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Original Research Article

COMPARATIVE EFFICACY OF TOPICAL VERSUS INTRASTROMAL VORICONAZOLE IN THE MANAGEMENT OF FUNGAL KERATITIS: A PROSPECTIVE COMPARATIVE STUDY

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ABSTRACT

Background: Fungal keratitis remains a significant cause of corneal morbidity and preventable visual impairment, particularly in agricultural communities and resource-limited settings. Management is challenging because of delayed presentation, deep stromal infiltration, and limited penetration of topical antifungal agents into infected tissue. Although topical antifungal therapy remains the mainstay of treatment, adjunctive approaches that improve drug delivery to the infected corneal stroma may offer additional benefits in selected patients. **Aim:** To compare clinical outcomes of intrastromal Voriconazole with topical Voriconazole versus topical voriconazole alone for treating deep fungal keratitis at a tertiary care centre in arid Rajasthan.

Materials and Methods: This comparative study was conducted at a tertiary-care ophthalmology centre in Rajasthan over 12 months and included 40 patients with microbiologically confirmed fungal keratitis. Patients were allocated to two groups of 20 each. Group A received topical 1% voriconazole, while Group B received intrastromal voriconazole (50 µg/0.1 mL) in addition to the same topical treatment regimen. Outcomes included ulcer healing initiation, time to complete epithelial healing, corneal scar formation, final visual acuity, and complications. We reviewed our data descriptively and performed exploratory comparisons of selected categorical outcomes using Fisher's exact test.

Results: Healing began within the first week in 18/20 patients (90%) in Group B and 11/20 patients (55%) in Group A. An exploratory Fisher's exact test showed a difference between these proportions (P = 0.031). By four weeks, 14/20 patients (70%) in Group B and 7/20 (35%) in Group A had healed, with P = 0.056 on exploratory Fisher's exact test. Corneal scarring occurred in 18/20 patients (90%) in Group B and 17/20 (85%) in Group A. Perforation was reported in one patient (5%) in Group B and two patients (10%) in Group A. Final visual outcome was similar in both groups.

Conclusion: In this small comparative study, adjunctive intrastromal voriconazole was associated with earlier healing initiation. However, the available data do not establish superiority in final visual acuity, scar formation, or complication prevention. Larger studies with clearly defined outcomes and appropriate between-group analyses are needed.

Keywords: Voriconazole, intrastromal, topical, fungal keratitis

INTRODUCTION

Infectious keratitis involves a breach in corneal epithelial continuity, with infiltration and cellular necrosis of the surrounding corneal tissue. Pathologically, it is characterised by oedema and cellular infiltration. Infectious keratitis is a leading cause of monocular blindness worldwide. In some settings, up to 50% of keratitis cases are due to fungal [1] infection. Fungal keratitis is difficult to treat, and visual outcomes are often poor. Limitations of antifungal therapy include poor antifungal penetration, the indolent nature of the ulcer that can lead to deep stromal abscesses with an intact overlying epithelium, and poor penetration of systemic antifungals. Surgical intervention (such as therapeutic keratoplasty, evisceration, or enucleation) is necessary in a significant number of patients due to advanced keratitis, failed medical therapy and progressive thinning with impending perforation.

Current treatment protocol

The most important antifungal agents are polyenes and azoles, which affect fungal cell membranes and interfere with fungal protein synthesis.[2] The current treatment protocol for fungal corneal ulcers is far from optimal because of fungal growth characteristics, late diagnosis, the scarcity of effective antifungal agents, and poor tissue penetration of currently available therapeutic agents.

New-generation triazoles

Promising reports suggest that newer-generation triazoles may overcome key shortcomings of current therapies.

Triazoles,[3] inhibit ergosterol synthesis, which is required for fungal cell membrane synthesis. The newer triazoles, voriconazole, isavuconazole, and posaconazole, have broad-spectrum activity.

Voriconazole is available in India as 30 mg sterile lyophilised dry Voriconazole powder. To prepare a 1% (10 mg/ml) solution, reconstitute it with 3 ml of water for injection. Voriconazole remains stable for 30 days, providing an eye drop solution suitable for topical treatment of fungal keratitis.[4] Voriconazole is a recent triazole antifungal agent that is highly effective against Aspergillus, Fusarium, and Candida species. Furthermore, voriconazole is one of the few drugs active against Scedosporium apiospermum. To treat keratomycosis, antifungal eye drops must be administered for an extended period (at least 6 weeks).

Wei LC et al. [5] investigated the penetration of topical 1% voriconazole through the cornea and found that topically administered voriconazole achieved minimum inhibitory concentrations in the aqueous for all organisms most commonly involved in fungal endophthalmitis and in the vitreous for some pathogenic fungi. Voriconazole concentrations were higher in the scraped group than in the non-scraped group.

There are 3 possible routes of administering voriconazole in the treatment of fungal keratitis: topical, intrastromal and intracameral. In a study by Ali M. Ismail,[1] published in a life science journal in 2012, intrastromal and intracameral routes showed promising results in ulcer resolution time, best-corrected visual acuity, and a lower complication rate.

MATERIALS AND METHODS

Study design – Prospective comparative interventional study

Study setting - A tertiary-care eye hospital in Jaipur, Rajasthan

Ethical considerations - Ethical approval was obtained from the Institutional Ethics Committee before the study began.

Study duration – 12 months after ethical committee approval

Study population - Patients with microbiologically confirmed fungal keratitis

Inclusion Criteria - Presence of corneal ulcer at the time of presentation (corneal epithelial defect with stromal infiltration & necrosis); evidence of fungal filaments in the corneal ulcer on the smear (KOH wet mount, Gram staining)

Exclusion Criteria - Corneal ulcer less than 0.5 mm at the time of presentation, corneal perforation, impending perforation or descemetocele; presence of herpetic keratitis, bilateral ulcer, previous history of penetrating keratoplasty, pregnancy, known allergy to study drug, no perception of light in affected eye, patient not willing to participate in study, corneal ulcer in immunocompromised and diabetic patients

Sampling technique - The sample size required to detect the difference at a 95% confidence interval and 80% power was 15 per group, but expecting a 20% dropout during an 8-week follow-up required adjusting the sample size to 20:20.

Sample size: The study included 40 fungal corneal ulcer patients who met the inclusion and exclusion criteria, were recruited on a first-come, first-served basis, and were randomly allocated to 2 groups using the “envelope method”.

Conduct of the study- After evaluating the above written criteria, 40 patients were randomly divided into two groups of 20 each:

Group A: Topical Voriconazole group

Group B: Intrastromal Voriconazole group

The study was conducted in accordance with the Declaration of Helsinki. Each patient signed informed consent.

After taking a detailed history, we performed a full clinical, ophthalmic, and systemic evaluation of all patients. We stained the ulcer, measured its extent (horizontal and vertical), and drew it on a corneal map. We performed corneal scraping for each selected eye and sent it for Gram stain, KOH stain, and culture on blood agar and Sabouraud’s dextrose agar.

Treatment Protocol:
After confirmation of fungal keratitis, the following treatment was started:
Group A: Moxifloxacin 0.5% eye drops every 2 hours, Voriconazole 1% eye drops every 2 hours, a cycloplegic (Atropine 1% eye drops) three times a day, and an intraocular pressure-lowering agent (Timolol 0.5% eye drops) twice daily.
Group B: Patients received intrastromal Voriconazole solution 50 micrograms/0.1 ml circumferentially around the fungal ulcer in a single dose at the junction of clear cornea and infiltrates to form a barrage around the ulcer, in addition to the above-mentioned regimen.
We followed up all cases every alternate day for the first week, then biweekly for 2 weeks, and then weekly until 8 weeks after initiating the treatment.
At 8 weeks, the following points were noted and compared in both groups:

- Visual outcome, including BCVA in log MAR.
- 'Start' of ulcer healing.
- 'Complete' healing (fluorescein negativity).

We measured scar size at the end of treatment using slit-lamp microscopy, in its longest diameter and the perpendicular longest dimension.
Statistical analyses -Statistical analyses were done using computer software (SPSS version 20 and Primer). Qualitative data were expressed as proportions and percentages, and quantitative data as means and standard deviations. We analysed differences in proportions using the chi-square test and differences in means using Student's t-test; we used the paired t-test to assess the pre- and post-treatment logMAR Vn variable. The significance level for tests was set at 95% ($P< 0.05$).

RESULTS

After taking a detailed history, we performed a complete clinical, ophthalmic, and systemic evaluation for all patients. We performed corneal scraping from each selected eye and sent it for Gram stain, KOH stain, and culture on blood agar and Sabouraud's dextrose agar before starting treatment in both groups.
In this study, the mean age of patients presenting with fungal keratitis was approximately 48.70 years in group 'A' (topical Voriconazole) and 50.25 years in group 'B' (Intrastromal Voriconazole), respectively (Table 1). The mean age for all patients was 49.48 years. Since fungal keratitis is commonly initiated by trauma, younger age groups are more commonly exposed to such trauma, especially in rural populations.
The male-to-female ratio was approximately 2.3:1 in both the groups 'A' and 'B' (Table 1). The overall male-to-female ratio was also approximately 2.33:1, as males are more prone to corneal injury due to their occupational exposure.
The rural-to-urban ratio was approximately 1.85:1 for group 'A' and 2.33:1 for group 'B'(Table-1). In both groups (group 'A' and 'B'), most of the patients belong to rural areas where trauma with vegetative matter and exposure to crops is common.

Table 1: Distribution of the cases according to mean age, gender and location

	Topical voriconazole (Group A)	Intrastromal voriconazole (Group B)
Age	48.70	50.25
Gender (male/female)	14/6	14/6
Rural /Urban	12/8	14/6

In this study, a history of use of topical steroids was present in 5% of the total patients recruited. Use of topical steroids increases the chance of fungal infection of the cornea. Use of topical steroids is contraindicated in fungal keratitis, and inadvertent use may lead to blinding complications. Patients who were on steroids in this study received the medication from over-the-counter sources or from general practitioners, which is a common practice in rural populations. Basak SK et al., [10] and Wong TY et al., [11] reported similar histories. Both studies showed the devastating complications of topical steroid use in corneal ulcers with secondary fungal infection. This emphasises the need for judicious use of topical steroids in corneal ulcers, regardless of aetiology.
The average lapse time from disease onset to presentation was more than 8-10 days in both groups, as the condition is comparatively less symptomatic and patients present late. Signs such as corneal ulcer size and congestion were out of proportion to symptoms such as photophobia and foreign body sensation. In this study, almost all cases had deep stromal infiltration, possibly because patients presented late to the ophthalmologist. We assessed healing based on clinical parameters such as decreased corneal ulcer size and reduced congestion and watering.
In our study, 5 patients were KOH-negative (12.5%) but culture-positive; i.e., KOH mount sensitivity was 87.5%. Sharma N et al. [7] reported similar results, with KOH sensitivity of 83.33%.
Aspergillus and Fusarium (filamentous) fungi were the most commonly identified fungi in fungal corneal ulcers (Table 2). Similar results were found in Sharma N et al. [7]; Chander J, Sharma et al. [9]; and Panda A et al. [12]

Table 2: Distribution of the cases according to Species of fungus on culture

	Group B (N=20)		Group A(N=20)	
Species of fungus on culture	**Number**	**%**	**Number**	**%**
Curvuleria	1	5	1	5

Alternaria fungi	2	10	0	0
Aspergillus fumigatus	1	5	1	5
Aspergillus fungi	4	20	5	25
Aspergillus Niger	0	0	1	5
Candida	1	5	0	0
Contaminated	0	0	1	5
Fusarium	5	25	6	30
Penicillium	2	10	1	5
Report not available	4	20	4	20
Total	20	100	20	100

Hypopyon was present in 19 (47.5%) patients at presentation, and all patients were positive on fluorescent staining. Healing started at approximately the same time in both groups, slightly earlier in the 'B' (Intrastromal Voriconazole) group, but this difference was not statistically significant.

In this study, treatment response for deep corneal involvement in group 'B' was noted within 7 days in 90% (approx.), whereas in group 'A' it occurred within 7 days in only 50% (approx.) of patients (Table 3). This may have been due to deep corneal penetration of the drug at the site of infiltration in the intrastromal group.

Table 3: Distribution of the cases according to Healing start time (weeks)

	Group B (N=20)		Group A(N=20)	
Healing start time (weeks)	**Number**	**%**	**Number**	**%**
within a week	18	90	11	55
1 to 2 weeks	0	0	1	5
2weeks	0	0	5	25
did not occur	2	10	0	0
No response	0	0	2	10
Worsening	0	0	1	5
	20	100	20	100

Time taken for re-epithelialization (complete healing) of corneal ulcers differed between the two groups (Table 4). In group 'B', complete healing occurred within 4 weeks in 70% of cases, whereas only 35% of corneal ulcers healed completely within 4 weeks in group 'A'. Earlier healing of corneal ulcers in the Intrastromal Voriconazole ('B') group was statistically significant, which can be attributed to the antifungal medication's deep infiltration into the infected tissue in the intrastromal group.

Table 4: Distribution of the cases according to Average complete healing time (weeks)

Average complete healing time (weeks)	Group B (N=20)		GroupA(N=20)		Total(N=40)	
	No	**%**	**No**	**%**	**No**	**%**
3 weeks	1	5	0	0	1	2.5
4 weeks	13	65	7	35	20	50
5 weeks	4	20	11	55	15	37.5
No response	0	0	2	10	2	5
not occurred	2	10	0	0	2	5
Total	20	100	20	100	40	100

In this study, scar size was relatively smaller than ulcer size in both groups 'A' and 'B' (Table 5). In group 'B', the mean ulcer area was 15.76±12.10, and the mean scar size was 10.08±8.49; in group 'A', the mean ulcer area was 17.74±9.90, and the mean scar size was 13.33±7.63. But overall, there was no significant difference in the per cent mean reduction in size between the two groups

Table 5: Distribution of the cases according to scar formation

Scar formed	Group B (N=20)		Group A(N=20)		Total(N=40)	
	Number	**%**	**Number**	**%**	**No**	**%**
NO	2	10	3	15	5	12.5
Yes	18	90	17	85	35	87.5
Total	20	100	20	100	40	100

In this study, pretreatment log MAR vision did not differ significantly between the groups. Both groups demonstrated statistically significant changes in log MAR visual acuity following treatment (Table 6). Group B showed a slightly larger absolute mean difference (0.664) than Group A (0.614). The narrower confidence interval and larger absolute t-value in Group B indicate a more precise estimate of within-group change. However, these results do not establish that Group B is superior to Group A.

Table 6: Distribution of the cases according to pre- and post-treatment logMAR Vision

Paired Samples Test									
	log MAR Vision	Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Group A	Pre -post treatment	-.614	.964	.216	-1.07	-0.16	-2.85	19	0.010 S
Group B	Pre -post treatment	-.664	.474	.106	-0.89	-0.44	-6.27	19	<0.001S

The number of non-responding patients in both Group 'A' and Group 'B' was 2. Non-responders were patients who did not respond to one therapy regimen by the end of three weeks; they were switched to another regimen and excluded from this study.

The number of patients with complications such as perforation was 2 (10%) in Group 'A', 1 (5%) in Group 'B', and 1 case worsened, which is defined as an increase in the size or depth of the ulcer or infiltrate by 20% or perforation, which is in accordance with the results seen in a study done by Ali M. Ismail et al., [1] in which complication rates were higher in the Topical Voriconazole group than the Intrastromal Voriconazole group.

In our comparison of Topical Voriconazole and Intrastromal Voriconazole, the intrastromal modality was effective and safe for treating fungal corneal ulcers, with faster healing. Regarding visual acuity improvement, these results do not show that Group B is superior to Group A.

DISCUSSION

Fungal keratitis remains a significant cause of corneal morbidity and preventable visual impairment, particularly in agricultural communities and resource-limited settings. Management is challenging because of delayed presentation, deep stromal infiltration, and limited penetration of topical antifungal agents into infected tissue. Although topical antifungal therapy remains the mainstay of treatment, adjunctive approaches that improve drug delivery to the infected corneal stroma may offer additional benefits in selected patients. This study compared clinical outcomes with topical 1% voriconazole alone versus intrastromal voriconazole as an adjunct to the same topical regimen in patients with microbiologically confirmed fungal keratitis.

The principal finding was that patients receiving adjunctive intrastromal voriconazole healed earlier and had a higher proportion of complete ulcer healing within four weeks than those receiving topical voriconazole alone. However, the improvements in visual acuity, reductions in scar size, and complication rates require cautious interpretation. These findings suggest a potential role for intrastromal voriconazole as an adjunctive treatment in selected cases of fungal keratitis, particularly when deep stromal involvement limits the effectiveness of conventional topical therapy.

Demographic profile and clinical presentation

The mean age of patients was 48.70 years in the topical voriconazole group and 50.25 years in the intrastromal voriconazole group, with an overall mean age of 49.48 years. The predominance of patients in the middle-age group may reflect occupational exposure to agricultural activities and an increased risk of corneal trauma. A similar age distribution has been reported by Nath et al.,[6] Ali M Ismail et al.,[1] and Sharma et al.[7] The male-to-female ratio was approximately 2.33:1 in both groups, consistent with the observations of Chowdhary and Singh et al., [8] and Ali M Ismail et al. [1] This male predominance may be associated with differences in occupational exposure and outdoor activities. Most participants in both groups belonged to rural areas. Agricultural work and exposure to vegetative matter are recognised risk factors for fungal keratitis. The predominance of rural patients in our study is therefore consistent with the epidemiological pattern of fungal corneal infections in agricultural populations. Chander and Sharma et al. [9] reported similar observations.

The mean interval between disease onset and presentation was approximately 8–10 days or longer. Delayed presentation may contribute to deep stromal involvement and poorer clinical outcomes. This highlights the importance of early diagnosis, appropriate microbiological investigation, and timely initiation of antifungal treatment.

A history of prior topical corticosteroid use was documented in 5% of participants. Inappropriate corticosteroid use in an undiagnosed corneal ulcer may suppress local immune responses and facilitate progression of an underlying fungal infection. This finding reinforces the importance of carefully evaluating infectious keratitis and using topical corticosteroids judiciously.

Microbiological profile

Fusarium and Aspergillus species were the most frequently reported fungal isolates in our study. Fusarium accounted for 11 cases, and Aspergillus species, including the reported subtypes, accounted for 12 cases across both groups. These findings broadly align with previous reports by Sharma et al.,[7] Chander and Sharma et al.,[9] and Panda et al.,[12] which noted filamentous fungi as important causes of fungal keratitis.

The predominance of filamentous fungi has therapeutic implications because antifungal susceptibility may vary by causative organism. Although voriconazole has broad-spectrum

antifungal activity, clinical response may vary across fungal species. Identifying the causative organism and, where appropriate, performing antifungal susceptibility testing may therefore guide treatment, particularly in severe or nonresponding infections.

Five patients had negative potassium hydroxide (KOH) microscopy results despite positive fungal cultures, corresponding to a reported KOH sensitivity of 87.5% in the study population. This observation demonstrates that a negative KOH smear does not necessarily exclude fungal keratitis.

Initiation of healing

We observed a difference in time to healing initiation between the two treatment groups. Healing began within the first week in 18 of 20 patients (90%) receiving intrastromal voriconazole, compared with 11 of 20 patients (55%) receiving topical voriconazole alone. The earlier clinical response with adjunctive intrastromal voriconazole may reflect direct delivery of the antifungal agent into the corneal stroma. In deep-seated infections, topical medication may not achieve adequate concentrations throughout the infected tissue, particularly when the stromal infiltration is extensive. Intrastromal administration may increase local drug exposure at the infection site and potentially facilitate earlier control of fungal proliferation.

Nevertheless, time to initial clinical improvement does not equate to microbiological eradication or complete ulcer healing. Moreover, because both groups received topical voriconazole, the observed difference represents the potential additional benefit of intrastromal administration rather than the effect of intrastromal treatment in isolation.

Time to complete epithelial healing

Time to complete ulcer healing was another important outcome. The intrastromal group reported complete healing within four weeks in 14 of 20 patients (70%), compared with 7 of 20 patients (35%) in the topical group. The intrastromal group therefore showed a higher proportion of early complete healing, with an absolute difference of 30 percentage points.

This finding suggests that adjunctive intrastromal voriconazole may accelerate healing and recovery in selected patients with fungal keratitis. One possible explanation is improved drug delivery to infected stromal tissue, leading to faster infection control and enabling subsequent epithelial repair. However, several factors influence epithelial healing, including the initial ulcer size and depth, the causative organism, the degree of stromal necrosis, and the development of secondary complications.

These results suggest a potentially faster healing response, but they do not prove intrastromal voriconazole's overall superiority. Longer follow-up and larger comparative studies are required to determine whether earlier epithelial healing translates into better final visual acuity and fewer long-term complications.

Corneal scar formation and scar size

Corneal scarring occurred in 18 patients (90%) in the intrastromal group and 17 patients (85%) in the topical group. Thus, the overall proportion of patients developing a scar was similar between the two groups. The mean ulcer area was 15.76 ± 12.10 in the intrastromal group and 17.74 ± 9.90 in the topical group, while the corresponding mean scar measurements were 10.08 ± 8.49 and 13.33 ± 7.63, respectively.

Although the mean scar measurement was smaller in the intrastromal group, the available results do not establish a statistically significant between-group difference. The reported reduction in scar size may reflect resolution of the active inflammatory process and healing of the infected corneal tissue. However, scar formation also depends on the initial extent and depth of infection, stromal tissue destruction, and the host inflammatory response.

Corneal scarring remains clinically important because its location, density, and relationship to the visual axis may affect final visual acuity. Consequently, scarring alone may not adequately reflect treatment outcomes. Future studies should evaluate scar size using clearly specified measurement units and reproducible methods such as scar densitometry, central corneal involvement, and final best-corrected visual acuity.

Visual acuity outcomes

Both treatment groups showed statistically significant within-group changes in log MAR visual acuity, based on the reported paired analyses. The reported absolute mean differences were 0.614 in the topical group and 0.664 in the intrastromal group. However, these findings do not show that intrastromal voriconazole produces superior visual outcomes.

Visual recovery after fungal keratitis depends not only on infection control but also on the extent of residual corneal scarring, involvement of the central visual axis, and other ocular complications. Consequently, an intervention that accelerates ulcer healing may not necessarily produce a proportionately greater improvement in visual acuity. Furthermore, the pre- to post-treatment change within each group does not differ significantly between groups.

Complications and treatment safety

Complications were reported in both groups. Corneal perforation occurred in two patients (10%) in the topical group and one patient (5%) in the intrastromal group. The lower perforation rate in the intrastromal group may suggest a potential benefit from faster infection control. However, the small number of events and limited sample size prevent a reliable conclusion about reduced complication risk. A larger study with clearly defined complication outcomes is needed to determine whether intrastromal voriconazole reduces the risk of perforation or other vision-threatening sequelae.

No drug-related toxic effects were noted following intrastromal injection in our study. Nevertheless, the

absence of observed toxicity in a small sample does not establish the procedure's safety in a broader population. Intrastromal injection is an invasive procedure and requires careful patient selection, appropriate preparation of the drug, and monitoring for procedure-related complications. Future studies should systematically document adverse events, including stromal damage, endothelial toxicity, injection-related complications, and any worsening of the infection.

Clinical implications

Our study suggests that adjunctive intrastromal voriconazole may be a useful treatment option in selected patients with fungal keratitis, particularly when there is deep stromal infiltration and an inadequate response to conventional therapy. Its potential advantage is delivering the antifungal agent directly at the site of stromal infiltration, which may improve local drug exposure when topical penetration is insufficient.

However, this study alone does not support intrastromal voriconazole as a replacement for established antifungal therapy. Treatment selection should consider the causative organism, infection depth and severity, response to initial therapy, and perforation risk. Further evaluation is needed to determine the optimal concentration, volume, injection technique, and frequency of intrastromal administration.

Our results support further investigation of intrastromal voriconazole as an adjunctive approach, rather than a definitive treatment recommendation for all cases of fungal keratitis.

Strengths and limitations

An important strength of this study is its direct comparison of two treatment strategies in patients with microbiologically confirmed fungal keratitis. Both groups received the same background topical treatment regimen, allowing assessment of the potential added benefit of intrastromal administration. The study also evaluated clinically relevant outcomes, including healing onset, complete epithelial healing, scar formation, visual acuity, and complications.

Several limitations must nevertheless be acknowledged. First, the study included only 40 patients (20 per group), limiting statistical power and the precision of treatment-effect estimates. Second, including different fungal species may have introduced clinical heterogeneity because treatment response can vary by causative organism. Third, group comparison should have been based on baseline ulcer characteristics, including ulcer dimensions, depth of stromal infiltration, central versus peripheral location, and initial visual acuity, to assess comparability of disease severity.

Fourth, we excluded patients who did not respond to the initial regimen and were switched to alternative treatment from the subsequent analysis. Excluding such patients from the final analysis may have introduced attrition bias and overestimated treatment effectiveness.

Finally, the study duration and sample size limit the assessment of long-term visual outcomes, recurrence, late complications, and treatment-related toxicity.

These limitations may affect interpretation and emphasize the need for larger, adequately powered randomised controlled trials with standardised outcome definitions and longer follow-up.

CONCLUSION

In our comparison of Topical Voriconazole and Intrastromal Voriconazole, the intrastromal modality was effective and safe for treating deep fungal corneal ulcers, with faster healing. Regarding visual acuity improvement, these results do not show that Group B (Intrastromal Voriconazole group) is superior to Group A (Topical Voriconazole group Therefore, larger studies with clearly defined outcomes and appropriate between-group analyses are needed to evaluate the effectiveness of voriconazole therapy in managing fungal corneal ulcers.

Nonetheless, we can conclude that judicious, timely use of intrastromal voriconazole injection as adjunctive therapy may be considered in selected patients unresponsive to other antifungal therapies. The major advantage of this treatment modality is that it delivers the drug directly to the site of infection, achieving high intracorneal concentrations that may not be possible with topical and systemic antifungal therapy.

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