

# Comparative Study of Topical 1% Voriconazole Versus 5% Natamycin in the Treatment of Fungal Corneal Ulcer

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## Abstract

**Introduction:** Infective corneal ulcer is leading cause of corneal blindness in India among which fungal elements make a handful of cases. With lack of health facilities, poor hygiene, poor socioeconomic status, and literacy level, it is a major challenge to treat this infection. However, with advent of new topical antifungals, majority of cases can be treated and cured.

**Materials and Methods:** One hundred patients of diagnosed cases of fungal corneal ulcer after fulfilling the inclusion and exclusion criteria were randomly assigned into two groups. One group received topical 5% natamycin and the other group was treated with topical 1% voriconazole, and compared based on their effectiveness and statistically tabulated.

**Results:** The study included age group in 41–50 [34%] with males [78%] predominating, occupation being farmers [49%] and trauma [74%] as main predisposing factor. Both the drugs were well tolerated in study group. There was no significant statistical difference in time for re-epithelization of corneal defect, in infiltrate regression, reduction in signs or symptoms. In randomized natamycin group, corneal ulcer was healed with opacity in 84% of patients and in voriconazole group, it was healed in 78% of patients. In both the groups, epithelial defect was started healing by 4<sup>th</sup> weeks. Fungal organism was isolated in 55% of patients, in which *Fusarium* was the most common organism.

**Conclusion:** The present study did not reveal any significant statistical difference in final outcomes with topical natamycin compared with topical voriconazole treatment.

**Key words:** Corneal blindness, Drug efficacy, Fungal corneal ulcer, Natamycin, Voriconazole

## INTRODUCTION

Corneal ulcer is defined as loss of corneal epithelium with underlying stromal infiltrate and suppuration associated with signs of inflammation, with or without hypopyon.<sup>[1]</sup>

In developing nations like India, cataract and corneal diseases are major cause of blindness.<sup>[2]</sup> According to the World Health Organization, world-wide, corneal diseases contribute a significant number. Coming to data in India,

it is estimated to be around 6.6 million having poor vision due to corneal cause. It is expected that the number of individuals with corneal blindness in India will increase to 10.6 million by 2020.<sup>[3]</sup>

Fungal keratitis was first described by Leber in 1879.<sup>[4]</sup> Scarring of cornea as a result of suppurative keratitis is a leading cause of monocular preventable blindness worldwide. Corneal infection of fungal etiology is very common and represents 30%–40% of all cases of culture-positive infectious keratitis in South India.<sup>[5-12]</sup> Fungal keratitis is a major ophthalmic problem.<sup>[5,13]</sup> However, within tropics as many as two-thirds of ulcers may be due to filamentous fungi, for example, *Aspergillus*, *Fusarium*, and yeasts like candida. The treatment of fungal keratitis is generally more challenging than that of bacterial ulcers, and resulting visual impairment is, on average, more severe.

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**Month of Submission :** 02-2022  
**Month of Peer Review :** 03-2022  
**Month of Acceptance :** 03-2022  
**Month of Publishing :** 04-2022

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Voriconazole 1% is a broad-spectrum, second-generation triazole antifungal agent with demonstrated efficacy in the treatment of invasive fungal infections caused by *Aspergillus* spp. and *Candida* spp.<sup>[14]</sup> Natamycin 5% is a tetraene polyene antifungal agent effective against variety of yeast and filamentous fungi. The present study is intended to compare the efficacy of topical 1% voriconazole with 5% natamycin ophthalmic solutions in fungal corneal ulcer patients in Tertiary Care Hospital.

## METHODOLOGY

This study titled “A COMPARATIVE STUDY OF TOPICAL 1% VORICONAZOLE VERSUS 5% NATAMYCIN IN THE TREATMENT OF FUNGAL CORNEAL ULCER” was carried out in the department of ophthalmology, for a duration of 2 years after obtaining ethical clearance.

It was a comparative study with 100 subjects. Sample size was calculated from the past hospital record, on average the fungal keratitis is around 5/month. Hence, we adopted 100% enumeration technique (all diagnosed fungal corneal ulcer) for the 2 year period.

### Inclusion Criteria

The following criteria were included in the study:

- All diagnosed cases of fungal corneal ulcers.

### Exclusion Criteria

The following criteria were excluded from the study:

- Age <18 years
- Subjects with impending perforation
- Subjects with history of corneal scar in affected eye
- Subjects with previous keratoplasty in affected eye
- Subjects with known allergy to study medications
- Subjects with history of pregnancy or breastfeeding
- Subjects with no light perception in affected eye and.

### Method of Collection of Data

One hundred patients of diagnosed cases of fungal corneal ulcer who fulfill the inclusion and exclusion criteria were included in this study. Data were collected using a piloted pro forma meeting the objectives of the study after an informed and written consent taken from all the patients.

A detailed history of each patient was obtained regarding the age, sex, place, and occupation and about all the risk factors such as history of trauma, diabetes, and prior use of any topical steroids. Patients were randomized to receive topical 5% natamycin or 1% voriconazole after determination of eligibility.

All the study subjects had a thorough ophthalmic evaluation which included a calibrated slit lamp examination to assess

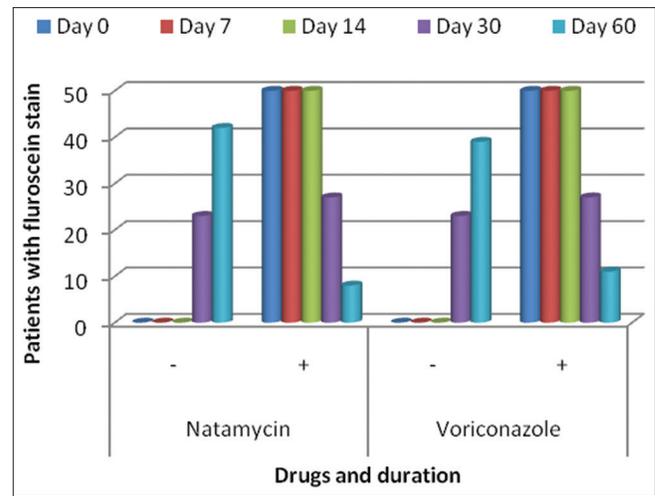


Figure 1: fluorescein stain am among two groups and progression after starting treatment

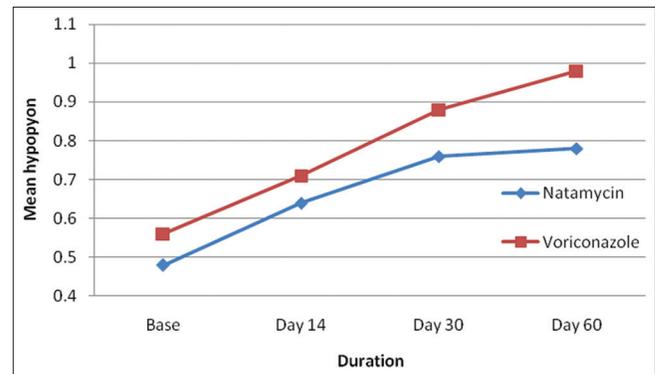


Figure 2: Mean hypopyon among two groups

the epithelial defect with fluorescein staining, depth, stromal infiltration, and hypopyon. Corneal lesion was measured using a vertical illumination source models. First, the slit is rotated to coincide with the axis that you want to measure. Then, the slit beam height is reduced or lengthened to match the lesion. The measurement is read from a slit length display window on the illumination arm. Corneal ulcer was graded using a modification of Jones’s grading for the severity of microbial keratitis. It was graded as Grade 1 (2 mm area, with superficial one-third of depth), Grade 2 (2–6 mm, with superficial two-thirds of depth), and Grade 3 (>6 mm, with full-thickness depth). The best-corrected visual acuity (BCVA) of eye was tested using Snellen chart at enrolment, 2<sup>nd</sup> day, 1<sup>st</sup> week, 2<sup>nd</sup> week, 1<sup>st</sup> month and 2<sup>nd</sup> month from enrolment.

All subjects were taken up for corneal scrapings. First, the ulcer was stained with fluorescein stain then using standard techniques, corneal scraping was performed to all corneal ulcer patients under aseptic condition using 22 gauge needle following the instillation of local anesthesia (proparacaine

eye drops). The material collected from the advancing edge and margin of the ulcer and it was obtained by multiple sites. It was inoculated directly onto blood agar, chocolate agar, for bacteria, and Sabouraud's dextrose agar for fungal culture. Two smears were made onto two slides. One slide was stained with Gram's stain and the other with 10% KOH preparation for direct microscopic examination.

If all inclusion criteria and no exclusion criteria were met, the subjects were enrolled in the study. Subjects were randomized to receive topical 5% natamycin or 1% voriconazole. Assessments of clinical characteristics (infiltrate, epithelial defect size), hypopyon, and BCVA were performed at enrolment, 2<sup>nd</sup> day, 1<sup>st</sup> week, 2<sup>nd</sup> weeks, 1<sup>st</sup> month, and 2<sup>nd</sup> months. Visual acuity measurements were performed using Snellen chart.

**Statistical Methods Applied**

Data were analyzed using Statistical Presentation System Software for windows (version 20.0).

Following statistical methods were employed

- Descriptive statistics
- Contingency coefficient analysis
- Chi-square test
- *t*-test – independent samples
- Repeated measures analysis of variance.

**RESULTS**

Among the 100 cases that were included in the study, majority of the cases, that is, 34 cases (34%) were in the age group of 41–50 years. This is followed by 25 (25%) cases in the age group of 51–60 years. Among the 100 patients, 78 (78%) were male and 22 (22%) were female. Out of 100 patients, 49 (49%) were farmers, followed by 15 (15%) coolies and 13 (13%) homemakers, 6 (6%) business, 5 (5%) shopkeepers, 4 (4%) office workers, and 2 carpenter and conductor one each of driver, mechanic, tailor, and teacher. Seventy-four (74%) are from rural and rest 26 (26%) from urban. About 74% of patients had history of trauma in this study. About 16% of patients had dacryocystitis, 17% of patients had diabetes mellitus, and 5% of patients were using topical steroids.

Many patients gave history of trauma with various agents. The majority of patients had trauma with vegetative matter [Table 1]. In our study, it showed that in both the groups, all were presented with redness and pain at presentation. In randomized natamycin group, redness was absent in 30 (60%) patients at 1 month and in voriconazole group, it was absent in 29 (58%) patients. At 2 months, it was absent in 42 (84%) patients in natamycin group and in

voriconazole group, it was absent in 39 (78%) patient. With regard to pain, it showed that at 2 weeks, 46 (92%) patients were having pain in randomized natamycin group and 48 (96%) patients in voriconazole group. At 1 month, pain was absent in 32 (64%) patients in natamycin group and was absent in 31 (62%) patients in voriconazole group. At 2 months, 3 (6%) patients were having pain in natamycin and 6 (12%) patients in voriconazole group [Table 2].

Table 3 shows 16 (32%) patients were presented with Grade 1 corneal ulcer in randomized natamycin group and 15 (30%) patients in voriconazole group. By the period of 1 month, 15 (30%) patients were healed in natamycin group and 13 (26%) patients in voriconazole group.

At enrolment, in natamycin group, 33 (66%) patients were presented with Grade 2 corneal ulcer and in that 8 (16%) patients were healed by 1 month and 5 (10%) patients had corneal perforation. In voriconazole group, 34 (68%) patients were presented and 10 (20%) patients were healed by 1 month and 6 (12%) patients had corneal perforation. By the end of 2 months, 7 (14%) patients had corneal perforation in natamycin group and 10 (20%) patients had perforation in voriconazole group with Grade 2 corneal ulcer [Table 4].

In each group, one patient was presented with Grade 3 corneal ulcer with full-thickness infiltrate and had perforation at 1 month [Table 5]. Figure 1 shows graphical explanation of fluorescein staining. It was negative in 23 (46%) patients in natamycin group at 1 month and 42 (84%) patients were negative at 2 months and 39 (78%) patients were having fluorescein stain negative in voriconazole group at 2 month.

In the present study, at enrolment, mean hypopyon in natamycin group was 0.48 and in voriconazole group, it was 0.56. At 1 month, mean hypopyon in natamycin group was 0.76. In voriconazole group, mean hypopyon at 1 month was 0.88. At 2 months, mean hypopyon in natamycin group was 0.78 and in voriconazole group, it was 0.98, as depicted in Figure 2.

**Table 1: Nature of trauma**

Nature of trauma	Number of patients
Sugar cane leaf	15
Ragi plant	10
Paddy leaf	12
Animal tail	10
Foreign body	14
Stick injury	08
Stone	05
Total	74

**Table 2: Progression of redness/pain in both the groups**

Examination day	Natamycin				Voriconazole			
	Redness	No redness	Pain	No pain	Redness	No redness	Pain	No pain
Day 0	50	0	50	0	50	0	50	0
Day 14	45	5	46	4	47	3	48	2
Day 30	20	30	18	32	21	29	19	31
Day 60	8	42	3	47	11	39	6	44

**Table 3: Grade 1 (with 2 mm area with anterior stromal infiltration)**

Examination day	Natamycin		Voriconazole	
	No. of patients with ulcer	No. of patients with healed opacity	No. of patients with ulcer	No. of patients with healed opacity
Day 0	16	0	15	0
Day 2	16	0	15	0
Day 7	16	0	15	0
Day 14	16	0	15	0
Day 30	1	15	2	13
Day 60	0	1	0	2

Table 6 shows that the visual acuity at enrolment in both natamycin and voriconazole group was in the range of CF 1 m to CF 5 m in 43(86%) patients. In randomized voriconazole group at 1 month, 2 (4%) patients had visual acuity in the range of 6/36–6/24. In randomized natamycin group, the visual acuity was in the range of 6/36–6/24 in 15 (30%) patients and the range of 6/18–6/9 was present in 15 (30%) patients at 2 months. In randomized voriconazole group at 2 months, the visual acuity was in the range of 6/36–6/24 in 15 (30%) patients and the range of 6/18–6/9 was present in 13 (26%) patients.

Figures 3, 4 and 5 fungal organism was isolated in 55 patients and in which *Fusarium* was 26 (47.27%) followed by *Aspergillus* 19 (34.55%) and *Candida albicans* 10 (18.18%). There was no fungal growth in 45 patients.

Twenty-three patients surgical treatment was done. Dacryocystectomy was done in 16 patients. Conjunctival hooding was done for four patients and debridement was done for three patients. In 77 patients, surgical treatment was not done. Out of 50 in randomized natamycin group, 8 (16%) patients had corneal perforation. In randomized voriconazole group, 11 (22%) patients had corneal perforation [Figure 6].

**DISCUSSION**

In this present study, most common age group presented with corneal ulcer was 41–50 years (34%) which was supported by Bharati *et al.*<sup>[5]</sup> study, in which the commonest



**Figure 3: *Fusarium* growth on SDA**



**Figure 4: *Aspergillus* growth on SDA**

age group was between 31 and 50 years and in Nath *et al.*<sup>[15]</sup> study, the most commonly affected age group was 41–50 years.

**Table 4: Grade 2 (with 2-6 mm area with mid stromal infiltration)**

Examination day	Natamycin			Voriconazole		
	No. of patients with ulcer	No. of patients with healed opacity	No. of patients with perforation	No. of patients with ulcer	No. of patients with healed opacity	No. of patients with perforation
Day 0	33	0	0	34	0	0
Day 2	33	0	0	34	0	0
Day 7	33	0	0	34	0	0
Day 14	33	0	0	34	0	0
Day 30	20	8	5	18	10	6
Day 60	0	18	2	0	14	4

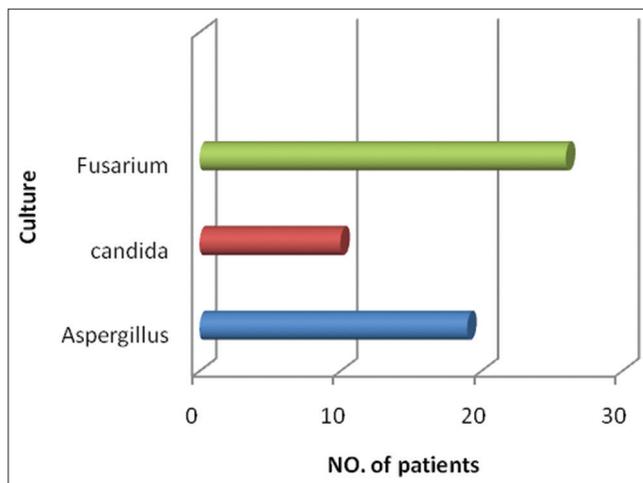
**Table 5: Grade 3 (with >6 mm area with full thickness)**

Examination day	Natamycin			Voriconazole		
	No. of patients with ulcer	No. of patients with healed opacity	No. of patients with perforation	No. of patients with ulcer	No. of patients with healed opacity	No. of patients with perforation
Day 0	1	0	0	1	0	0
Day 2	1	0	0	1	0	0
Day 7	1	0	0	1	0	0
Day 14	1	0	0	1	0	0
Day 30	0	0	1	0	0	1

**Table 6: BCVA among both the groups**

Visual acuity	Natamycin			Voriconazole		
	Day 0	Day 30	Day 60	Day 0	Day 30	Day 60
6/18-6/9	0	0	15	0	0	13
6/36-6/24	0	3	15	0	2	15
Counting fingers (CF) 6 mt-6/60	1	20	9	1	19	8
CF 1 mt-CF 5 mt	43	19	3	43	18	3
HM-PL	6	8	8	6	11	11

BCVA: Best-corrected visual acuity



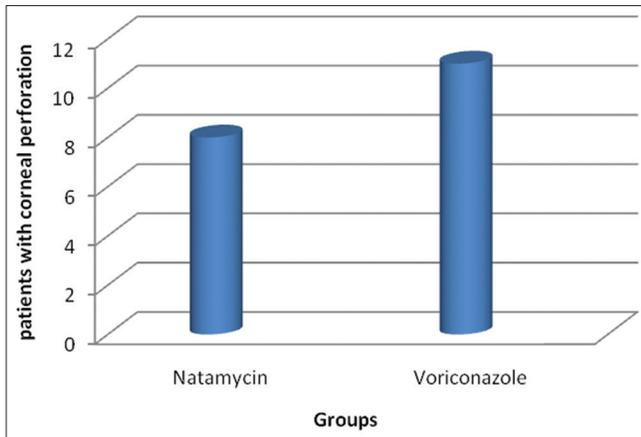
**Figure 5: Culture findings**

In the present study, males (78%) were predominantly affected than females (22%). In Srinivasan *et al.*<sup>[10]</sup> study, 61.3% were male and 38.7% were female. In the other similar studies, male preponderance ranged between 65% and 68%.

In this study, majority of the patients (49%) were farmers, followed by coolie (15%), homemaker (13%) and then business (6%) and others. By the nature of their outdoor activities, men are more vulnerable to disease. In Bharati *et al.*<sup>[5]</sup> study, farmers contributed to 64.5% followed by homemaker (5.1%). In Srinivasan *et al.*<sup>[10]</sup> study, the majority of ulcer patients were agricultural workers, homemakers, or laborers which are in favor of the present study.

In this study, 74% patients were from rural areas and 26% from urban areas. In Bharati *et al.* study, 80.27% patients were from rural areas. The most common predisposing factor in the present study is trauma (74%) and in Bharati *et al.* study, corneal trauma was identified in 92.15%. In Tilak *et al.*<sup>[6]</sup> Mycotic keratitis in India study, ocular trauma was predisposed to infection in 54% of patients. In the study done by Chander *et al.*<sup>[7]</sup> in Chandigarh, 76.62% were from rural background and majority of them (89.83%) were farmers which supports the present study.

In this present study, dacryocystitis was present in 16% of patients. In Nath *et al.* study, blocked nasolacrimal duct was the local predisposing factor in 11.1% of cases which support the present study. In the present study, diabetes mellitus was present in 17% of patients. In Bharati *et al.* study, 15.71% of patients had diabetes mellitus which is in favor of the present study. Diabetes was a significant systemic predisposing factor in fungal infections in 11.1% cases in Nath *et al.* study. The use of topical steroids was present in 5% of cases in this study. In Bharati *et al.* study, the use of corticosteroids associated with development of



**Figure 6: Number of eyes with perforation among the two groups**

fungal keratitis accounted for 7.85% patients which support the current study. Similarly in Srinivasan *et al.* study, 8.0% were on corticosteroids. The probable reason for this was that these drugs are easily available over counter in our country and amount of illiteracy level.

All patients in this study group were positive for 10% KOH wet mount because that was the chosen inclusion criteria for the recruitment of patients in the study. Out of 100 patients, 55 (55%) were fungal culture proven and the remaining 45 (45%) were culture negative. In Nath *et al.* study, 65% of patients showed culture positive. Out of the 100 cases of corneal ulcer, fungal growth was seen in 32 eyes in Dutta *et al.* study.<sup>[1]</sup> In the study done by Chander *et al.* in Chandigarh, 53.12% were positive on fungal culture. In Ghana study, 57.3% were cultures positive,<sup>[18]</sup> which are in favor of the present study.

In this study, *Fusarium* was the most common organism (47.27%), followed by *Aspergillus* (34.55%) and *C. albicans* (18.18%). This is supported by Srinivasan *et al.* study where fungal isolates cultured from corneal ulcers, *Fusarium* spp, was the most common followed by *Aspergillus* spp, and the remaining organisms. Among 100 patients, 19 (19%) patients had corneal perforation. In Nath *et al.* study, 12.1% cases had perforation. In randomized natamycin group, 8 (16%) patients had corneal perforation and in voriconazole group 11 (22%) patients had perforation. This was statistically not significant ( $P = 0.44$ ).

## CONCLUSION

In this study of fungal keratitis, the analysis showed no significant statistical difference in time for re-epithelization of corneal defect, no difference in infiltrate regression. There was no significant statistical difference in time taken for resolution of hypopyon, final visual acuity outcome, or adverse events between the topical natamycin treatment compared with topical voriconazole.

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**How to cite this article:** Krishnamurthy H, Sudharani BK, Shivamurthy A, Naik GT, Neeralgi M. Comparative Study of Topical 1% Voriconazole Versus 5% Natamycin in the Treatment of Fungal Corneal Ulcer. *Int J Sci Stud* 2022;10(1):90-95.

**Source of Support:** Nil, **Conflicts of Interest:** None declared.