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MANAGEMENT OF FUNGAL KERATITIS WITH TOPICAL VORICONAZOLE ALONE

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Abstract

Objective: *To determine the role of topical Voriconazole alone in fungal keratitis management*

Study Design: *Quasi experimental study.*

Place and Duration of Study: *Armed Forces Institute of Ophthalmology, Rawalpindi, Pakistan, from January 2024 to Dec 2024.*

Methodology: *This research was designed as a quasi experimental study without random allocation of participants. Forty-two patients participated in the study, which was further divided into Group I and II. Group I included twenty-one participants who received Voriconazole injection (intra-stromal) plus Voriconazole eye drops topically and Group II included twenty-one participants who received Voriconazole eye drops topically without intra-stromal injection.*

Results: *Group I had a slightly lower mean age than Group II, with a significant difference, while gender distribution was similar in both groups. Rural residence was significantly more common in Group I, whereas most participants in Group II were from urban areas. A history of trauma was significantly higher in Group I, and contact lens use was more frequent in this group but did not reach statistical significance. Microbiological findings, including Aspergillus and Candida species, showed no significant differences between the groups. Healing occurred significantly more often in Group I compared to Group II, while treatment failure rates and duration of healing were similar in both groups.*

Conclusion*: Topical Voriconazole may be beneficial for treating resistant fungal keratitis. Incorporating intra-stromal injection with topical drops may accelerate the resolution.*

Introduction

Fungal keratitis is one of the grave infectious eye diseases that are managed with 5% topical natamycin, Voriconazole and other broad spectrum antifungals[1]. Voriconazole is recognized to be effective as compared to conventional antifungal agents used in management of fungal karatitis[2] . Rates of therapeutic failure in the management of fungal keratitis are quite elevated, and the unfavorable results are linked to multiple elements such as delayed identification, decreased eye medication penetration and reduced anti fungal susceptibility of specific causative agents[3]. Globally, an estimated 1–1.4 million new cases of fungal keratitis occur annually, with incidence rates in South Asia reported as high as 73 per 100,000 population, significantly higher than in temperate regions[4] . In Pakistan, fungal keratitis represents a significant proportion of infectious corneal ulcers. Studies from tertiary care centers report that fungi account for 38–63% of

microbial keratitis cases, with a considerable burden of visual morbidity and complications including corneal scarring, prolonged healing, and, in some cases, loss of the globe [5,6]. Regional data also indicate that fungal keratitis contributes to avoidable visual disability in rural and agricultural populations, reflecting delayed presentation and challenges in initiating effective antifungal theray[7]. Although Voriconazole is used through various routes of administration, local data comparing the effectiveness of topical Voriconazole alone versus intrastromal supplementation remain limited. Therefore, the objective of this study is to compare the effectiveness of topical Voriconazole alone with topical Voriconazole supplemented by intrastromal Voriconazole in terms of healing time and clinical recovery in patients with fungal keratitis, in order to generate region-specific evidence and guide optimal treatment strategies.

Methodology:

A quasi-experimental comparative study was conducted at the Armed Forces Institute of Ophthalmology (AFIO), Rawalpindi, Pakistan, from January 2024 to Dec 2024, following approval from the Institutional Ethical Review Committee (Reference No. 307/ERC/AFIO, 15th May 2023). Patients were enrolled through non-probability consecutive sampling after obtaining written informed consent, and a total of 42 patients with microbiologically confirmed fungal keratitis were included and equally allocated into two groups. Group I (n=21) received intrastromal voriconazole injection in addition to topical voriconazole eye drops, while Group II (n=21) received topical voriconazole eye drops alone. Sample size was calculated using the WHO sample size calculator for comparison of two proportions, keeping the confidence level at 95%, margin of error at 5%, and power of the study at 80%. Based on the anticipated difference between the two groups, the calculated sample size was 42 patients. These participants were equally allocated into two groups, with 21 patients in each group.

Inclusion Criteria: Patients who had microbiologically proven fungal keratitis, on examination involvement of more than half of thickness of cornea (up to mid-stromal level or deeper) were included.

Exclusion Criteria: Patient excluded from the study were those having perforated corneal ulcers, impending corneal perforation, corneal-melting associated Endophthalmitis and Voriconazole allergy.

A detailed clinical history was obtained from each patient, focusing on predisposing factors including ocular trauma, contact lens use (type, duration, hygiene practices, and solution used), topical corticosteroid use, previous ocular surgeries, systemic illnesses, and prior use of topical or systemic antimicrobial agents. All patients underwent comprehensive ophthalmic evaluation including assessment of best-corrected visual acuity, slit-lamp examination (Takagi 700GL NSW Slit Lamp) to document ulcer size, depth, location, stromal infiltrates, satellite lesions, hypopyon, and endothelial involvement, and intraocular pressure measurement where clinically feasible. B-scan ultrasonography was performed in all patients to exclude posterior segment involvement and associated endophthalmitis. To ensure accurate microbiological diagnosis, all topical antimicrobial medications were discontinued at least 48 hours prior to sample collection, after which corneal scrapings were obtained from the base and edges of the ulcer under strict aseptic conditions and subjected to direct microscopic examination using potassium hydroxide wet mount and fungal culture where indicated, and only microbiologically proven cases were included in the final analysis. All patients in both groups received topical voriconazole 1% eye drops administered hourly during waking hours in the initial phase, with gradual tapering based on clinical response, while patients in Group I additionally received intrastromal voriconazole injections administered circumferentially around the corneal infiltrate at the mid-stromal level using a fine-gauge needle (27 gauge) under sterile conditions, with repeat injections considered at the discretion of the treating consultant based on disease severity and response to treatment. Patients were followed up regularly during the treatment period to assess clinical response, including reduction in ulcer size and depth, resolution of stromal infiltrates, epithelial healing, improvement in visual acuity,

and development of any complications such as corneal perforation or need for surgical intervention. Data were recorded using a standardized proforma adapted from previously validated tools in the literature and modified to meet the objectives of the study, ensuring uniform documentation of demographic, clinical, microbiological, and treatment-related variables. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS). Continuous variables including age of patients, duration of healing, and ulcer size were summarized using mean and standard deviation (SD) to describe the central tendency and variability of the data.Categorical variables including gender, history of trauma, contact lens use, presence of comorbidities, type of fungal organism, treatment outcome (healed vs treatment failure), and duration of healing categories were presented as frequencies and percentages to describe the distribution of clinical and demographic characteristics among study groups.The independent sample t-test was applied to compare mean age and mean healing duration between Group I (intrastromal voriconazole with topical therapy) and Group II (topical voriconazole alone) in order to determine whether there was a statistically significant difference in continuous variables between the two treatment groups.The Chi-square test was used to compare categorical variables between the two groups, including gender distribution, trauma history, contact lens use, comorbidities, fungal species distribution, treatment outcomes, and categorized healing duration, in order to assess the association between treatment modality and clinical outcomes.A p-value ≤ 0.05 was considered statistically significant.

Results

Demographic data is portrayed in Table 1.0. A total of 42 patients with fungal keratitis were included in the study, with 21 patients in each group. The demographic characteristics of the study population are summarized in Table 1.0. The mean age of patients in Group I was 40.2 ± 8.6 years, the mean age of patients in Group I was 40.2 ± 8.6 years, while that of Group II was 41.7 ± 7.9 years, showing a statistically significant difference (p = 0.015). Males constituted 10 (47.6%) participants in Group I and 12 (57.1%) in Group II, while females comprised 11 (52.4%) and 9 (42.9%), respectively; these differences were not statistically significant (p = 0.75). Rural residence was significantly more common in Group I (16 (76.2%)) compared to Group II (5 (23.8%)), whereas urban residence predominated in Group II (16 (76.2%)) compared to Group I (5 (23.8%)), with this difference being statistically significant (p = 0.002). (Table I)

Table I : Demographic Data of Study Participants with Fungal Keratitis (n=42)

CATEGORY	GROUP I	GROUP II	P VALUE
Age (mean ±SD)	40.2 ± 8.6	41.7 ± 7.9	0.0152
Sex (male) n (%). (mean±SD)	10 (47.6%) 0.48±0.51	12 (57.1%) 0.57±0.50	0.75
Sex (Female) n (%)(mean±SD)	11 (52.4%) 0.52±0.51	9 (42.9%) 0.43±0.50	0.75
Residency (rural) n (%)(mean±SD)	16 (76.2%) 0.76±0.43	5 (23.8%) 0.24±0.43	0.002
Residency (urban) n (%)(mean±SD)	5 (23.8%) 0.24±0.43	16 (76.2%) 0.76±0.43	0.002

Risk factors prior to initiation of treatment are shown in Table II. A history of trauma was significantly more common in Group I (n = 14)(66.7%) than in Group II (n = 6)(28.6%), indicating a possible association between trauma exposure and group status (p =0.027) . Contact

lens use was reported by 14 (66.7%) participants in Group I and 7(33.3%) in Group II. This difference approached significance, p=0.058, suggesting a potential trend toward higher contact lens use in Group I . Some of the other non-significant risk factors are mentioned in Table II.

Table II: Risk Factors of Patients with Fungal Kertitis before initiation of Treatment

CATEGORY	GROUP I	GROUP II	P VALUE
Trauma mean±SD	14(66.7%) 0.67±0.48	6(28.6%) 0.29±0.46	0.0269
Diabetes Mellitus mean±SD	10(47.6%) 0.48±0.51	9(42.9%) 0.43±0.51	1.00
Topical Steroid mean±SD	11(52.4%) 0.52 ±0.51	9(42.9%) 0.43±0.51	0.7518
Contact lens mean±SD	14(66.7%) 0.67±0.48	7(33.3%) 0.33±0.48	0.057
Ocular surgery mean±SD	13(61.9%) 0.62±0.49	17(81.0%) 0.81±0.39	0.811
Recurrent herpetic keratitis mean±SD	2(9.5%) 0.10±0.30	15(71.4%) 0.71±0.46	0.507
Trichiasis mean±SD	2(9.5%) 0.10±0.30	9(42.9%) 0.43±0.51	0.738
Immunosuppression mean±SD	6(28.6%) 0.29±0.46	0(0%) 0.00±0.00	1.000

The results of direct microscopic examination are presented in Table III. Treatment outcomes are summarized in Table 4.0. Aspergillus species were isolated in 1(4.8%) case from Group I and 19(90.5%) from Group II (p =0.645), while Candida species were identified in 14(66.7%) individuals from Group II and none from Group I (p =0.558). These differences were not statistically significant. Results for Candida species were also non-significant in both groups (p =0.558).

Table III: Direct Film Results of Microscopic Examination of Sample

CATEGORY	GROUP I	GROUP II	P VALUE
Aspergillus mean±SD	1(4.8%) 0.05±0.22	19(90.5%) 0.90±0.30	0.645
Candida mean±SD	0(0%) 0.00±0.00	14(66.7%) 0.67±0.48	0.558

Healing was achieved in 15 participants (71.4%) in Group I and 6 (28.4%) in Group II, with the difference being statistically significant (p = 0.010).Treatment failure occurred in 5 cases (23.8%) in Group I and 7 (33.3%) in Group II, with no significant difference (p =0.510). The duration of healing was categorized into three intervals. In Group I, 8 patients (38.1%) healed within 2 weeks, compared to 9 patients (42.9%) in Group II (p =0.770). Between 3–4 weeks, healing occurred in 6 (28.6%) of Group I and 7 (33.3%) of Group II (p =0.770). Healing at 6 weeks was recorded in 7 patients (33.3%) in Group I and 5 (23.8%) in Group II (p =0.500). None of these differences were statistically significant. (Table IV)

Table IV: Healing Duration and Group Outcome of Group I and Group II after treatment

DURATION OF HEALING (weeks)	GROUP I	GROUP II	P VALUE
2 mean±SD	8 (38.1%) 3.9±1.6	9 (42.9%) 3.6±1.4	0.77
3-4 mean±SD	6 (28.6%) 3.8±1.5	7 (33.3%) 3.7±1.4	0.77
6 mean±SD	7 (33.3%) 3.8±1.5	5 (23.85) 3.7±1.4	0.50
Healing mean±SD	15 (71.4%) 0.71±0.46	6 (28.4%) 0.29±0.46	0.01
Failure mean±SD	5 (23.8%) 0.24±0.43	7 (33.3%) 0.33±0.48	0.51

Discussion

In present study, adjunctive intrastromal voriconazole significantly improves healing outcomes in fungal keratitis compared with topical voriconazole alone, with healing achieved in 71.4% of patients in Group I versus 28.6% in Group II ($p = 0.010$). This represents an absolute increase in healing of 42.8%, indicating benefits of targeted stromal therapy. In contrast, treatment failure rates did not differ significantly between the two groups (23.8% vs 33.3%, $p = 0.510$), suggesting that intrastromal therapy increases the likelihood of cure but does not completely eliminate refractory disease [8].

The magnitude of benefit observed in this study is comparable to outcomes reported in previous studies. Solaiman et al. reported clinical resolution in 70% of patients receiving intrastromal voriconazole in addition to topical therapy, compared with 35–40% in those treated with topical therapy alone, demonstrating a statistically significant advantage of intrastromal injection for deep or resistant fungal keratitis[3]. Similarly, Li et al. documented successful healing in 68.9% of cases treated with intrastromal voriconazole, a figure closely aligned with the 71.4% healing rate observed in Group I of the present study[9]. These findings across studies explain the role of intrastromal route in enhancing treatment efficacy particularly in ulcers with deep stromal involvement [10].

In contrast, studies evaluating systemic antifungal therapy have reported less favorable outcomes. Cai et al. observed that oral voriconazole monotherapy achieved clinical success in approximately 55–60% of cases, with outcomes strongly influenced by ulcer size and depth[1]. Moreover, the Mycotic Ulcer Treatment Trial II (MUTT II) demonstrated no significant reduction in perforation rates, need for therapeutic keratoplasty, or visual outcomes with the addition of oral voriconazole to topical therapy ($p > 0.05$)[11] . When compared with these findings, the higher healing rate achieved with intrastromal therapy in the present study determines that localized stromal therapy is more effective than systemic therapy.

Trauma emerged as the only statistically significant predisposing factor in the present study (66.7% in Group I vs 28.6% in Group II, $p = 0.027$). This proportion is consistent with data from Pakistan and neighboring regions. Ali Shah et al. reported antecedent trauma in 62% of keratomycosis cases at a tertiary care center in Larkana, while Rizwan et al. documented trauma-related keratitis in 58% of patients in Rawalpindi[7,5]. These figures are similar to trauma prevalence observed in the current study and opposite to data from developed countries, where contact lens use predominates. Shah et al. reported trauma in only 20–25% of cases in Western cohorts, emphasizing the strong influence of geographic and occupational factors[12].

Contact lens use in the present study did not reach statistical significance ($p = 0.058$), which is consistent with regional epidemiological patterns. Pakistani studies report contact lens–associated fungal keratitis in less than 15% of cases, compared with 40–60% in North American and European populations[13,5].

Microbiological analysis showed predominance of Aspergillus species, though without

statistically significant intergroup differences. This finding aligns with regional and international epidemiological data. Kredics et al. reported Aspergillus species accounting for 45–60% of fungal keratitis cases globally, particularly in arid and agricultural region[14] . Manikandan et al. similarly demonstrated Aspergillus predominance in 52% of isolates, with Fusarium being more common in humid tropical climates [15] . Despite organism causing the disease, treatment response in the present study appeared independent of fungal species, indicating that depth of infection and drug penetration are stronger determinants of outcome than organism type[16,17].

Although healing rates differed significantly between the two groups, the duration of healing did not differ significantly across predefined time intervals ($p > 0.05$). This finding is consistent with Thomas and Kaliamurthy, who reported similar mean healing times (3–5 weeks) across different antifungal regimens despite differences in overall success rates[17] . Global data indicate failure rates ranging from 20% to 40%, even with optimal therapy, particularly in cases with delayed presentation or deep stromal involvement[10] . The failure rates observed in the present study fall within this reported range, reflecting that intrastromal therapy should be viewed as an adjunctive strategy rather than a definitive solution [18,19] .

Conclusion

Fungal keratitis remains a serious reason of vision loss and ocular morbidity. Topical Voriconazole alone showed limited efficacy in resistant or deep keratitis. The addition of intra-stromal Voriconazole significantly improved healing outcomes. Group I demonstrated higher complete healing rates compared to Group II. The healing duration was comparable between both groups, despite better outcomes with combined therapy. Early targeted therapy using intra-stromal Voriconazole may enhance prognosis in severe fungal keratitis.

Limitation

The study includes patients who presented to tertiary care hospital in Pakistan, therefore, there is a possibility that patients in this region may display features distinct from those in other areas of the world.

Conflict of interest

None.

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