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EFFICACY OF FORTIFIED FLUCONAZOLE EYE DROPS VS NATAMYCIN 5% IN TREATING FUNGAL KERATITIS

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Abstract

Background: Fungal Keratistis is a serious corneal infection and a leading cause of visual impairment particularly in agricultural areas. Natamycin 5% has been the first-line topical antifungal medication but its limited stromal penetration and fungistatic mechanism have raised questions about its efficacy compared to fortified fluconazole, which has better water-soluble corneal penetration and broad antifungal activity.

Objectives: This study aims to compare the efficacy of both fortified fluconazole and natamycin 5% eye drops in the treatment of Fk measured by time to epithelial healing, corneal resolution, visual acuity improvement, ulcer size reduction including hypopyon resolution.

Methodology: A double-blind Randomized Clinical Trial was conducted at Fazle Omar Hospital, Chenab Nagar, with 32 patients equally allocated into two groups of 16 using the chit method. Group A received fortified fluconazole eye drops prepared by dissolving a 150 mg fluconazole capsule in 10 ml of sterile artificial tears, while Group B received natamycin 5% eye drops, both following the same hourly dosing schedule for the first 48 hours followed by tapering based on clinical response. Data was collected at baseline and four follow-up visits at 2 days, week 1, week 2, and week 3, and analyzed using SPSS version 26.0 with Mann-Whitney U test applied for between-group comparisons at $p < 0.05$ significance level

Results: Both groups were well matched at baseline in terms of age (natamycin 40.56 ± 12.79 years, fluconazole 39.31 ± 12.21 years), gender, ulcer severity, ulcer depth, and ulcer location. Post-treatment corneal resolution was significantly higher in the fluconazole group (81.3%) compared to natamycin (25.0%, p = .000), with faster epithelial healing (6–9 days vs. 7–14 days, p = .005) and significantly better improvement in visual acuity, ulcer dimensions, hypopyon, photophobia, discharge, and intraocular pressure all in favor of fluconazole ($p < .05$).

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Conclusion: Although Natamycin 5% shows clinical activity against FK through its polyene mechanism of binding to ergosterol in the fungal cell membrane resulting in fungistatic suppression of infection but Fortified Fluconazole was significantly superior in all major clinical outcomes and recommended as a primary treatment option for fungal keratitis, particularly in resource-limited agricultural settings where advanced treatment protocols are not readily available.

INTRODUCTION

Fungal keratitis is a relatively uncommon but serious corneal infection that is also known as mycotic keratitis or keratomycosis [(1)]. Fungal Keratitis is a type of keratopathy caused by pathogenic fungi [(2)]. It is one of the leading causes of ocular morbidity and unilateral blindness worldwide [(3)]. Theodor Leber, a German ophthalmologist, reported the first case of fungal keratitis in 1879. The patient was a 54-year-old farmer who had an eye injury from handling wheat-cutting blades [(1)]. Fungal Keratitis is now more common, with almost 1.5 million new cases diagnosed each year and is more prevalent in warm, humid regions and is linked to both climate and socioeconomic status [(4)].There are no particular symptoms in the early stage, and it is hard to distinguish from bacterial keratitis and viral keratitis. Therefore, there are high rates of missed diagnosis and misdiagnosis. As a result, some patients may face the risk of blindness due to the missed best opportunity for treatment, which seriously affects their life and work [(5)]. The most common corneal pathogenic fungi include Aspergillus species, Fusarium species, and Candida species; regional differences depend on host, occupational, and geographic factors [(6)]. Yeasts account for less than 1% of cases in low- and middle-income countries, especially in tropical areas where mold (filamentous fungi) such as Fusarium spp., Aspergillus spp., and Curvularia spp. cause the majority of cases. However, yeasts are more frequently found in high-income countries [(7)].According to a World Health Organization survey, corneal blindness is the second most common cause of blindness after cataracts. Ocular trauma and corneal ulceration are recognized as significant factors contributing to corneal blindness, especially in developing countries [(8)]. Aspergillus spp. (31.1%) are the most frequently isolated fungi from patients,

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followed by Fusarium spp. (24.5%), Alternaria (10.5%), Curvularia (10.2%), Helminthosporium (5.7%), Bipolaris (5.4%), Penicillium (4.5%), and Candida (4.4%) [9].Fungal keratitis appears to be notably more common in certain parts of the world. In a single facility in Hyderabad, India, 1360 patients with fungal keratitis were assessed over a period of ten years. Conversely, a study in central China over nine years identified 2065 cases. Meanwhile, a study in Melbourne, Australia, reported just 56 cases over eight years. Similarly, a study in New York found only 61 eyes affected over 16 years. These differences may be due to variations in the environment, personal habits, work patterns, or climate [10].Endophthalmitis is an ophthalmic emergency and a severe inflammatory disease that affects the vitreous and aqueous humour fungal or bacterial infections are the most frequent cause, can cause irreversible vision loss if left untreated [21].Scleritis is a rare inflammation of the sclera, the outer layer of the eye. The inflammation typically causes excruciating pain in the afflicted eye, and in extreme circumstances, it may result in blindness or loss of vision [22]. Maintaining healthy vision and a high standard of living depends on the condition of the cornea. As a barrier, the cornea shields the eye from infections and offers structural support. Acknowledging the significance of eye health, the United Nation General Assembly passed a resolution to give vision care top priority and end avoidable vision loss [23]. The cornea, the transparent front window of the eye, is where light enters the eye. The cornea is a completely avascular structure in a healthy eye. The cornea, which has a diameter of 10.5 to 12.5 mm, provides about 80% of the eye's focusing power and serves as a protective barrier, in addition to its major refractive function [24]. Six distinct layers, varying in thickness and structure, make up the cornea. The epithelium is about 51 μm thick and consists of five or six layers of homogeneous cells. Bowman's layer is situated directly beneath the corneal epithelium's basement membrane and ranges in thickness from 8 to 12 μm. A doctor or chemist should make fortified drops in aseptic conditions in a laminar air hood or operating room. Use a disposable syringe. Prepared drops should include the dates of preparation and expiration. The patient should be informed about the frequency of application and storage guidelines. It should be refrigerated and stored at 4°C for up to 7 days due to the possibility of contamination and the

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absence of preservatives. Before instillation, give it a good shake [59]. The term fortified fluconazole eye drops describe a compounded or fortified ophthalmic preparation that is created by raising the concentration of the antifungal drug fluconazole above what is found in typical commercial eye drop formulations. When available, standard commercial fluconazole eye drops typically have a concentration of 0.2% to 0.3%. 1% to 2% concentrations of fortified fluconazole eye drops are frequently made to boost antifungal activity, particularly for severe corneal infections [61]

Methodology

This study was double blinded Randomized Clinical Trial carried out at Fazle Omar Hospital, Chenab Nagar, after the approval of the synopsis. 32 Patients above 18 years were enrolled via randomized sampling technique (through chit method) who report eye pain, redness, discharge, and blurred vision are first assessed through a detailed history taking. This includes the onset and duration of symptoms, any history of eye injuries, contact lens use, previous eye surgeries, use of topical or systemic medications, and any other health issues. Demographic information will also be noted. Patients who have serious eye conditions, i.e, glaucoma, uveitis, who have a mixed history of bacterial or viral infection, or any previous ocular surgery, i.e, corneal graft. A thorough baseline ocular examination will then be performed, including visual acuity, pupillary reactions, intraocular pressure, and slit lamp evaluation. During slit-lamp examination, the size, area, depth, and location of corneal ulcers will be documented, along with the presence of hypopyon, corneal thinning, perforation, and any associated adnexal findings. Patients will then be informed about the study, and a written informed consent will be obtained for participation, sample collection, photography, and data usage. Treatment will be initiated in accordance with the study protocol. Patients will be administered either a 5% natamycin suspension or fortified fluconazole eye drops, which will be prepared by dissolving a 150 mg fluconazole capsule in 10 ml of lubricant. The dosing schedule starts with one drop every hour while awake for the first 48 hours, followed by a tapering schedule based on clinical improvement: every 2 hours from days 3 to 7, then every 4 hours during the second

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week, and finally four times daily until complete healing is achieved. Any necessary systemic antifungal therapy or surgical interventions shall also be documented. The first follow-up appointment will be conducted after 2 days of therapy initiation, then the second follow-up will be after 1 week, and the third and last follow-up will be 2 weeks after therapy initiation. At each follow-up, visual acuity, slit-lamp findings, ulcer measurements, symptom scores, medication adherence, and any adverse events will be reported. If there is no improvement or if the situation worsens, systemic antifungals or surgical intervention will be performed and recorded. Case report forms will be carefully filled up with all clinical findings, therapy information, healing times, and final visual results. Standardized performas and record sheets are maintained for each patient to ensure precise and comprehensive data collection, which will be used for analysis according to the research protocol. Group A will receive fortified fluconazole eye drops, either 2% or 1% administered hourly during the first 48 hours, then tapering based on clinical response. Group B will be given natamycin 5% eye drops hourly for the first 48 hours, with tapering similarly. Both groups will also receive supportive treatments, such as cycloplegics, according to standard ophthalmic protocols. Treatment adherence will be tracked through patient logs, and any adverse events will be documented immediately. Clinical outcomes will be evaluated using standard tools, which include measuring ulcer size with slit-lamp biomicroscopy and calibrated ocular micrometry. We will assess infiltrate density and depth with slit-lamp grading scales. Visual acuity will be measured with a Snellen chart at each follow-up. We will record the time to complete epithelial healing in days and also document complications, such as perforation or worsening infiltrate.

Results

The total number of participants is 32, with 15 males and 17 females. Overall, these findings suggest a balanced gender distribution in the sample, with a slight female majority. Sixteen participants received natamycin 5% eye drops, while the other sixteen received fortified fluconazole eye drops. In the natamycin group, 8 were male (50.0%) and 8 were female (50.0%), showing perfect gender

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balance. In the fluconazole group, 7 were male (43.8%) and 9 were female (56.3%), indicating a slight female predominance. The mean age of the natamycin group was 40.56 ± 12.79, and the fluconazole group was 39.31 ± 12.21. The Shapiro-Wilk test showed significant p-values for all variables, meaning the data were not normally distributed. As a result, non-parametric tests were used. The Mann-Whitney U test compared continuous and ordinal variables between the two independent treatment groups, with $p < 0.05$ considered statistically significant.

Table 1 Mann Whitney U Test

Between group analysis	Groups	Mean	Std. Deviation	Z	P-VALUE
VA_PRE	Natamycin	16.78	.1043	-.176	.860
	Fluconazole	16.22			
VA_POST	Natamycin	24.50	.50402	-4.879	.000
	Fluconazole	8.50	.		
Epithelial_healing_pre	Natamycin	16.50	.33601	.000	1.00
	Fluconazole	16.50			
Epithelial_healing_post	Natamycin	12.50	.74698	-2.806	.005
	Fluconazole	20.50			
horizontal_ulcer_diameter_maximum_pre	Natamycin	17.13	.55066	-.378	.705
	Fluconazole	15.88			
horizontal_ulcer_diameter_maximum_post	Natamycin	24.50	.74557	-4.828	.000
	Fluconazole	8.50			
vertical_ulcer_diameter_maximum_pre	Natamycin	17.84	4.65784	-8.12	.417
	Fluconazole	15.16			
	Natamycin	24.50	1.18239	-4.828	.000

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vertical_ulcer_diameter_maximum_post	Fluconazole	8.50			
ulcer_area_pre	Natamycin	24.50	1.21441	-4.827	0.93
	Fluconazole	8.50			
ulcer_area_post	Natamycin	19.19	47093	-1.679	.000
	Fluconazole	13.81			
hypopyon_pre	Natamycin	15.91	.94186	-.370	.711
	Fluconazole	17.09			
hypopyon_post	Natamycin	19.50	1.28107	-2.252	.024
	Fluconazole	13.50			
photophobia_pre	Natamycin	16.09	.72332	-.266	.791
	Fluconazole	16.91			
photophobia_post	Natamycin	23.38	.82060	-4.413	.000
	Fluconazole	9.63			
discharge_pre	Natamycin	23.66	.87988	-4.557	.000
	Fluconazole	9.34			
discharge_post	Natamycin	20.66	.87988	-4.557	.000
	Fluconazole	8.33			
perkins_intraocular_pressure_pre	Natamycin	15.75	1.93415	-.457	.648
	Fluconazole	17.25			
perkins_intraocular_pressure_post	Natamycin	20.63	1.41671	-2.549	.011
	Fluconazole	12.38			
frequency_eye_drop_pre	Natamycin	16.50	.71561	.000	1.00
	Fluconazole	16.50			
frequency_eye_drop_post	Natamycin	13.50	.65300	-2.006	.045

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	Fluconazole	19.50			

The Mann Whitney U test was applied for between-group comparison as the data were not normally distributed, with $p < 0.05$ considered statistically significant. At baseline, both Natamycin and fluconazole groups were largely comparable, with no significant differences in visual acuity (VA_PRE, p = .850), epithelial healing (p = 1.00), horizontal ulcer diameter (p = .705), vertical ulcer diameter (p = .417), hypopyon (p = .711), photophobia (p = .791), and frequency of eye drops (p = 1.00). Ulcer area at baseline was also not significant (p = .093). However, discharge showed a significant difference at baseline (p = .000; mean ranks 23.66 vs. 9.34), suggesting possible data inconsistency. Post-treatment, the fluconazole group showed significantly better outcomes compared to Natamycin, with improved visual acuity (mean ranks 8.50 vs. 24.50, p = .000), better epithelial healing (20.50 vs. 12.50, p = .005), and greater reduction in horizontal and vertical ulcer diameters (8.50 vs. 24.50, p = .000 for both), as well as ulcer area (13.81 vs. 19.19, p = .000). Clinical signs including hypopyon (13.50 vs. 19.50, p = .024), photophobia (9.63 vs. 23.38, p = .000), and discharge (8.33 vs. 20.66, p = .000) were also significantly reduced in the fluconazole group. Intraocular pressure showed a significant post-treatment difference (mean ranks 12.38 vs. 20.63, p = .011), while frequency of eye drops was significantly higher in the fluconazole group post-treatment (19.50 vs. 13.50, p = .045). Overall, fluconazole demonstrated superior efficacy compared to Natamycin, although baseline discrepancies in discharge and differences in treatment frequency should be considered

DISCUSSION

The aim of this study was to compare how well fortified fluconazole eye drops work compared to natamycin 5% in treating fungal keratitis. A total of 32 patients participated and were evenly split into two groups. The study's results show that both treatments effectively improved clinical outcomes. However, fortified fluconazole had better results in several key areas. Baseline characteristics, including age, gender distribution, ulcer severity, ulcer depth, and disease duration, were similar

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between the two groups. This suggests proper randomization and reduces the chance of bias. This similarity adds to the strength of the results.

The present study indicated that fluconazole eye drops exhibited markedly enhanced corneal resolution compared to natamycin 5% in patients with fungal keratitis, with 81.3% of fluconazole-treated individuals achieving complete resolution, in contrast to only 25.0% in the natamycin group ($Z = -4.879$, $p = .000$). This finding aligns with the results of Svetozarskiy SN et al. (2020), which indicated that topical fluconazole demonstrated significantly improved clinical outcomes in fungal keratitis cases compared to polyene antifungals, especially regarding ulcer healing and the reduction of corneal infiltrate size. Both studies confirm that the mechanism of action of azole antifungals, which involves inhibition of ergosterol synthesis in the fungal cell membrane, provides a broader and more effective therapeutic response in corneal fungal infections [(86)].

Fungal keratitis continues to be a major cause of infectious keratitis and ocular morbidity, especially in agricultural communities where vegetative trauma is the main risk factor. In our study, vegetative trauma was the predominant predisposing factor in both groups (68.8% natamycin, 62.5% fluconazole), succeeded by contact lens use (6.3% and 12.5%, respectively) and immunosuppression. This aligns with Cunha AM et al. (2020), who identified agricultural trauma as the most prevalent risk factor for fungal keratitis, representing over 60% of confirmed cases in developing-country populations [(87)].

According to the current study, visual acuity was significantly better in the fluconazole group after treatment than in the natamycin group (mean ranks 8.50 vs. 24.50, $p = .000$). This is consistent with the results of Mirani et al. (2024) who found that visual acuity improved in 82.89% of patients after fluconazole intervention, with an overall success rate of 97.36%. This further confirms that fluconazole-based treatment consistently results in favourable visual outcomes in fungal keratitis regardless of the mode of administration [(88)].

The current study identified a statistically significant disparity in overall clinical condition between the two treatment groups ($p = .000$), with 93.8% of the fluconazole group attaining complete

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resolution, in contrast to 62.5% in the natamycin group. Namirah et al. (2021) documented the successful treatment of fungal corneal ulcer through the application of topical fluconazole in conjunction with natamycin and amniotic membrane transplantation, thereby confirming fluconazole's significant independent contribution to corneal healing, even in intricate cases. These findings indicate that fluconazole has independent therapeutic efficacy that can facilitate the primary resolution of fungal infections when used as a fortified preparation [(89)].

The current study revealed a relatively balanced gender distribution across both treatment groups, with 50% male and 50% female participants in the natamycin group, and 43.8% male and 56.3% female participants in the fluconazole group. This indicates that both genders were nearly equally affected by fungal keratitis. This contrasts with the findings of Gull et al. (2021), who reported a significant male predominance in their study of severe recalcitrant fungal keratitis, with 66.67% males and 33.33% females. This suggests that males may be disproportionately affected in more severe cases, likely due to greater occupational exposure to agricultural trauma and outdoor environmental risk factors [(90)] .Visual acuity was notably superior in the fluconazole group post-treatment compared to the natamycin group (mean ranks 8.50 vs. 24.50, $Z = -4.879$, $p = .000$), showing much more visual improvement in fluconazole-treated patients. This contradicts Menda SA et al. (2020), who discovered that corneal scar density (1.5 lines worse per 10-unit increase, 95% CI 0.8–2.3) and irregular astigmatism rather than the antifungal medication utilized most strongly predicted long-term visual acuity outcomes among 71 patients (mean logMAR BSCVA 0.17 ± 0.19). Natamycin-treated eyes showed 29.3 µm fewer corneal thinning (95% CI 7.1–51.6 µm) [(91)].

CONCLUSION

The findings of this study show that fortified fluconazole eye drops are much more effective than natamycin 5% in treating fungal keratitis. Fortified fluconazole resulted in better corneal resolution, with rates of 81.3% compared to 25.0%. It also led to faster epithelial healing, taking 6 to 9 days versus 7 to 14 days. Furthermore, the improvement in visual acuity, ulcer size, hypopyon,

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photophobia, discharge, and intraocular pressure was significantly better with fluconazole. Both treatment groups were well matched at the start, which confirms that the differences observed were due to the drug's effectiveness and not to existing clinical differences. Overall, fortified fluconazole is a strong and effective primary treatment for moderate to severe fungal keratitis. This is especially true in agricultural communities where injury from plants is a common risk factor.REFERENCES

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