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Efficacy of Topical Voriconazole 1% As Compared to Topical Natamycin 5% in the Treatment of Fungal Keratitis

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ABSTRACT

Background: Infectious keratitis is a major cause of monocular blindness globally, with fungal infections accounting for a significant proportion of corneal ulcers. Fungal keratitis is challenging to treat and often results in severe visual impairment. **Objective:** To compare the clinical efficacy of topical 1% Voriconazole versus 5% Natamycin in the treatment of fungal keratitis. **Study Design:** Cross-sectional prospective study. **Settings:** Ophthalmology Department, Madina Teaching Hospital, Faisalabad Pakistan. **Duration:** Jul 31, 2025, to Dec 31, 2025. **Methods:** 120 patients were included in the study. Group A patients having fungal keratitis were treated with topical Voriconazole 1%, while Group B patients having fungal keratitis were treated with topical Natamycin 5%. Best-corrected visual acuity, scar size, and pain perception were assessed at the time of the procedure and after 1 and 3 months of the procedure. Follow-up was done and all the information was recorded on proforma. **Results:** Mean ulcer scar size in Group A at 0,1, and 3 months post-treatment was 5.035±0.460, 3.506±0.121, and 2.990±0.310 mm, respectively, as compared to 5.051±0.450, 4.143±0.244, and 3.518±0.12 mm, respectively in Group B ($p<0.05$). Mean modified pain perception score at 0 and 3 months post-treatment in Group A was 4.416±0.497 and 4.483±0.536, respectively, versus 1.283±0.454 and 1.483±0.503 in Group B with statistically significant p-values ($p<0.05$). **Conclusion:** Topical 1% Voriconazole was found to be superior to 5% Natamycin in terms of clinical outcomes such as best-corrected visual acuity, ulcer scar size improvement, and pain perception in the treatment of fungal keratitis in patients presenting to Eye OPD.

Keywords: *Topical voriconazole 1%, Topical natamycin 5%, Fungal keratitis.*

INTRODUCTION

For the past 30 years, the incidence of fungal keratitis (FK), which was first reported in 1879, has been rising. About 40–50% of all instances of microbial keratitis are caused by it. Therefore, early identification and treatment are crucial to avoid blindness and other long-term consequences.[1] One of the main causes of monocular blindness in the globe is infectious keratitis.[2,3] In certain situations, fungal infections account for up to 50% of all corneal ulcers.[4] According to some institutes, fungi are responsible for a growing percentage of infectious keratitis cases.[5] Compared to bacterial ulcers, fungal keratitis is typically more difficult to treat, and the ensuing visual impairment is typically more severe.

FK is frequently caused by fungal entry into the corneal stroma via a corneal epithelial defect; this is most likely the cause of the elevated risk of FK concerning trauma and foreign substances, which compromise the integrity of the protective epithelium. When vegetative matter is damaged, fungal conidia that are present on its surface may be directly inoculated into the corneal stroma, causing an infection to begin, or the corneal epithelium may be damaged, allowing fungal invasion.[6] Once within the tissue, fungi begin to multiply in the stroma, reaching Descemet's membrane and ultimately, the anterior

chamber by penetrating deeply into the stroma and spreading circumferentially with satellite lesions. If the body's natural defenses do not eliminate the infection or if appropriate treatment is not given, this might ultimately result in corneal perforation and endophthalmitis. It is simple for fungus to colonize the cornea since it is avascular and immunologically privileged, with few defensive systems, dendritic cells, immune cells, and immunoglobulins. To aid in corneal invasion and colonization, fungi also produce a variety of poisons and enzymes, such as matrix metalloproteinase and serine proteases.[4]

Since Natamycin was licensed in the 1960s, the Food and Drug Administration has not approved any new ocular antifungal drugs, and there is only one published randomized study of antifungal treatment for mycotic keratitis.[7] Recently, Voriconazole, a triazole that is effective against both filamentous fungi and Candida species, has emerged as the preferred therapy for systemic illnesses, including pulmonary aspergillosis. Aspergillus species and other filamentous fungi frequently cause fungal keratitis and the use of topical ocular preparations of Voriconazole has been documented in several case reports in the ophthalmic literature.[9,10] Nevertheless, no systematic effort has been made to ascertain if it is clinically more or less effective than the Natamycin that is sold commercially. There is little information available for doctors to make an informed, evidence-based choice on the antifungal treatment they should use, despite indications both in vitro and in vivo that some fungi react better to one agent than another. Voriconazole's higher penetration and better in vitro susceptibility profile than Natamycin may be advantageous, especially for corneal ulcers that are deeply rooted in the stroma.[11,12] Although case studies and in vitro findings can generate hypotheses, they are not enough to address the issue of which medication is best for people with fungal keratitis. Therefore, we conducted this study to compare the efficacy of Voriconazole and Natamycin in fungal corneal ulcers.

METHODS

This is a cross-sectional prospective study conducted from Jul 31, 2025, to Dec 31, 2025, after approval from the Institutional Ethical Committee (ERC letter TUF/IRB/465/24 dated 27/11/2024). Our research enrolled 120 patients (60 in each group) from the Department of Ophthalmology, Madina Teaching Hospital, Faisalabad, who presented to the Eye OPD and were included in the study after meeting the inclusion and exclusion criteria based on history of vegetative trauma and slit lamp appearance. Each patient signed an informed consent and provided a detailed history. The contact number of each patient was recorded in biodata in addition to other information. All the patients were randomly divided into two groups.

- Group A: Fungal keratitis treated with topical Voriconazole 1%.
- Group B: Fungal keratitis treated with topical Natamycin 5%.

Presence of corneal ulcer at presentation (Epithelial defect, stromal inflammation), history of vegetative trauma, and informed consent patients is included in the study.

Patients with impending perforation or Perforated cornea, evidence of bacterial keratitis on history or examination, evidence of viral keratitis on history or examination, history of bilateral ulcers, age less than 15, living 150 km away from the hospital, evidence of acanthamoeba, having a known allergy to medicines being prescribed during research, visual acuity of No Light perception in the affected eye and best corrected visual acuity of less than 6/36 in the other eye were excluded in the study.

Voriconazole 1% was prepared by the same experienced ophthalmologist under an aseptic environment (commercially available injection Voriconazole mixed with commercially available tears), while Natamycin 5% was prescribed by the same brand to all patients and was easily available in the market. Patients were called for follow-up after every week for 3 months. Other supportive medications, including antibiotic cover and cycloplegic drugs, were prescribed.

Best corrected visual acuity was assessed by the Snellen chart and converted into logMAR as follows: Snellen to logMAR = -1 * log10 (Snellen_frac). Scar size was evaluated under a slit lamp biomicroscope with Vernier calipers in horizontal and vertical meridian. Pain score was assessed by using a pain perception scale, which stated that: 1- No pain, 2- Mild pain, 3- Moderate pain, 4- Severe pain, 5- Very severe pain. Best-corrected visual acuity, scar size, and pain perception were assessed at the time of the procedure and after 1 and 3 months of the procedure. Follow-up was done by taking the patient's contact number, and all the information was recorded on proforma.

Based on the study done by Prajna NR, the sample size was calculated to be 120 (60 patients in each group) with the help of the OpenEpi sample size calculator, taking a confidence level of 95% and a power of the test of 80% to detect a 0.3 logMAR effect size.[17] All the data was analyzed using SPSS V-25. Mean ± Standard Deviation was calculated for all quantitative variables like age, best-corrected visual acuity, scar size, and pain perception at the time of treatment and after 1 and 3 months of

treatment. Frequency and percentages was calculated for all qualitative variables, like gender, comorbidities present, and the frequency of ulcer healing in patients post-treatment. An independent sample t-test was used to compare best corrected visual acuity, scar size, and pain perception between the two groups of patients. P-value ≤ 0.05 was considered significant. A two-way ANOVA test for Repeated Measures was applied to look at the trend at the start of treatment and at 1 month and 3 months post-treatment between the two groups of patients regarding clinical outcomes such as best corrected visual acuity, scar size, and pain score.

RESULTS

The study included 120 total patients with 60 patients in each Group A and B. Regarding age and gender, the groups were similar. See Table I.

Baseline visual acuity in both groups was comparable, but at months 1 and 3 Voriconazole group showed better visual acuity than Natamycin group. Improvement in BCVA at t 1 and 3-month treatment: Voriconazole (20/50) shows better visual acuity compared to Natamycin (20/80). Regarding logMAR improvement, Voriconazole (0.9 logMAR improvement) shows greater improvement when compared to Natamycin (0.7 logMAR improvement).

Independent sample t-test comparison suggests that topical Voriconazole is more effective in improving BCVA in fungal keratitis patients when compared to topical Natamycin ($p<0.05$) However, individual results may vary, and treatment outcomes depend on various factors, including the type of fungal infection and patient response. Baseline mean scar size and pain score in both groups was comparable, but at months 1 and 3 Voriconazole group showed better response than Natamycin group. See Tables II, III and IV. The Two-way ANOVA test for Repeated Measures showed clinical outcomes in terms of best-corrected visual acuity and scar size with significant alterations in group A patients after treatment when compared to Group B patients. See Figure 1,2 and 3.

Table 1: Demographics of patients in both groups of patients (n=120)

Clinico- Demographics	Mean ± SD: Group A (Treatment with topical 1% Voriconazole) n=60	Mean ± SD: Group B (Treatment with topical 5% Natamycin) n=60	*P Value*
Age (years)	61.100±3.99	62.416±3.57	0.091
Gender (male: female)	43:17	35:25	0.090
Comorbidity present (Diabetes: Hypertension)	36:12	35:21	**0.040**

Table 2: Comparison of Best corrected visual acuity in terms of logMAR in both groups of patients (n=120)

Clinical outcomes	Mean ± SD: Group A (Treatment with topical 1% Voriconazole) n=60	Mean ± SD: Group B (Treatment with topical 5% Natamycin) n=60	P Value
Best-corrected visual acuity at the start of treatment	1.298±0.012	1.303±0.018	0.245
Best corrected visual acuity at 1 month post-treatment	0.883±0.037	1.000±0.000	**<0.001**
Best corrected visual acuity at 3 months post-treatment	0.360±0.049	0.603±0.018	**<0.001**

Table 3: Comparison of Ulcer scar size (mm) in both groups of patients (n=120)

Clinical outcomes	Mean ± SD: Group A (Treatment with topical 1% Voriconazole) n=60	Mean ± SD: Group B (Treatment with topical 5% Natamycin) n=60	*P Value*
Ulcer scar size at the start of treatment	5.035±0.460	5.051±0.450	0.753
Ulcer scar size at 1 month post-treatment	3.506±0.121	4.143±0.244	**<0.001**
Ulcer scar size at 3 months post-treatment	2.990±0.310	3.518±0.121	**<0.001**

Table 4: Comparison of Modified pain score in both groups of patients (n=120)

Modified pain perception	Mean ± SD: Group A (Treatment with topical 1% Voriconazole) n=60	Mean ± SD: Group B (Treatment with topical 5% Natamycin) n=60	*P value*
Modified pain score at the start of treatment	4.416±0.497	4.483±0.536	0.123
Modified pain score at the end of treatment (last follow-up visit)	1.283±0.454	1.483±0.503	**<0.001**
The ulcer healed at the end of treatment (yes: no)	54:6	46:14	**0.042**

Figure 1: Comparison of Best corrected visual acuity between both groups of patients

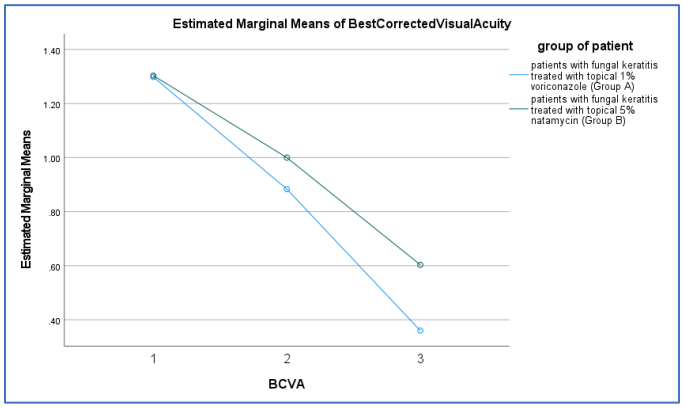


Figure 2: Comparison of Ulcer scar size between both groups of patients

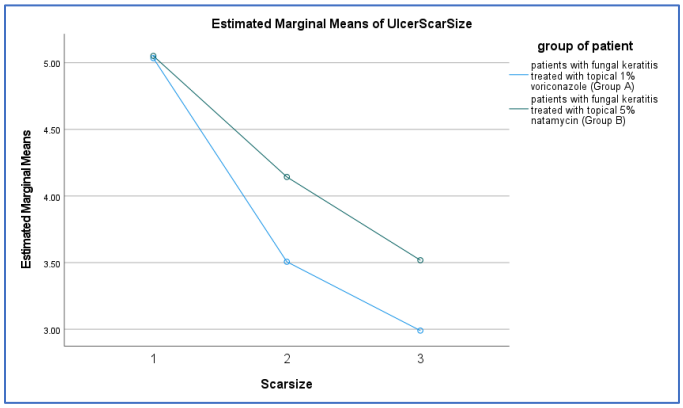
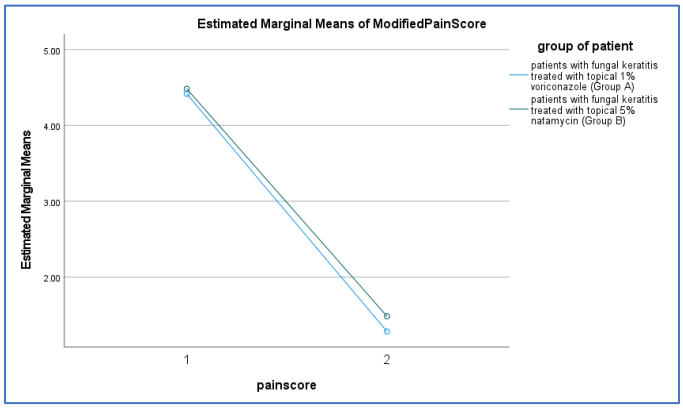


Figure 3: Comparison of Modified pain score between both groups of patients



DISCUSSION

Voriconazole 1% and Natamycin 5% are both used to treat fungal keratitis, but their effectiveness varies slightly.[13] The primary analysis of this fungal keratitis trial revealed a discernible difference between voriconazole and Natamycin topical therapy in terms of ultimate visual acuity, scar size, and pain perception among patients of both groups. Similar results were observed in a study conducted by Prajna and his colleagues, which showed a tendency toward a 2-line advantage with voriconazole therapy in a sub-analysis of patients who could read at least some of the letters on the eye chart at enrollment (visual acuity, 20/40 to 20/400). However, in his study, the two treatment groups did not vary in terms of adverse events, time to re-epithelialization, or ultimate infiltrate/scar size. It was observed that in every analysis done at 3 weeks and 3 months post-treatment, respectively, there was a tendency for scraping to be linked to poorer clinical results.[14]

Although it has never been investigated in human corneas, repeatedly scraping the epithelium during therapy has been considered beneficial. Voriconazole is believed to have better permeability through the epithelium than Natamycin, which penetrates an intact epithelium weakly. According to a recent poll of cornea specialists, more practitioners choose Natamycin rather than Voriconazole for treating fungal keratitis.[15] We were unable to show that scraping enhanced the results of fungal ulcers treated with Natamycin. Although we didn't do corneal scrapings in our study, scraping was linked to a 2.5-line worse BSCVA with Natamycin and a 1-line worse BSCVA with Voriconazole at 3 months.[16] A study conducted by Prajna et al., does not support corneal scraping beyond its usefulness in obtaining a microbiologic sample for culture, as they were unable to show any benefit in treating fungal keratitis, and scraping almost reached statistical significance in its association with poor outcomes. The use of oral and topical Voriconazole to treat fungal corneal ulcers is growing in clinical practice; nevertheless, it is unclear if these treatments are better than Natamycin. In vitro, antifungal susceptibility testing favors Voriconazole over Natamycin, and topical Voriconazole has significant penetration into the anterior chamber.[17]

Since topical Voriconazole is not yet commercially accessible, it can only be purchased through compounding pharmacies. Although a subgroup analysis revealed a trend towards better results with oral Voriconazole, however, the application of oral Voriconazole for fungal keratitis was not examined by us. Voriconazole has strong systemic penetration into the eye and can be administered orally.[18] It provides broad-spectrum protection without the expense and side effects of intravenous antifungal therapy using drugs like amphotericin B. However, a clinical study with suitable cost-effectiveness analysis would need to address the routine use of oral Voriconazole due to its high cost and potential for systemic side effects. Our research provides a lot of advantages. It was blinded, prospective, and had a suitable sample size. Excellent follow-up and adherence to study treatments were observed. Enrolling patients from the whole spectrum of acuity is one of the limitations, which could have made it more difficult for us to compare the medications' actual efficacy. Furthermore, there are concerns with unmasking because Voriconazole is a solution and Natamycin is a suspension; nonetheless, we took all necessary precautions to ensure masking, such as using opaque bottles and having ward staff remove any residue before study evaluations. Even more challenging for refractions is the fact that our key endpoint, visual acuity at three months, was assessed after the antifungal medication was finished and without their knowledge of the treatment assignment.

We used best-corrected visual acuity (BCVA) to measure treatment success. Focusing on patients with baseline vision between 20/40 and 20/400, we found that Voriconazole treatment led to a significant improvement in visual acuity, equivalent to a 2-Snellen line gain. These findings suggest potential efficacy and warrant further confirmatory studies.

CONCLUSION

Our research indicates that individuals treated with Voriconazole may see a 1-line improvement in best spectacle-corrected visual acuity (BSCVA) after three months, which is a small improvement when compared to those treated with Natamycin. There were appreciable variations between the two treatment groups, and the results of both drugs are statistically significant in terms of scar size and modified pain perception of patients. Topical Voriconazole may be a useful addition to natamycin treatment for patients not responding to Natamycin alone.

LIMITATIONS

Patients were enrolled across the full spectrum of visual acuity, which may have made it harder to directly compare the true efficacy of voriconazole versus natamycin.

SUGGESTIONS / RECOMMENDATIONS

The choice between Voriconazole and Natamycin may depend on the type of fungal infection, such as Aspergillus or Candida. It's essential to consult with an eye care professional to determine the best treatment plan for fungal keratitis, as the most effective approach may involve a combination of medications or other interventions.

CONFLICT OF INTEREST / DISCLOSURE

The authors have no conflict of interest.

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