Clinical Profile and Evaluation of Topical Voriconazole for Management of Fungal Corneal Ulcer in North Western Rajasthan

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Abstract

Aim:- *Fungal keratitis is a suppurative and sight-threatening infection of the cornea that sometimes leads to loss of the eye. The study was done to know the efficacy of topical voriconazole in the management of fungal keratitis and prevalent species of fungal corneal ulcer in North Western Rajasthan.*

Materials and Methods:- *It was a prospective cohort study at a tertiary care center. Fifty patients of fungal corneal ulcer were included in study of either age or sex. All patients were treated with topical voriconazole and response was noted.*

Results:- *60% patients were males and 40% females. Agricultural workers were most commonly affected and the most common cause of injury was vegetative matter (40%). Aspergillus was the most common fungal species (46%). Hypopyon was present in 25 patients. Hypopyon was completely disappeared with topical voriconazole by first week in 18 patients. Improvement in BCVA statistically significant. The mean duration of healing was 5.5 weeks after treatment with topical voriconazole.*

Conclusion:- *Ophthalmic mycosis is emerging as a major cause of visual morbidity and can be life-threatening. Voriconazole eye drops appear to be effective and safe when used for the treatment of fungal keratitis.*

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Keywords: *mycosis, voriconazole, corneal ulcer*

Introduction

Corneal ulcer is one of the important ophthalmic conditions causing significant morbidity especially in the developing countries. The corneal ulcer is the second commonest cause of treatable blindness after cataract among people in Asia, Africa and Middle East.[1] Worldwide, the reported incidence of mycotic keratitis is 17% to 36% while in India it is 44% to 47%.[2-5] Filamentous fungi are responsible for a larger proportion of fungal corneal infections in tropical climates particularly following trauma with vegetative matter. Voriconazole is a triazole having a structure similar to fluconazole. Voriconazole is potent against a wide spectrum of fungi. Voriconazole demonstrated the lowest MIC90. Voriconazole is used in different routes and formulations as eye drops, intrastromal, intracameral and intravitreal injection and also systemically by oral route and intravenous routes.

Aims and Objectives

The study was done to know the efficacy of topical voriconazole in treatment of fungal corneal ulcer and the prevalent species of fungal corneal ulcer.

Material and Methods

It was a single centre prospective tertiary care hospital based study conducted in the Department of Ophthalmology in S.P. Medical College & PBM Hospital and Associated group of hospitals. It included 50 corneal ulcer patients attending outdoor and/or indoor of ophthalmology department of any age group and either sex who had culture and/or smear positive fungal corneal ulcer. Patients not willing to give informed consent or having impending or frank corneal perforation, concomitant endophthalmitis and immunocompromised patients were excluded from study. After obtaining informed consent patient underwent routine clinical and ophthalmological examination. All patients were subjected to routine laboratory investigations RFT, LFT, ELISA for HIV, HBs Ag, VDRL, special test like Grams staining, KOH mount and microbial culture. Topical antifungal therapy was started as soon as the fungus was identified by KOH wet-mount preparation/ culture. The topical therapy included voriconazole 1%w/v every two hours, drops of 1% atropine thrice a day and tablet fluconazole 150 mg OD. Voriconazole eye drops are aseptically constituted by diluting 30 mg voriconazole powder commercially available in the market. The powder is reconstituted with 3 mL of distilled water to produce a voriconazole solution with concentration of 1%w/v. Patients were examined every day when admitted in hospital and then at interval of one week, 15, 30 45 and 60 days and response to the therapy was recorded, including best corrected visual acuity (BCVA) and measurement of size of abscess on slit-lamp biomicroscopy. The infection was considered resolved when there was complete healing of the epithelial defect with resolution of corneal abscess and scar formation. Statistical analysis was done using Chi square test.

Results

The age range of the study population was 11-75 years with 60% patients being male. There was no statistical difference between male and female groups with respect to age.

Table 1: Distribution of patients according to their occupation

Occupation	Male N (%)	Female N (%)	Total N (%)
Farmers	12 (24%)	11(22%)	23 (46%)
Labour	6 (12%)	1 (2%)	7 (14%)
House Wives	0	5 (10%)	5(10%)
Students	5 (10%)	3 (6%)	8 (16%)
Shopkeeper	3 (6%)	0	3 (6%)
Driver	3 (6%)	0	3 (6%)
Army personnel	1 (2%)	0	1 (2%)
Total	30 (60%)	20 (%)	50 %

Table 2: Distribution of Patients of Keratomycosis by Etiology

Etiology	N (%)
Vegetative Matter	20 (40%)
Insect Trauma	6 (12%)
Sand	8 (16%)
Fingernail	3 (6%)
Cow tail	3 (6%)
Stone	1 (2%)
Rope	1 (2%)
Steroid use	4 (8%)
Unknown	4 (8%)
Total	50 (100%)

Keratomycosis is seen mostly in farmers (46%) followed by students (16%) and (14%) labourer (Table 1). In majority of the cases corneal injury was an important predisposing factor. Most common cause of injury was vegetative matter (40%) followed by sand trauma (16%) and insect trauma (12%) (Table 2). In majority of keratomycosis Aspergillus (46%) species was observed followed by Fusarium species (30%). Other less common species were Candida (12%), Alternaria (6 %), Curvularia, Epicoccum and Rhizopus 2 % each (Table 3). The size of the ulcer varied from 2.0 to 8.3 mm, and the size of infiltrate varied from .5 to 3.5 mm area around the ulcer (Figure 1). Out of 45 patients, 50% of patients were categorized under moderate group, followed by severe (42%) and mild (8%). In majority of the cases (80%) the ulcer depth was 1/4th to 2/3rd of cornea i.e. moderate followed by mild (14%) and severe (6%). Hypopyon was present in 25 patients. Forty five cases of fungal ulcers improved clinically within seven days of starting treatment. Five cases did not show any improvement up to 15 days of treatment. These five cases were treated further with intrastromal voriconazole. After starting topical voriconazole, hypopyon completely disappeared in the first week in 18 patients and by the second week in the rest of the cases. Most of the cases of keratomycosis involve the stroma, so macular opacity formed in 78% cases. Nebular opacity was seen in 20% cases and leucomatous opacity in 2% (Figure 2). At the time of presentation, 29 patients presented with visual acuity of perception of light to <1/60. After treatment with topical voriconazole out of these 29 patients visual acuity improved up to 1/60-6/60 in 25 patients, 6/12-6/6 in 2 patients and remained same in 2 patients. The improvement was clinically and statistically significant (p=<0.0001). Out of 45 patients, 26% patients were healed by 8th week followed by 6th week (20%), 7th week (18%). The average duration of healing was 5.5 weeks.

Table 3 Distribution of Patients with Type of Fungi

Types of Fungus	Male N (%)	Female N (%)	Total N (%)
Aspergillus	11 (22%)	12 (24%)	23 (46%)
Fusarium	12 (24%)	3 (6%)	15 (30%)
Candida	3 (6%)	3 (6%)	6 (12%)
Curvularia	1 (2%)	0	1 (2%)
Epicoccum	1 (2%)	0	1 (2%)
Rhizopus	1 (2%)	0	1 (2%)
Alternaria	1 (2%)	2 (4%)	3 (6%)
Total	30 (60%)	20 (40%)	50 (100%)

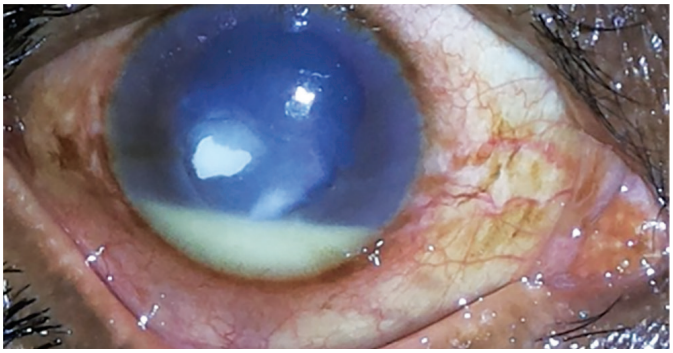

Figure 1: *Fungal corneal ulcer with hypopyon*

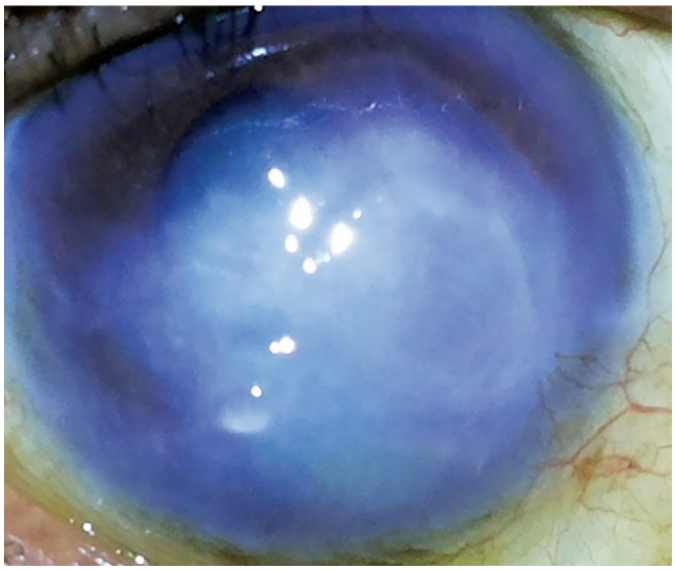

Figure 2: *Leucomatous opacity after complete healing of same patient*

Discussion

Mycotic keratitis is an infection of the cornea by the fungus that causes ulceration and inflammation, usually following trauma or prolonged use of steroid drops. Due to increasing incidence in past three decades and insignificant response to antifungal agents, fungal keratitis has become one of the leading causes of visual loss in many developing countries. Fungal keratitis remains a diagnostic and therapeutic challenge to the ophthalmologist. The difficulty lies in isolating the etiologic fungal organisms in the laboratory, and treating the keratitis effectively with available old topical antifungal agents. Therefore, we tried a newer antifungal drug Voriconazole. Voriconazole is potent against a wide spectrum of fungi, namely, Candida albicans, Candida parapsilosis, Candida tropicalis, Aspergillus fumigatus, Aspergillus flavus, Fusarium solani, and other less common pathogens from the Paecilomyces, Histoplasma, Scedosporium, Curvularia, and Acremonium species etc.

Approximately 49% of the patients are in the age group 21 to 50 years, although it has been reported in extremes of age also. The age group of patients included in our study ranged from 12 years to 75 years. The most common age group affected was 6th decade (24.4%). Our results correlated with the study of Saha et al[6] where the mean age was 53 years. It is mainly due to poor general health condition and less medical attention. In our study, out of 45 patients, 27 patients were male (60%) and 18 patients were females (40%). Male: female ratio was 3:2. Similar results were found in a study done by Tukaram et al[7] where 24 cases (60%) were males and 16 (40%) were females. Our results also correlated with the study by Gopinathan et al[8], who also reported that males (962) were affected more significantly ($p < 0.0001$) than females (390). The higher incidence of keratitis in males can be attributed to more outdoor activity of males in field activities related to agriculture and farming.

Our study data showed that keratomycosis is seen mostly in farmers, both in males (20%) and females (20%). The other less common involved occupations are labourers (15.6%) in males and housewives (22.22%) in females. Our results correlated with the study of Bharathi et al[9], who also reported farming (64.75%) as the most common occupation in their study population. Sathyanarayan et al[10] also observed agricultural occupation (52.94%) to be most commonly affected in their study population. This is attributed to ubiquitous fungal spores and presence of these on senescent plant material.

The most common etiology implicated in our study was trauma with vegetative matter (37.8%) followed by sand (15.6%) and insect trauma (13.3%). Panda et al also observed that vegetative trauma (60.5%) was the most common causative factor in their study population.[11] Bharathi et al also identified vegetative trauma (61.28%) as the predominant predisposing factor for fungal corneal ulcer.[9]

Contact lens wear was reported as one of the major associated conditions in industrial countries in many studies but there was no case of contact lens wear in our study.[12,13] The possible reason is that the habit of wearing contact lens is not common in rural background, particularly in the poor farmers. This study showed that Aspergillus (40%) was the most common fungal species followed by Fusarium species (33.3%). Other less common fungal species were Candida (13.3%), Alternaria (6.7%), Curvularia, Epicoccum and Rhizopus 2.2% each. Our results correlated with the study of Chander et al[14], who also reported Aspergillus (41.18%), as the commonest fungal species followed by Fusarium species (23.53%). These results were also consistent with the study done by Rautaraya et al[15] as Aspergillus species (27.9%) and Fusarium species (23.2%) were the major isolates in their study population. Sathyanarayan et al[10] also observed that Aspergillus spp. was the commonest isolates (16/23 isolates- 69.56%), followed by Fusarium spp., and dematiaceous fungi.

In our study, the size of the ulcer varied from 2.0 to 8.3 mm, the size of infiltrate varied from .5 to 3.5 mm area around the ulcer and the depth of ulcer varied from <1/4th cornea to >2/3rd cornea. The majority of patients were categorized under the moderate group, both according to size (55.6%) and depth of ulcer (77.7%). This was mainly because most of the patients presented within the second and third week (62%). The results of a study done by Reddy et al were also consistent with our study.

In our study, 45 patients who responded to topical voriconazole got symptomatic relief and by the end of the first week, a reduction in the ulcer size and infiltration was noted. The voriconazole eye drops helped in early and complete resolution of the ulcer with no adverse effects in our study. Complications were not reported in this study. At the end of healing, a corneal opacity remained which was mainly of the macular type (78%). After completion of treatment with topical voriconazole, visual acuity improved which was clinically and statistically significant ($p=<0.0001$). In patients treated with topical voriconazole, the mean duration of healing was 5.5 weeks.

Conclusion

Voriconazole is a more recent azole antifungal. Voriconazole therapy helped in early and complete resolution of the ulcers with no adverse effects. Agricultural workers are most commonly affected and vegetative trauma is the most common predisposing factor in fungal keratits. Aspergillus was the predominant species in North Western Rajasthan.

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