



Original Research Article

Randomized trial for fungal corneal ulcer- A comparison of outcome between two regimes of medical treatment with topical natamycin and topical voriconazole in a tertiary care Centre

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ABSTRACT

Background: Inflammation of the cornea is known as keratitis. Microbial keratitis is a great challenge for the physicians due to its varied presentation, overlapping symptoms and rapid progression. Though bacterial keratitis is the most prevalent in developing countries but recent increasing trend of fungal keratitis carries a significant risk factors and one of the leading causes of vision loss. Early diagnosis and treatment are the cornerstone for its effective control. Purpose: To determine the outcome and efficacy of treatment with topical natamycin and topical voriconazole in different groups.

Materials and Methods: It was a randomised, prospective, comparative, experimental study. The study populations were selected according to inclusion and exclusion criteria after proper evaluation. The study populations were divided into Group A (treated with 1% topical natamycin) and group B (treated 5% topical voriconazole). The patients were followed up subsequently. Data were collected, tabulated in Excel sheet and analyzed in percentage, proportion, t-test and chi square (χ^2) test. The statistically significant was considered if p value <0.05 .

Result: The average age of the study populations was 39.32 ± 14.99 years. Topical voriconazole was found better against primary fungal ulcer than natamycin but not statistically significant ($\chi^2=0.283$, $p=0.59$). The mean healing times of group A and group B were 25.42 ± 4.59 and 24.92 ± 3.99 days respectively.

Conclusions: This study concluded that it had male predominance, commonly involved younger people and poor socioeconomic agricultural workers. Both drugs were found effective against primary ulcer but voriconazole was slightly better.

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1. Introduction

Cornea is the major refractive and protective outer layer of eye. Inflammation of the cornea is known as keratitis. There are several causes of keratitis: infectious, physical, chemical or immunogenic. Infectious or microbial keratitis

is a predictor of general health due to its higher incidence in community and associated complications. Microbial keratitis has long been a challenge for the physicians due to its varied presentation, overlapping symptoms and rapid progression. Bacterial keratitis is the most prevalent amongst microbial keratitis. But there has been a constant surge in fungal keratitis in the recent times due to multiple overlaying factors. Despite, being a slow process

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in comparison to bacterial counterpart, fungal keratitis possesses considerable ocular morbidity. Fungal keratitis carries a significant risk in developing countries and is one of the leading causes of vision loss.¹ Fungal keratitis was first described by Leber in 1879.² This entity is a very common cause of corneal ulcer in developing countries.

Historically, it was epidemic in warmer climates such as India. It has higher prevalence in tropical country like India. During the last four decades, the increasing incidence of this disease entity has been reported in different parts of the world). Recently, increasing incidence of fungal keratitis among the all infectious keratitis has been reported by various centers of India. As many as 50% of fungal cornea ulcer was found in Madurai, South India.³ Infectious keratitis is a leading cause of mono ocular blindness worldwide.⁴ Corneal ulcers are the second most-common cause of preventable blindness after cataract in tropical developing countries. Fungal corneal ulcers or fungal keratitis constitute 30 to 62% of the total microbial culture-positive corneal ulcers.⁵ It is one of the leading causes of ocular morbidity. Its increasing trend can be attributed to the use of contact lenses, non-judicial corticosteroids use, DM, immunocompromised and vegetative trauma.

Treatment of fungal keratitis is generally more difficult than that of bacterial ulcers because of its slow pathologic progress, overlapping features, diagnostic difficulty and potential complications thereby resulting severe visual impairment. But there have been only few studies related to randomized trial of antifungal therapy for mycotic keratitis and no new ocular antifungal medication have been approved by the food and drug administration since natamycin was approved in 1960.⁶

The triazole derivative, voriconazole is active against both filamentous fungi and *Candida* species. Recent, this drug is used as topical, intracorneal and intracameral preparations in fungal corneal ulcer. Early diagnosis and treatment are the corner stone for its effective control.

2. Aims and Objectives

2.1. General

To compare the outcome of treatment with topical natamycin versus topical voriconazole in fungal keratitis

2.2. Specific

1. To compare efficacy of treatment with topical natamycin versus topical voriconazole
2. To find out the clinical outcome of these drugs used in fungal ulcers.

3. Materials and Methods

3.1. Study design

Randomized, prospective, comparative, experimental study.

3.2. Study setting and timelines

Outpatient department (OPD) and emergency (ER) Calcutta National Medical College and Hospital (CNMCH), Kolkata.

3.3. Place of study

Department of Ophthalmology, CNMCH, Kolkata.

3.4. Period of study

12 Months

3.5. Study population

All fungal keratitis or corneal ulcer patients attended in OPD and ER. The study populations were randomly selected depending upon the inclusion and exclusion criteria. The study populations were divided into groups depending upon the treatment regime. Group A (experiment group) was treated with topical Voriconazole and group B with topical Natamycin. Before starting the treatment, patients were randomly enrolled to include in the groups by performing a toss with coin.

3.6. Sample size

The sample size was calculated statistically for obtaining statistical significance. It was thirty in number.

3.6.1. Inclusion criteria

1. Newly diagnosed patient.
2. Presence of corneal ulcer at presentation (defined by an epithelial defect and signs of stromal inflammation).
3. Evidence of filamentous fungus on smear (KOH mount).
4. All the patients were willing to participate in the study.
5. Overlying epithelial defect > 0.5 mm at its greatest dimension at presentation.
6. All diabetic patients whose HbA1c was < 8.

3.6.2. Exclusion criteria

1. Impending perforation, corneal perforation or descemetocele
2. Evidence of bacteria on Giemsa stain at time of enrolment
3. Evidence of acanthamoeba by stain
4. Evidence of herpetic keratitis by history or examination
5. Corneal scar not easily distinguishable from current ulcer
6. Younger than 16 years
7. Bilateral ulcers
8. Previous penetrating keratoplasty
9. Pregnancy (by history or urine test)
10. Patient residing outside 200 km radius of hospital
11. BCVA worse than 6/60(20/200) in the fellow eye

12. Known allergy to medication (antifungal or preservatives)
13. No light perception in the affected eye
14. Unwilling to participate or to return for follow up visits
15. Uncontrolled diabetic mellitus (HbA_{1c} is more than 8).

3.7. Study variables

1. Independent variable –Treatment with topical natamycin and topical voriconazole.
2. Dependent variable- BCVA (best corrected visual acuity) at 3 weeks, 3 months and predetermined clinical characteristics.

3.8. Data collection and interpretation

3.8.1. Procedure for selection of study population

All patients with keratitis or corneal ulcer attended to eye OPD and ER were evaluated clinically and by corneal scraping using spatula for gram stain and KOH wet mount to confirm the diagnosis. The study populations were randomly selected depending upon the inclusion and exclusion criteria. The study populations were divided into groups depending upon the treatment regime. Group A (comparator group) was treated with topical Voriconazole (1%) and group B (experiment group) with topical Natamycin (5%). Before starting the treatment, patients were randomly enrolled to include in the groups by performing a toss with coin. The medicine was applied topically every hourly while awake for 1week. Then 2 hourly intervals for until 3 weeks after enrolment, then the dose was adjusted according to the severity of the case. Assessment of BCVA (best corrected visual acuity) with the help of Snellen's chart and then converted to log MAR and assessment of clinical characteristics of the corneal ulcer (size, shape infiltration, corneal thinning, descemetocoele, perforation etc.) were performed at sub sequent follow up on 1st week, 3rd week and at 3rd month from the date of enrolment.

3.9. Laboratory investigations, parameters and procedures

3.9.1. Investigations

1. KOH mount of the corneal scrapings.
2. Fungal culture on Sabouraud Dextrose Agar (SDA) media.
3. IOP measurement.
4. Fasting Blood Sugar (FBS) level.
5. Post Prandial Blood Sugar (PPBS) level.
6. Glycosylated hemoglobin estimation (HbA_{1c})

3.9.2. Parameters

1. Best corrected visual acuity (BCVA) with the help of Snellen's chart by a single observer optometrist.
2. Assessment of clinical characteristics of the corneal ulcer (size, shape infiltration, corneal thinning, descemetocoele, perforation etc.)

3.10. Outcome definition and parameters

3.10.1. Fungal Keratitis

Fungal Keratitis is a corneal inflammation. It is most commonly associated with bacterial or viral microorganisms that invade into the corneal stroma, resulting in inflammation and ultimately, destruction of these structures. Fungal keratitis results from fungal infection; aspergillus is the most common causative agent.

Natamycin- Natamycin continues to be the first line treatment in fungal keratitis and the first antifungal agent approved for FK.⁷ Natamycin is currently considered the most effective medication against Fusarium and Aspergillus. Natamycin binds preferentially to ergosterol on the fungal plasma membrane and causes localized membrane disruptions by altering membrane permeability.⁸

3.10.2. Voriconazole

It is a new generation triazole. The azole group of medication targets the ergosterol biosynthesis pathway by inhibition of cytochrome p450 dependent C14 α demethylase converted lanosterol to ergosterol, an essential component of the fungal cell wall.⁹

3.10.3. Predetermined clinical characteristics

Infiltrate/scar size - it was characterized by the geometric mean of the longest dimension and the longest perpendicular.

3.10.4. Healing of ulcer

It is defined as complete re-epithelization of the ulcer accompanied by non-progressive stromal infiltrate for two consecutive examinations made one week apart. The date of the first examination of the two was taken into consideration while calculating the time period required for the ulcer to heal.

3.10.5. Central cornea

4 mm diameter of the central part of the cornea i.e. 2 mm radius from the corneal light reflex.

The Grade I ulcers who didn't get themselves admitted were followed up twice weekly for 15 days or more till the symptomatic improvement or signs of healing of the ulcer. After that, they were followed up once a week. All corneal ulcers of Grade II and Grade II were admitted and were followed up on a regular basis.

Table 1: Grading of ulcer: the patients were graded into three grades according to the severity of disease:

Characteristics	Mild (I)	Moderate (II)	Severe (III)
Size of ulcer(mm)	<2	2-5	>5
Depth of ulcer (%)	<20	20-50	>50
Infiltrate	May be dense, but superficial, limited to ulcer	Dense, extending to mid stroma	Dense, extending deeper than the stroma

Symptoms: Patients’ symptoms were categorized in to 3 categories: Mild symptoms: Mild pain, redness, irritation. Moderate symptoms: Mild to moderate pain, redness, mild to moderate photophobia. Severe symptoms: Moderate to severe pain (like inability to sleep), redness, and severe photophobia. Socio-economic status: Monthly per capita income has been calculated by total monthly income divided by the family members. Then categorization of study population according to the socio-economic status was done according to Modified BG Prasad Socio-economic

Table 2: Classification, (Update – 2020) as follows:

Social Class	Revised for 2020 (in Rs. /month)
I	7533 and above
II	3766-7532
III	2260-3765
IV	1130-2259
V	1129 and Below

3.11. Statistical analysis plan

Data collected were entered in Microsoft Excel sheet then into statistical database SSPS (statistical package for social sciences, version 20.0, windows compatible). Data were analyzed using standard statistical technique like tabulation, proportion, percentage, mean and standard deviation. Suitable statistical test was performed (chi square test, t-test etc.). Statistically significant was considered when p value < 0.05.

4. Results

Altogether more than 100 cases of corneal ulcers were examined and sent for laboratory examinations. A total 34 cases were included in the study after excluding both fungal and bacterial smear positive (mixed infection) as well as KOH positive but culture negative cases among the total corneal ulcer cases examined in laboratory.

A total number of male and female patients were 19(56%) and 15(44%) respectively among the study

population. The average age of the study populations was 39.32 ± 14.99 years. The maximum number of patients were between 16 to 30 years of age group in both the groups (group A- 38.9% and group B- 37.5%). The most of the patients (group A- 67.8% and group B- 68.8%) came from rural area. The most of patients were cultivators (n=11, 32%), illiterate (53.0%) and low Socio-economic condition (n=14, 41.2%). (Table 3) Traumatic corneal ulcer was found in 25 (73%) patients. The commonest type of trauma was with vegetative material (n=16, 47.06%). (Table 4) The maximum number of patients occurred during the month of July to September (n=11, 32%). Aspergillus species were the commonly detected fungal isolates in both the groups. Topical voriconazole was found better against fungal corneal ulcer than topical natamycin but not statistically significant ($\chi^2= 0.283, p = 0.59$). 12(75%) and 12(67%) corneal ulcer patients were responded to topical voriconazole and natamycin respectively. (Table 5) The average time for healing of ulcer was 25.17 ± 4.31 days. The average time for healing of ulcer in group A and group B was 25.42 ± 4.59 and 24.92 ± 3.99 days respectively. (Table 6) The baseline mean visual acuity for group A and group B was 0.91 ± 0.23 and 0.99 ± 0.24 log MAR respectively. (Table 7 & Figure 1) The mean visual acuity improvement for group A and group B was 0.36 ± 0.089 and 0.40 ± 0.078 log MAR respectively. (Figure 2)

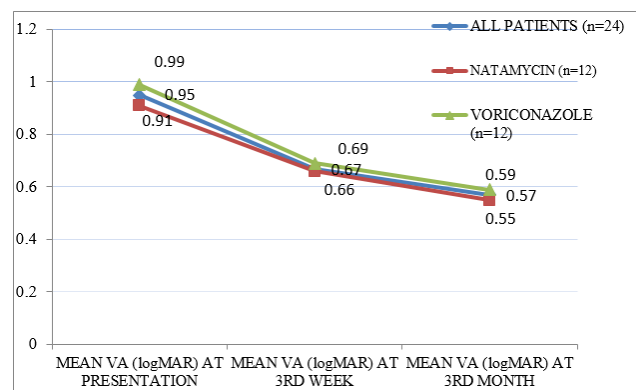


Fig. 1: Graphical presentation of mean visual acuity in different study groups (log MAR)

5. Discussion

Leber (1879) gave the first description of fungal Keratitis.² The present study was intended to compare outcome of treatment with topical natamycin versus topical voriconazole for the treatment of fungal keratitis.

Altogether 34 corneal ulcer patients with different age, religion, residence, occupation, etc. were studied to compare the two groups in relation to response of treatment to fungal corneal ulcer. In this study, 20 cases yielded aspergillus species (59%), 11 cases yielded Fusarium species (32%) and

Table 3: Distribution of study population according to socio-demographic profile

Age in months	Group A Number (%)	Group B Number (%)	Total	Chi square (χ^2) value	P value
16-30	7 (38.9)	6 (37.5)	13 (38.2)	0.1025	0.9915
31-45	5 (27.8)	5 (31.2)	10 (29.4)		
46-60	4 (22.2)	3 (18.8)	7 (20.6)		
>60	2 (11.1)	2 (12.5)	4 (11.8)		
Total	18 (100)	16 (100%)	34 (100)		
Education					
Illiterate	10(55.5)	8(50.0)	18 (53.0)	0.7739	0.8557
Primary	5(27.8)	5(31.3)	10 (29.4)		
Secondary	2(11.1)	1 (06.2)	3 (08.8)		
Higher secondary	1 (05.6)	2 (12.5)	3 (08.8)		
Total	18(100)	16(100)	34 (100)		
Occupation					
Cultivators	6 (33.3)	5 (31.3)	11(32.4)	0.7536	00.9445
Students	2 (11.1)	1 (06.2)	3 (08.8)		
Worker	5 (27.8)	4(25.0)	9 (26.5)		
House wife	4 (22.2)	4 (25.0)	8 (23.5)		
Business	1 (05.6)	2 (12.5)	3 (08.8)		
Total	18(100)	16 (100)	34 (100)		
Locality					
Urban	6 (33.3)	5 (31.2)	11 (32.4)	0.0168	0.8969
Rural	12 (66.7)	11 (68.8)	23 (67.6)		
Total					
Per-capita monthly income (Revision of the Prasad's social classification for the year 2020)					
Social class (In Rs/ month)					
≤1129 (V)	7 (38.9)	7(43.8)	14 (41.2)	0.3077	0.9586
1130-2259 (IV)	6 (33.3)	5 (31.2)	11 (32.4)		
2260-3765 (III)	3 (16.7)	3 (18.8)	6 (17.6)		
3766-7532 (II)	2 (11.1)	1 (06.2)	3 (08.8)		
≥ 7533(I)	0	0	0		
Total	18(100)	16 (100)	34 (100)		

Table 4: Distribution of study populations according predisposing factors

Predisposing factors	Group A Number (%)	Group B Number (%)	Total	Chi square (χ^2)	p value
Woody Material	2 (11.10)	2 (12.50)	4 (11.76)	1.3333	4.3332
Vegetative Matter	8 (44.40)	8 (50.00)	16 (47.06)		
Unknown	4 (22.20)	3 (18.75)	7 (20.60)		
Trauma with Cement	1 (05.60)	1 (06.25)	2 (5.88)		
Diabetes	1 (05.60)	1 (06.25)	2 (5.88)		
Trauma with Iron Material	2 (11.10)	1 (06.25)	3 (8.82)		
Total	18 (100)	16 (100)	34 (100)		

Table 5: Percentage of treatment response to individual drug

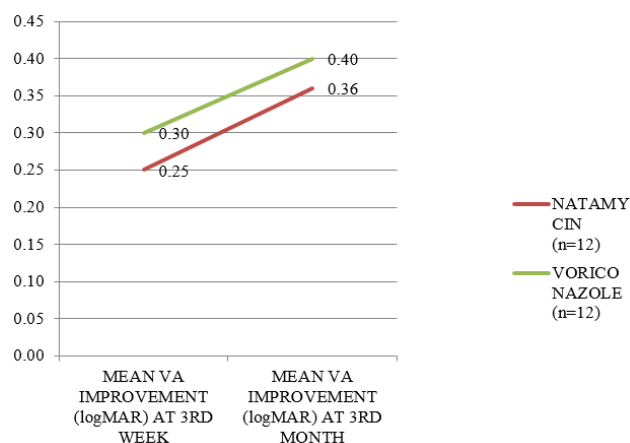
Groups	Present	Absent	Total	Chi-square (χ^2)	p value
Natamycin (Group A)	12 (67%)	6 (33%)	18 (100%)	0.283	0.59
Voriconazole (Group B)	12 (75%)	4 (25%)	16 (100%)		
Total	24(70.59%)	10 (29.41%)	34 (100%)		

Table 6: Mean healing times (in days) in different study groups

Groups	Mean Duration ± SD	t score	p value
Natamycin (Group A) (N=12)	25.42 ± 4.59 Days	0.28	0.78
Voriconazole (Group B) (N=12)	24.92 ± 3.99 Days		

Table 7: Mean visual acuity in different study groups (log MAR)

Groups	Mean VA At presentation (Log MAR)	Mean VA At 3 rd week (Log MAR)	Mean VA At 3 rd month (Log MAR)
All Patients (N=34)	0.95 ± 0.24	0.67 ± 0.28	0.57 ± 0.23
Natamycin (Group A) (N=12)	0.91 ± 0.23	0.66 ± 0.28	0.55 ± 0.24
Voriconazole (Group B) (N=12)	0.99 ± 0.24	0.69 ± 0.27	0.59 ± 0.21

**Fig. 2:** Graphical presentation of mean visual acuity improvement in different study groups (log MAR)

3 cases yielded *Candida* species (9%).

In the present observation, male and female patients were 56% and 44% respectively. A study done by Bandyopadhyay S et al.¹⁰ revealed that most of the younger people (269; 67.41%) was 21 - 50 years of age group. A study conducted by Saha S, Banerjee D, Khetan A and Sengupta J.⁶ shown that study was male preponderance (65%).

In present study maximum number of cases (n=13, 38%) were between the age group of 16 to 30 years. Mean age group of the patients were 38.32 ± 14.99 years. A study was conducted in Sundarban region of West Bengal by Bandyopadhyay S et al.¹⁰ where the younger people of 21 - 50 years of age, were particularly prone to this disease (269; 67.41 %).

The study showed most of the patients (n=22, 65%) came from rural area. A study conducted by Kibret T and Bitew A¹¹ found that rural populations significantly affected than patients in urban (P = 0.005).

In the present observation, 14 patients (41%) from class I SES (i.e. lowest position in SES according to Modified

BG Prasad Socio-economic Classification, 2019) and 11 patients (32%) from class II SES were more sufferers from fungal corneal ulcers. The other was from class III (n=6, 18%) and IV (n=3, 9%). There was no patient from class V (i.e. highest position in SES). A study was conducted in a tertiary care Centre of eastern Odisha.¹² In their study also majority of patients (68.75%) belong to low socioeconomic class. In the present observation, the poor (n=14, 41%) and the lower middle class (n=11, 32%) patients were more sufferers from fungal corneal ulcers.

The cultivators (n=11, 32%) were the commonest occupational group developed fungal corneal ulcer followed by skilled and unskilled workers (n= 9, 26%) in the present study. A study conducted in Sundarban region of West Bengal found that majority of patients (49.12%) were involved in agricultural activities (P < .0001).

M Jayahar Bharathi et al.¹³ also found majority of patients (64.75%) with fungal keratitis were agricultural workers. Another study of Ethiopia¹¹ also shown that fungal keratitis was significantly associated with farmers (P = 0.0001), daily labourers (P = 0.0001).

In present study, traumatic fungal corneal ulcers were 73%. Commonest type of trauma was with vegetative material (n=16, 47.06%). A study done by Bandyopadhyay S et al.¹⁰ found that 61.41 % had trauma with vegetative matter (P < .0001). Another study by Bharathi MJ, Ramakrishnan R, Meenakshi R, Shivakumar C, Raj DL.¹⁴ also identified injuries due to vegetative matter (61.2%) as significant risk for fungal keratitis (P < 0.0001).

In the study, the incidence of the disease was highest in the monsoon season, July to September (n=11, 32%). In a study conducted at Sundarban region, the researcher found that it was in the months of June to September (192; 48.12 %).¹⁰

In the present study, aspergillus species (59%) were found as the most common etiologic agent followed by *Fusarium* species (32%) and 3 cases yielded *Candida* species (9%). The study done by Saha S, Banerjee D, Khetan A and Sengupta J(2009)⁶ and Arora R, Gupta D, Goyal J, Kaur R (2011),^{10,15} they found that *Aspergillus*

species was the most common etiologic agent followed by *Candida albicans*. A study was conducted in a tertiary care Centre of eastern Odisha^{7,12} found that the predominant fungal isolate was *Aspergillus* spp. in 43.75% followed by *Fusarium*, *Candida*, and *Curvularia* spp.

This study was done to evaluate the efficacy of topical 1% voriconazole versus 5% natamycin in treatment of fungal corneal ulcers in a tertiary care hospital and it had been found that voriconazole was better than natamycin in fungal corneal ulcer but it was not statistically significant. (Chi-square value =0.281, p=0.59). Arora R, Gupta D, Goyal J, Kaur R¹⁵ conducted same study. They also found topical 1% voriconazole be safe and effective drug in primary management of fungal keratitis, its efficacy matching conventional natamycin.

The average time taken for healing of ulcer is 25.17±4.31 days (n=24). The healing time for group A and group B was 25.42±4.59 and 24.92±3.99 days respectively. Here voriconazole was marginally better than Natamycin (χ^2 =0.283, p=0.78). Sharma A et al.¹⁶ found the average time of complete resolution of corneal ulcer in group receiving natamycin was 25.86 days, and in group voriconazole, it was 28 days.

In the present study, the baseline mean visual acuity for group A and group B was 0.91 ± 0.23 and 0.99 ± 0.24 log MAR respectively. At 3rd month mean visual acuity improvement for Group A and group B was 0.36 log MAR and 0.40 log MAR respectively. (t score =0.18, p= 0.86). Here, mean visual acuity improvements of the both were comparable with slightly better in the voriconazole-treated arm.

In the mycotic ulcer treatment trial¹⁷ (2013) the researcher found the baseline mean visual acuity of the patients was 0.64 log MAR and that of patients selected for voriconazole was 0.64 log MAR and that of patients selected for natamycin was 0.66 log MAR. The 3-week mean BSCVA was 0.49 log MAR (95% CI, 0.42 to 0.57) in the natamycin-treated arm and 0.60 log MAR (95% CI, 0.51 to 0.70) in the voriconazole-treated arm. The mean BSCVA was 0.39 log MAR (95% CI, 0.30 to 0.48) in the natamycin-treated arm and 0.57 log MAR (95% CI, 0.46 to 0.68) in the voriconazole-treated arm.

6. Conclusion

The study had male predominance, commonly seen in 25-55 years age group, in rural, lower socioeconomic agricultural workers. Trauma especially with vegetable matter was the most important predisposing factors to develop fungal corneal ulcer. It was more seen during the rainy season. Diabetes was the commonest systemic disease associated with corneal ulcers. The average time of resolution of the ulcer was 21-29 days and almost equal in both groups. Most common fungi associated with corneal ulcer were *aspergillus* sp. Both 1% topical voriconazole and 5% natamycin eye drop were found to be effective against in

primary fungal corneal ulcer but voriconazole was found slightly better result.

7. Limitation of the study

Large sample size, subsequent follow up, and long-term study were essential to assess clinical significance of treatment responses. Elderly, rural, low socio-economic patients and advanced disease might hinder the clinical assessment of the study populations.

8. Conflict of Interest

The authors declare that there are no conflicts of interest in this paper.

9. Source of Funding

None.

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