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Original Research Article

# Topical 1% voriconazole ophthalmic solution in the treatment of mycotic corneal ulcer

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ABSTRACT

Fungal keratitis is a major cause of ocular morbidity and unilateral blindness[1] worldwide. In India it contributes to 50% of culture positive cases.[2] Despite the emergence of many new drugs, a cure remains difficult in many cases. Compared to anti- bacterial, anti-fungal have lower efficacy, lower tissue penetration and indolent nature of the infection.
This article aims to study effectiveness of topical 1% voriconazole as first line of treatment in 50 patients of mycotic corneal ulcer.



## 1. Introduction

An antecedental history of trauma with a vegetative matter or animal tail is almost always present, more common in hot and humid climate. Causative organism in filamentous fungi are aspergillus, fusarium sps,[3,4] and in yeast is candida. Predisposing factors are immunocompromised state, use of ocular lens, resistant cases, organ transplant patients, trauma.

Patients present with pain, foreign body sensation, lacrimation, blurred vision due to greyish white opacity with feathery margins. The symptoms are less in proportion as compared to signs.

The ulcer is generally dry looking or chalky white. A sterile immune ring called Wesley ring, multiple punctate satellite lesions surrounding the ulcer, a hypopyon in anterior chamber are important signs in fungal corneal ulcers.

Clinical diagnosis is made by signs of mycotic corneal ulcer correlating with typical history of ocular trauma and a definite diagnosis is established only after staining with wet KOH or after positive culture reports from the corneal scrapings which takes one week.

A presumptive diagnosis of fungal corneal ulcer requires prompt empirical treatment.

## 2. Treatment of mycotic corneal ulcer

The ultimate goal of the treatment is to preserve visual function. For this timely diagnosis and adequate dose of antifungal is required.

Recommended treatment includes atropine and anti-fungals.

Anti-fungals are grouped into polyenes (amphotericin B, nystatin, natamycin), azoles(ketoconazole, fluconazole, miconazole, voriconazole & posaconazole) Allylamines(terbinafine) and echinocandins (capsofungin).[5]

Amphotericin B: topical AMB has poor penetration through intact cornea. This drug is available as i.v preparation. But it has poor corneal penetration and hence higher doses are required,[6,7] which results in systemic toxicity. It is better to avoid this drug as better and safer alternatives are present in the market. AMB is seen to be active against Aspergillus and candida keratitis but it has no activity against fusarium.[8,9]

Natamycin is FDA approved antifungal drug for superficial fungal keratitis and is routinely used for filamentous fungi.however it has poor penetration into deep structures of the eye. It adheres to the corneal epithelium

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and is easily degraded.[10] Frequent dosing is required.

Nystatin rarely used clinically as more potent and safer drugs is available.

Itraconazole has good activity against candida and aspergillus species, but not against fusarium species. Gastrointestinal side effects are well known with this drug.

Ketoconazole available only as oral formulation, hence not frequentlu used as fungal keratitis.

Voriconazole is potent against wide spectrum of fungi-C.parapsilosis, C.tropicalis, A.fumigatus, A.flavus and fusarium solani,[11–13]it acts by inhibiting synthesis of ergosterol in fungal membrane. It binds to the active site of P450 dependent enzyme lanosterol 14-demethylase(cyp51 or erg11p)and ligates the non-haem iron. This results in depletion of ergosterol and accumulation of lanosterol, affecting the integrity of cell membrane.

Voriconazole is a fluconazole derivative with addition of methyl group to the propyl backbone and a fluropyridine group replace the triazole moiety. Such alternations increases its potency making it ideal for the treatment of mycotic ulcer.

Posaconazole is a recently introduced triazole. It is an improvement over itraconazole and is indicated in invasive fungal infection mostly in onco-hematological patients. It is available as oral solution formulation as 400mg twice a day. Gastrointestinal complaints are the only side effets noted till date.

Echinocandins as capsofungin and micafungin are semi-synthetic lipoproteins that inhibit the synthesis of glucan in fungal cell wall through non-competitive inhibition of 1,3-glucan synthase, causing osmotic imbalance and cell lysis. They are fungicidal against yeast and fungistatic against aspergillus. They can be given topical and intra venous as well.

## 3. Materials and Methods

1. A prospective case study including 50 patients with mycotic ulcer was done in department of ophthalmology, PMCH, Patna. Duration of study was one year.
2. Written informed consent from the patients was taken.
3. Age group: 23to 75 yrs (mean age- 53.6yrs)
4. Males – 32 female- 18

### *3.1. Inclusion criteria*

1. Patients above 5 yrs
2. Resident of the study area willing to follow up

### *3.2. Exclusion criteria*

1. Unwilling or non-compliant patients
2. Impending corneal ulcer patients
3. Adjacent sclera involvement or
4. Concomitant endophthalmitis were excluded from the study

At their first visit to opd complete history, visual acuity and slit lamp biomicroscopic examination was done. Findings as size, location, depth, hypopyon, satellite lesions were noted.

Diagnosis was made after staining and culture examination. Fungal filament/ hyphae and pseudohyphae were confirmatory. When fungal hyphae were seen they were labelled moulds, and when pseudohyphae were seen they were labeled yeast.

### *3.3. Treatment*

1. Every patient in the first visit was given atropine eye ointment twice a day and 1% voriconazole eye drops, one drop every two hourly for 2 days. They were kept in patient for a week.
2. Then for next 4 days, eye drop was given every 4 hourly for next 4 days, and afterwards every 6 hourly.
3. Patients were followed every week in opd.
4. Progresses in sign and symptom, best corrected visual acuity, time of healing, resolution of hypopyon, complications in the process & adverse reaction to the drug from initiation to the end of the therapy were recorded.

## 4. Results

The patients belonged to the age group 23 to 75years (mean 53.6yrs) of which 32 (64%) are males and 18(36%). While most had no comorbidity 42 (84%) few had type 2 diabetes mellitus 8 (16%).

Mean duration of treatment is 43.58± 7.38 and mean time of healing was 18.32±7.38 days. The left eye was more commonly involved than the right. Culture reports showed that most common fungal causative agent is fusarium species(30% cases), followed by aspergillus(22% cases), KOH positive slides with hyphae (36% cases) & unidentified hyphae (12% cases). Two patients were negative for both stain and culture and hence were already excluded from the study. Mean size of the infiltrate and the ulcer measured along the longest axis was 3.5-8.00mm and 2-5.5mm respectively. Size of the infiltrate decreased significantly with treatment but there wasn't any significant change in the size of ulcer. 43 patients had satellite lesions that regressed gradually with medication. Hypopyon was also seen in around 10 cases in which 9 completely resolved. In two (4% cases) patient the ulcer perforated and had to be treated with keratoplasty. One patient was a case of uncontrolled diabetes mellitus, and the other was a 75yrs old elderly. Organism identified in both the cases was fusarium. 96% cases were completely cured.

**Table 1:**

| **Age group** | **23-75yrs** |
|---|---|
| Males | 32(64%) |
| Females | 18(36%) |
| **Involvement** | |
| Right | 17 (34%) |
| Left | 33 (66%) |
| **Systemic illness** | |
| Diabetes mellitus | 8 (16%) |
| No morbidity | 84% |

### *4.1. Safety analysis*

No adverse effect as visual disturbance, lacrimation, burning sensation, photophobia was associated with the drug.

### *4.2. Efficacy analysis*

Visual acuity is most important outcome from patients' point of view so, we considered it as our primary outcome of the study. The vision depends on the location of ulcer. Central and paracentral ulcer compromises vision more as compared to peripherally located ulcer.

**Table 2:**

| | |
|---|---|
| Paracentral ulcer | 30 (60%) |
| Peripheral ulcer | 13 (26%) |
| Central ulcer | 07 (14%) |

**Table 3:**

| **Visual scale** | **Initial vision at first visit** | **Visison after 3 months of treatment** |
|---|---|---|
| HM | 2 | 1 |
| CF | 9 | 3 |
| 20/400- 20/200 | 13 | 7 |
| 20/100 | 10 | 5 |
| 20/80 | 9 | 8 |
| 20/63 | 5 | 10 |
| 20/40 | 2 | 9 |
| 20/20 | nil | 7 |
| logMAR units | 1.77±0.65 | 1.05±0.7 |

HM: Hand Motion; CF: Counting Fingers

In our study mean BCVA after healed eithilium improved significantly (p=0.001).

### *4.3. Resolution of hypopyon*

Hypopyon was seen in 10 patients, out of which 9 healed completely. One patient had trace hypopyon which was gradually healing.

### *4.4. Healing of ulcer and other outcome*

The time required to heal varied from ulcer to ulcer. It lied between 7 days to 120days. Mean time of healing was 18.32±7.38 days. 96%cases were completely cured. 4% cases perforated and had to undergo keratoplasty.

## 5. Conclusion

Our study demonstrated that 1% topical voriconazole can be effectively used to treat mycotic corneal ulcer and it is well tolerable and its efficacy is comparable to the conventional natamycin drug.

## 6. Discussion

Fungal keratitis is a vision threatening infectious disease. It is mainly managed by anti-fungals. For decades natamycin has been the choice for clinicians, but it can serve as a good alternative. First, susceptibility studies imply that voriconazole is not only effective against filamentous fungi, but also against candida. Second, it has wide therapeutic window and can be used safely. The result of a toxicity study of voriconazole on rodents showed that though it has good permeability into the aqueous humour, it has no adverse effects on retina of an animal model in concentrations as high as 25$\mu$g/ml. The problem with voriconazole is that it is commercially available as lyophilized power which needs to be reconstituted with distilled water. It can remain stable for at least four weeks when stored at 4ºC. Keratoplasty is reserved for acute management of perforated corneal ulcer and for visual rehabilitation following corneal scarring.

## 7. Disclosure

There isn't any financial assistance from any funding body and the author also declares that there are no competing interest involved.

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