abdominal pain	0(0.0%)	2(5.0%)	2(5.0%)

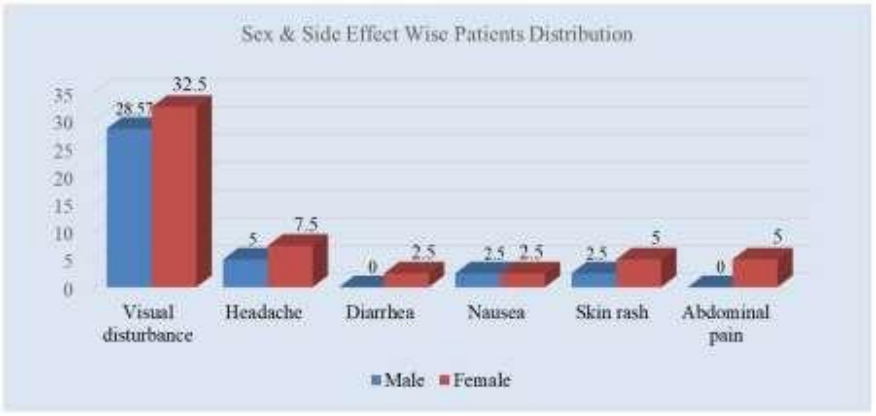

Figure VI: Bar Chart showed sex wise side effects distribution of Patients (n=40)

DISCUSSION

Dermatophytosis is a worldwide health-related problem. The species of dermatophytes causing the infection may vary from region to region. Some species are restricted to a specific region while some species are distributed worldwide [13]. Trichophyton rubrum is the most common cause of dermatophytosis in developed countries while Trichophyton mentagrophyte is the most common cause in developing countries including Bangladesh [14]. A number of antifungal agents have been introduced to treat dermatophytosis and more are in development [15]. Terbinafine and Itraconazole are the most commonly used oral antifungal agents for the treatment of superficial fungal infections because of their efficacy, broad-spectrum activity, and keratin-binding properties. They have been used extensively as standard treatments and higher dosages have been found to be safe and well-tolerated. However, in recent year's treatment failure and relapses have been observed in the patient with tinea infection along with an increase in the incidence of terbinafine and itraconazole resistance [16] 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 [10]. 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 [16, 17]. Sharma *et al.*, in another study with itraconazole 200mg/ day for 3 weeks found a cure rate of 50%, much lower than that of previous studies, which showed a variable cure rate of 72.7- 96.6% following 2 weeks of itraconazole in patients with Tinea corporis, cruris and pedis. This decreasing

efficacy of itraconazole was also well observed in the literature [15,17]. 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 [18]. 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 h after dosing. The oral bioavailability of voriconazole is estimated to be 96%. The presence of high-fat food affects voriconazole absorption; oral voriconazole should be taken at least 1 hr. before or after a meal [18]. The drug is metabolized by the hepatic cytochrome P450 isoenzymes, CYP2C19, CYP2C9, and CYP3A4, and approximately 80% of a single, radiolabelled dose of voriconazole is excreted in the urine and rest 20% in the faeces. Common adverse events of voriconazole are abnormal vision, photophobia, photosensitivity, nausea, headache, abdominal pain, skin rash, and diarrhea [18]. As there were no new oral antifungal agents available right now in Bangladesh to treat therapy-resistant dermatophytosis, we decided, based on recent scientific papers on voriconazole, to try this molecule in patients with recurrent, extensive, and treatment-failure cases of dermatophytosis. In our study, voriconazole was given 200mg twice daily for 4 weeks. This dosage was chosen because it has been found safe and effective in other studies [19, 20]. A Complete cure was seen in 82% of cases, mycological cure was seen in 12% of cases, and failure to treatment was seen in 6% of cases. Treatment-related adverse events were seen in 40% of patients and among them, visual disturbances were observed in 27% and were present during the first week of treatment but none of these adverse effects were severe to stop treatment. Our study had some limitations. Fungal culture was not performed; KOH microscopic examination was performed during the screening visit for confirmation and at the final efficacy assessment but not at follow-up visit. Long-term follow-up after treatment was not taken to observe recurrence.

CONCLUSION

It can be concluded from this clinical trial that Voriconazole a new oral antifungal agent is highly effective and well tolerated by patients and can be considered a treatment option for recurrent, therapy-resistant cases of Dermatophytosis. As Voriconazole is a very expensive drug and is indicated for invasive fungal infections, physicians should be very careful and judicious in using it in dermatophytosis and should be used only in cases where truly needed. Our study was a single-centre study with small sample size. Multi-centre randomized comparative control study using a larger sample with different dosages and duration may provide a rationale for the systemic use of voriconazole in different superficial fungal infections.

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