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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

Objective: *To compare the efficacy of topical Voriconazole 1% with topical Natamycin 5% in the treatment of fungal keratitis in terms of visual acuity, ulcer scar size, and pain perception.*

Study Design: *Prospective cross-sectional comparative study.*

Study Setting: *This study was conducted at the Department of Ophthalmology at Madina Teaching Hospital, Faisalabad*

Study Duration: *Seven Months (Nov 24 to May'25).*

Methodology: *A total of 120 patients diagnosed with fungal keratitis were enrolled and divided into two groups (60 each). Group A received topical Voriconazole 1%, while Group B received topical Natamycin 5%. Patients were evaluated at baseline, 1 month, and 3 months for best corrected visual acuity (BCVA), ulcer scar size, and pain perception. Data were analyzed using SPSS version 25. Independent sample t-test and two-way ANOVA for repeated measures were applied, with $p \leq 0.05$ considered statistically significant.*

Results: *Topical Voriconazole showed significantly better improvement in BCVA compared to Natamycin at 1 and 3 months ($p<0.001$). Ulcer scar size reduction was greater in Group A (from 5.035±0.460 mm to 2.990±0.310 mm) compared to Group B (from 5.051±0.450 mm to 3.518±0.121 mm), with statistically significant differences ($p<0.001$). Pain perception scores also improved significantly in both groups, with better outcomes in the Voriconazole group ($p<0.001$). Ulcer healing was observed in 90% of patients in Group A versus 76.7% in Group B ($p=0.042$).*

Conclusion: *Topical Voriconazole 1% is more effective than topical Natamycin 5% in improving visual acuity, reducing ulcer scar size, and alleviating pain in patients with fungal keratitis. It may serve as a superior therapeutic option, particularly in cases requiring enhanced drug penetration and clinical response.*

INTRODUCTION

The occurrence of fungal keratitis (FK), first documented in 1879, has been increasing over the last 30 years. It is responsible for about 40–50% of all cases of microbial keratitis. [1] So, it's very important to find and treat the problem early to avoid blindness and other long-term problems.Infectious keratitis is one of the main reasons why people go blind in one eye.[3] In some cases, fungal infections make up as much as half of all corneal ulcers.[4] Some research shows that fungi are causing more and more cases of infectious keratitis.[5, 6, 7] Fungal keratitis is usually harder to treat than bacterial ulcers, and the resulting vision loss is usually worse.[8]

FK is often caused by fungi getting into the corneal stroma through a defect in the corneal epithelium. This is probably why FK is more likely to happen after trauma or exposure to foreign substances that damage the protective epithelium. When vegetative matter is harmed, fungal conidia on its surface may be directly introduced into the corneal stroma, initiating an infection, or the corneal epithelium may be compromised, facilitating fungal invasion.[9]

Once inside the tissue, fungi start to grow in the stroma, reaching Descemet's membrane and eventually the anterior chamber by going deep into the stroma and spreading around it with satellite lesions. If the body's natural defences don't get rid of the infection or the right treatment isn't given, this could lead to corneal perforation and endophthalmitis. The cornea is avascular and immunologically privileged, which makes it easy for fungus to grow there. It has few defensive systems, including dendritic cells, immune cells, and immunoglobulins. Fungi also make a number of poisons and enzymes, like matrix metalloproteinase and serine proteases, to help them invade and colonise the cornea. [2] The Food and Drug Administration has not approved any new antifungal drugs for the eyes since natamycin was approved in the 1960s. There is only one published randomised study of antifungal treatment for mycotic keratitis.[10] Voriconazole, a triazole that works against both filamentous fungus and Candida species, has recently become the best treatment for systemic diseases like pulmonary aspergillosis.[11] Aspergillus species and other filamentous fungi are common causes of fungal keratitis. There are many case reports in the ophthalmic literature that show how topical ocular preparations of voriconazole can be used to treat this condition. [12]

However, there has been no organised attempt to find out if it is more or less effective in a clinical setting than the natamycin that is sold in stores. Doctors don't have much information to help them make an informed, evidence-based decision about which antifungal treatment to use, even though in vitro and in vivo tests show that some fungi respond better to one agent than another. Voriconazole's superior penetration and enhanced in vitro susceptibility profile compared to natamycin may be beneficial, particularly for corneal ulcers that are deeply embedded in the stroma.[13, 14] Case studies and in vitro findings can formulate hypotheses; however, they are insufficient to determine the optimal medication for individuals with fungal keratitis. [15, 16]

METHODOLOGY:

This is a cross-sectional prospective study conducted from December'24 to May'25, following approval from the CPSP and Institutional Ethical Committee (Ref: TUF/IRB/465/24, Dated:27-11-2024). Our study involved 120 patients (60 in each group) from the Department of Ophthalmology at Madina Teaching Hospital, Faisalabad, who presented to the Eye OPD for the treatment of fungal keratitis and were enrolled in the study after fulfilling the inclusion criteria. Each patient gave a full medical history and signed a form giving their permission. The patients were split into two groups at random: Group A: Fungal keratitis treated with 1% Voriconazole applied to the skin. And Group B: Fungal keratitis treated with topical Natamycin 5%.

The criteria for inclusion were: Corneal ulcer at presentation (epithelial defect, stromal inflammation, and other signs), history of vegetative

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trauma, and exclusion criteria were: Patients with impending perforation or perforated cornea, evidence of bacterial keratitis in history or examination, evidence of viral keratitis in history or examination, history of bilateral ulcers, age under 15, residence beyond 150 km from the hospital, or evidence of acanthamoeba on stain, There was a known allergy to the medications being prescribed during the study, and the affected eye could not see light. The best corrected visual acuity in the other eye was less than 6/36.

The same experienced ophthalmologist made Voriconazole 1% in a clean room. They also prescribed natamycin 5% of the same brand to all patients, which was easy to find in stores. Patients were called every week for three months to check on their progress. They also gave them other medications to help, such as antibiotics and cyclopegic drugs.

The Snellen chart was used to measure best corrected visual acuity, which was then changed to logMAR as follows: To convert Snellen to logMAR, use the formula -1 * log10 (snellen_frac). We used Vernier callipers to measure the size of the scar in both the horizontal and vertical meridian. We used a pain perception scale to rate the pain, which said: 1- No pain, 2- Mild pain, 3- Moderate pain, 4- Severe pain, 5- Very severe pain. The best corrected visual acuity, scar size, and pain perception were measured before the procedure and again one and three months later. We followed up by getting the patient's phone number and writing down all the information on a performa.

Prajna NR's study used the OpenEpi sample size calculator to figure out that the sample size should be 120 (60 patients in each group). The confidence level was 95% and the power of the test was 80% to find a 0.3 logMAR effect size.17 SPSS V-25 will be used to look at all the data. We will find the mean and standard deviation for all of the numbers, such as age, best corrected visual acuity, scar size, and pain perception at the time of treatment and again after 1 and 3 months of treatment. We will figure out the frequency and percentages for all the qualitative variables, such as gender, comorbidities, and how often ulcers healed in patients after treatment. The independent sample t-test was utilised to compare best corrected visual acuity, scar size, and pain perception between the two patient groups. A P-value of 0.05 or less will be seen as important. We used a two-way ANOVA test for repeated measures to look at the trend in clinical outcomes like best corrected visual acuity, scar size, and pain score at the start of treatment, 1 month after treatment, and 3 months after treatment for both groups of patients.

RESULTS:

There were 120 people in each of Groups A and B in the study. The groups were similar in terms of age and BMI. The two groups of patients had different comorbidities. The predominant fungus identified in our patients with fungal keratitis was Fusarium spp, succeeded by Aspergillus spp. Look at Table I.

Patients with fungal keratitis treated with topical Voriconazole 1% exhibited the following visual acuity as measured by the Snellen chart: Before treatment, the patients' vision was 20/400 (logMAR 1.3). One month after treatment, it was 20/160 (logMAR 0.9), and three months after treatment, it was 20/50 (logMAR 0.4). For patients who received topical Natamycin 5%, their vision was: Before treatment: 20/400 (logMAR 1.3), one month after treatment: 20/200 (logMAR 1.0), and three months after treatment: 20/80 (logMAR 0.6). At 1 and 3 months of treatment, Voriconazole (20/50) shows better visual acuity than Natamycin (20/80). In terms of logMAR improvement, Voriconazole (0.9 logMAR improvement) is better than Natamycin (0.7 logMAR improvement).

An independent sample t-test comparison indicates that topical Voriconazole is superior in enhancing BCVA in patients with fungal keratitis compared to topical Natamycin. But individual results may differ, and the results of treatment depend on a number of things, such as the type of fungal infection and how the patient responds. ($p<0.05$) At 0, 1, and 3 months after treatment, the average scar size in Group A was 5.035±0.460, 3.506±0.121, and 2.990±0.310 mm, while in Group B it was 5.051±0.450, 4.143±0.244, and 3.518±0.12 mm ($p<0.05$). The average modified pain perception score for Group A was 4.416±0.497 at 0 months and 4.483±0.536 at 3 months after treatment. For Group B, it was 1.283±0.454 at 0 months and 1.483±0.503 at 3 months after treatment. The difference was statistically significant ($p<0.05$). Refer to Tables II and III. The Two-way

ANOVA test for Repeated Measures revealed significant differences in clinical outcomes, specifically best corrected visual acuity and scar size, between Group A patients post-treatment and Group B patients. Look at Figures 1, 2, and 3.

TABLE I: 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: Multiple comorbidities: None)	36:12:5:7	35:21:0:4	**0.040**
Type of fungal keratitis (Fusarium spp: Aspergillus spp: Curvularia/Candida spp etc)	41:16:3	32:25:3	0.214

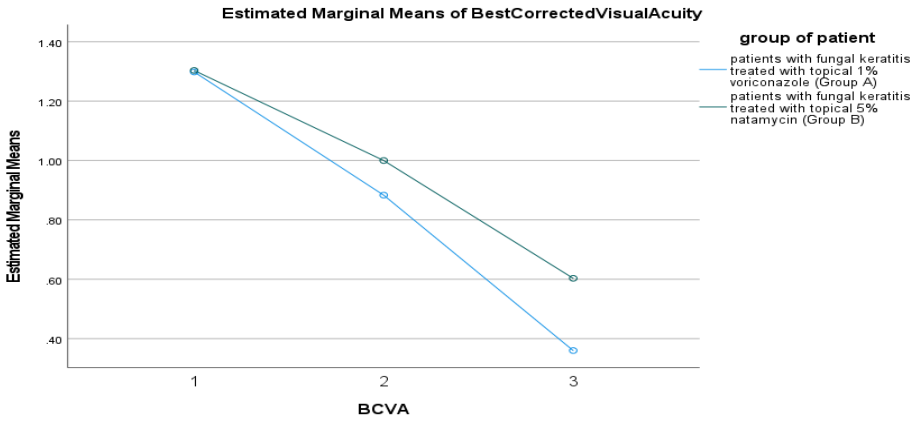


FIGURE 1: COMPARISON OF BEST CORRECTED VISUAL ACUITY BETWEEN BOTH GROUPS OF PATIENTS

TABLE-II: COMPARISON OF BEST CORRECTED VISUAL ACUITY IN TERMS OF LOGMAR AND ULCER SCAR SIZE (MM) IN BOTH GROUPS OF PATIENTS

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**
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-III: Comparison of Modified pain score in both groups of patients

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 start of treatment	4.416±0.497	4.483±0.536	0.123
Modified pain score at end of treatment (last follow up visit)	1.283±0.454	1.483±0.503	**<0.001**
Ulcer healed at the end of treatment (yes: no)	54:6	46:14	**0.042**

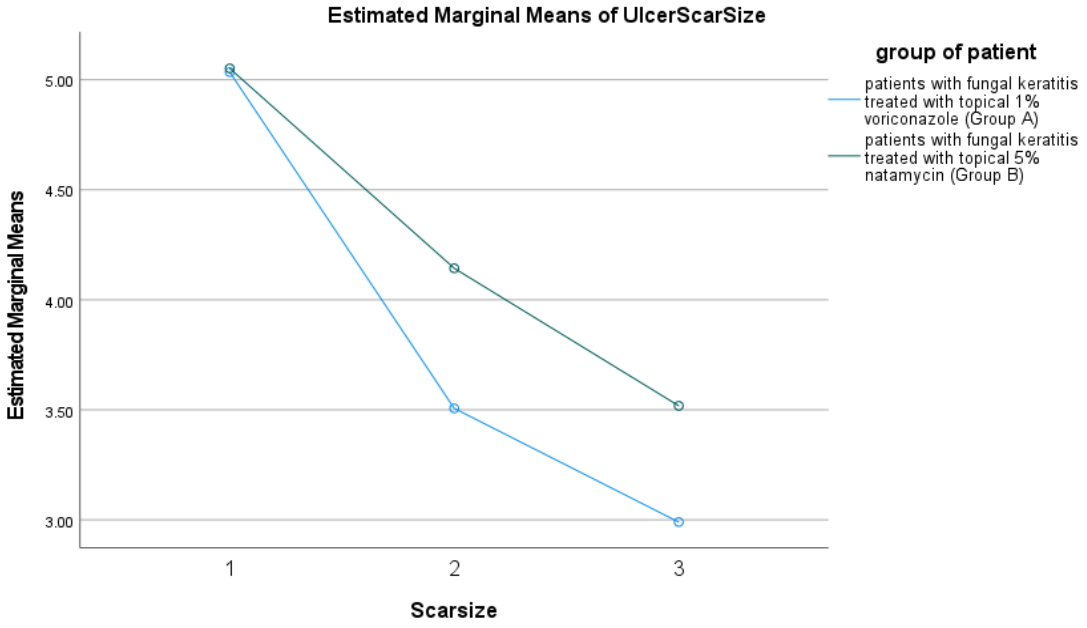


FIGURE 2: COMPARISON OF ULCER SCAR SIZE BETWEEN BOTH GROUPS OF PATIENTS

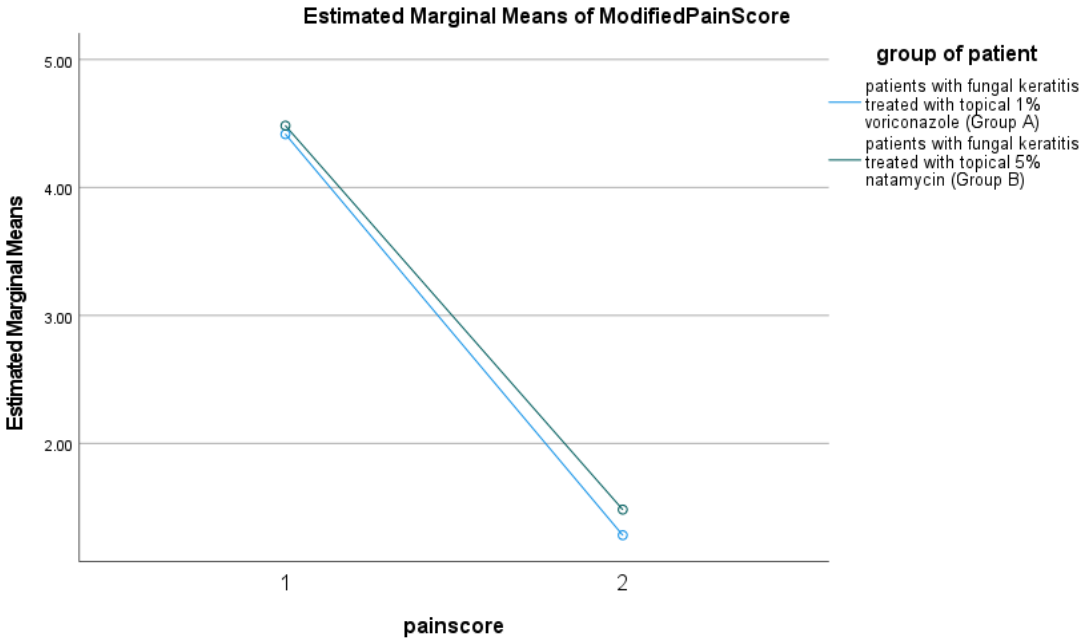


FIGURE 3: COMPARISON OF MODIFIED PAIN SCORE BETWEEN BOTH GROUPS OF PATIENTS

DISCUSSION:

Both Voriconazole 1% and Natamycin can be used to treat fungal keratitis, but they work a little differently.[17] The primary analysis of this fungal keratitis trial indicated a significant difference between voriconazole topical therapy and natamycin regarding final visual acuity, scar size, and pain perception in patients from both groups. Prajna and his colleagues conducted a study that yielded analogous results, revealing a propensity for a 2-line

advantage with voriconazole therapy in a subanalysis of patients capable of reading a portion of the letters on the eye chart at enrolment (visual acuity, 20/40 to 20/400). Nevertheless, in his study, the two treatment groups exhibited no differences in adverse events, time to re-epithelialization, or final infiltrate/scar size. It was noted that in each analysis conducted at 3 weeks and 3 months post-treatment, there was a propensity for scraping to correlate with inferior clinical outcomes.[18]

Repeatedly scraping the epithelium during therapy is believed to be beneficial, although it has never been studied in human corneas. Voriconazole is thought to be able to pass through the epithelium better than natamycin, which doesn't pass through an intact epithelium very well. A recent poll of cornea specialists found that more of them prefer natamycin over voriconazole to treat fungal keratitis. [19] We could not demonstrate that scraping improved the outcomes of fungal ulcers treated with natamycin. We did not perform corneal scrapings in our study; however, scraping was associated with a 2.5-line reduction in BSCVA with natamycin and a 1-line reduction in BSCVA with voriconazole at 3 months. [18]

Prajna et al. assert that their study does not endorse corneal scraping beyond its utility in acquiring a microbiologic sample for culture, as they failed to demonstrate any advantage in the treatment of fungal keratitis, with scraping approaching statistical significance in its correlation with adverse 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 indicates a preference for voriconazole over natamycin, and topical voriconazole demonstrates substantial penetration into the anterior chamber.[20]

Topical voriconazole is not yet available for sale in stores, so the only place to get it is through compounding pharmacies. A subgroup analysis indicated a trend towards improved outcomes with oral voriconazole; however, we did not investigate the use of oral voriconazole for fungal keratitis. Voriconazole has strong systemic penetration into the eye and can be given by mouth. [14, 20, 21] It protects against a wide range of infections without the high cost and side effects of intravenous antifungal therapy with drugs like amphotericin B. A clinical study with a proper cost-effectiveness analysis would need to look into the regular use of oral voriconazole because it is so expensive and could cause systemic side effects. There are many benefits to our research. It was blinded, prospective, and had a good number of people in the sample. There was great follow-up and compliance with the study treatments. One of the limitations is that we enrolled patients from all levels of acuity, which may have made it harder for us to compare how well the medications worked in real life. There are also worries about unmasking because voriconazole is a solution and natamycin is a suspension. However, we took all the necessary steps to make sure masking, like using opaque bottles and having ward staff clean up any residue before study evaluations. It was even harder for refractionists because we measured our main goal, visual acuity at three months, after the antifungal medication was done and they didn't know what treatment they were getting.

We chose visual acuity as our main outcome because it might be the most important outcome for the patient. Because a lot of local patients can't afford contact lenses, BCVA was the result that best showed how well the patients could see. There are some built-in problems with using BCVA as a result. Including patients with significant infiltrates that obscure the pupil provides limited information, as their likelihood of enhancing visual acuity beyond 20/400 is negligible. There is also a small chance of recovery for ulcerated eyes with a visual acuity of more than 20/40. We believe it is pertinent to examine the subgroup of individuals whose enrolment visual acuity ranges from 20/40 to 20/400. Patients with exceptionally high or low baseline visual acuities are often excluded from other clinical studies due to specific inclusion criteria, such as those pertaining to age-related macular degeneration. In the subgroup of patients with baseline visual acuity ranging from 20/40 to 20/400, we noted a nearly statistically significant improvement of 2 Snellen lines in visual acuity after three months of voriconazole treatment. It is imperative that this finding be validated in a confirmatory treatment study involving participants

whose initial visual acuity is within this range. Clinical studies are necessary to provide a comprehensive evidence base to inform treatment, despite the increasing use of voriconazole in clinical practice for fungal keratitis, supported by in vitro and anecdotal success in patients.[22]

CONCLUSION:

Our research suggests that individuals administered voriconazole may experience a one-line enhancement in best spectacle-corrected visual acuity (BSCVA) after three months, representing a modest improvement relative to those receiving natamycin. There were significant differences between the two treatment groups, and the effects of both drugs were statistically significant when it came to scar size and how patients perceived their pain. Topical voriconazole may be a beneficial adjunct to natamycin therapy for patients unresponsive to natamycin monotherapy. The decision between voriconazole and natamycin may hinge on the specific fungal infection, such as Aspergillus or Candida. To find the best treatment for fungal keratitis, you should talk to an eye care professional. The best plan may involve a mix of medications or other treatments.

CONFLICT OFF INTEREST:

Nil

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