OPEN ACCESS
Saudi Journal of Medical and Pharmaceutical Sciences
Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) |ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com/journal/sjmps/home

Original Research Article

# To Compare Therapeutic Efficacy of Topical Voriconazole Eye Drops Alone Versus Topical Voriconazole Eye Drops Combined With Intrastomal Injection of Voriconazole in Recalcitrant Deep Fungal Keratitis

Ashok Rathi[1*], R. S Chauhan[2], Nidhi Singh[3]
[1]Professor, Regional Institute of Ophthalmology, Pt. B D Sharma Postgraduate Institute of Medical Sciences, Rohtak-124001, Haryana, India
[2]Regional Institute of Ophthalmology, Pt. B D Sharma Postgraduate Institute of Medical Sciences, Rohtak-124001, Haryana, India
[3]Resident, Regional Institute of Ophthalmology, Pt. B D Sharma Postgraduate Institute of Medical Sciences, Rohtak-124001, Haryana, India

***Corresponding author:** Ashok Rathi
| **Received:** 10.02.2019 | **Accepted:** 20.02.2019 | **Published:** 28.02.2019
**DOI:** 10.36348/sjmps.2019.v05i02.009

## Abstract

Fungal corneal ulcers usually difficult to diagnose and treat especially in primary and secondary hospital level and abrupt use of antibiotics and steroids lead to resistance to treatment. Our study realized that while treating a recalcitrant deep fungal keratitis in combination with intrastomal injection of voriconazole along with use of topical voriconazole eye drop increases the healing rate and hastens the resolution period without significant complications leading to severe visual loss as compared to the treatment with use of topical voriconazole eye drop alone.
**Keywords:** Recalcitrant Fungal Keratitis, Voriconazole.


## INTRODUCTION

The corneal blindness is the most common cause of blindness and visual loss [1, 2]. The incidence of fungal keratitis is has increased in the recent years due to injudicious use of antibiotics and steroids. Fungal keratitis is the most common constituting about 50% of keratitis in tropical and developing countries [3, 4]. Fungal keratitis remains a significant cause of morbidity and mortality despite advance in medical treatment and emergence of newer antifungal agents. Immunocompromised patient are particularly at risk of developing fungal keratitis especially with Candida and Aspergillus species [5].

Superficial keratomycosis fairly responds to topical antifungal like natamycin 5% eye drops. Fungal corneal infections involving the deeper part of the stroma are not amenable to topical antifungal therapy due to poor penetration. To overcome such situations, site directed drugs deposit have been made in posterior segment pathology in the form of intravitreal injections and sub tenon injections of antifungal drugs. In recent years broad spectrum antifungal agents such as Variconazole have been tried as topical and/or intracorneal to treat deep resistant fungal keratitis [5, 6].

## MATERIALS AND METHODS

The study was conducted on 40 patients diagnosed as recalcitrant deep fungal keratitis who presented in the cornea clinic. The recalcitrant deep fungal keratitis was diagnosed by direct smear and/or culture examination, infiltrates involving equal or more than half depth of the stroma and evidence of resistance to other conventional antifungal therapy for last two weeks. After admission, detailed history especially of any trauma by vegetative matter or animal tail trauma, immunocomprised conditions like diabetes mellitus, prolonged used of topical steroid or contact lens was taken. The patients were examined by taking visual acuity, slit lamp detailed examination for fungal features especially dry rough elevated firm slough, irregular feathery, hyphae with branching pattern ulcers, microbiological evaluation of smear and posterior segment ultrasonography to rule out fungal vitritis or any retinal detachment. Inclusion criteria included patients who were diagnosed as recalcitrant deep fungal keratitis where as exclusion criteria included patients with perforated corneal ulcers, total keratomalacia, allergic or sensitive to voriconazole or patients with any hepatic functions impairment.

In our study 40 diagnosed patients of recalcitrant deep fungal keratitis were enrolled. The

study cohort was randomly divided into 2 groups of 20 patients each. Group A included patients who were treated with topical voriconzole 1% eye drops alone and group B patients were treated with topical voriconazole 1% eye drops combined with the intrastromal injection (s) of voriconazole (50 µg/0.1 ml).

**Technique of preparation of voriconazole 1% eye drops**

The 200 mg lyophilized powder in the voriconazole glass vial was reconstituted with 19 ml of sterile distilled water for injection to make a 20ml aqueous voriconazole solution with concentration of 10 mg/ml (1%). Variconazole eye drops 1% are given one drop at hourly interval and continued for atleast 2 weeks after complete resolution of infection.

**Preparation and technique of administration of intrastromal voriconazole injection**

The commercially available 200 mg lyophilized powder in the voriconazole glass vial was reconstituted with 19 ml of sterile ringer lactate solution to obtained 20ml of clear concentrate aqueous voriconazole solution with concentration of 10 mg/ml. One ml of this voriconazole injection was further diluted with 20 ml of ringer lactate solution to get concentration of 0.5 mg/ml (50 µg/0.1 ml). This reconstituted voriconazole solution the loaded in disposable 1ml tuberculin syringe with a 30 gauge needle. After topical or peribulbar anesthesia and all aseptic conditions the preloaded voriconazole drug administered in OT under microscope. With bevel down, the needle was inserted obliquely from the uninvolved clear area to reach involved fungal mid stromal area. 3 to 4 divided doses were given around the ulcer to form a barrage of intrastromal voriconazole around the entire ulcer. The total amount of the drug injected intrastromally ranged from 0.05 ml to 0.1 ml for each injection. When clinical improvement seen in the patient, no further injection was given but if there was no improvement observed within 3 days, another injection was given within 3 successive times.

Outcome variability depends on changes in the best corrected visual acuity (BCVA) which was measured by using Snellen's visual acuity chart. Reduction in the size of the active ulcer on flourescein staining which was determined by slit lamp examination. Patient was evaluated for these outcome variable once before the treatment and then reviewed after 6 weeks of treatment for the purpose of comparative study.

## OBSERVATIONS AND RESULTS

The study included 40 eyes with recalcitrant deep fungal keratitis, that were randomly distributed between the two groups A and B. Group A included 20 patients who were treated with topical voriconzole 1% eye drops alone and group B 20 patients were treated with topical voriconazole 1% eye drops combined with intrastromal injection (s) of voriconazole (50 µg/0.1 ml).

Demographic parameters, Therapeutic efficacy of topical voriconazole eye drops in patients and Therapeutic efficacy of topical voriconzole eye drops combined with intrastomal injection of voriconazole in patients.

Patient's demographic data are shown in Table 1-3 with no statistically significant difference between both groups as regards age, sex and residency status. Out of 40 patients 40% (16) were farmers and 25% (10) were agriculture labourers. Both the groups were statistically similar 65% (13) as in both the groups majority of patients belongs to same occupations Table-4.

**Table-1: Age wise distribution of patients in Group A and Group B**

| Age (years) | Group A (Nos.20) | | Group B (Nos.20) | |
|---|---|---|---|---|
| | No. | % age | No. | % age |
| **21-30** | 2 | 10 | 2 | 10 |
| **31-40** | 7 | 35 | 6 | 30 |
| **51-60** | 4 | 20 | 4 | 20 |
| **Mean ± S.D.** | 41.40 ±9.47 | | 42.65 ±8.10 | |

P-value >0.05 NS

**Table-2: Gender wise distribution of cases**

| Sex | Group A (Nos.20) | | Group B (Nos.20) | |
|---|---|---|---|---|
| | No. | % age | No. | % Age |
| **Male** | 16 | 80 | 17 | 85 |
| **Female** | 4 | 20 | 3 | 15 |

P-value >0.05 NS

**Table-3: Residence wise distribution of cases**

| Residency | Group A (Nos.20) | | Group B (Nos.20) | |
|---|---|---|---|---|
| | No. | % age | No. | % Age |
| **Rural** | 15 | 85 | 18 | 90 |
| **Urban** | 5 | 15 | 2 | 10 |

P-value >0.05 NS

**Table-4: Distribution of patient according to Occupation**

| Occupation | Group A (Nos.20) | | Group B (Nos.20) | |
|---|---|---|---|---|
| | No. | % age | No. | % Age |
| **Farmer** | 7 | 35 | 9 | 45 |
| **Agriculture Labourer** | 6 | 30 | 4 | 20 |
| **House Wife** | 4 | 20 | 3 | 15 |
| **Others** | 3 | 15 | 4 | 20 |

P-value >0.05 NS

In regards to distribution of patients, trauma with vegetative matter was found to be the major predisposing factors in both the groups. 65% patients from Group A and 75% patients from Group B complained of trauma with vegetative matter Table-5. Thus two groups were statistically similar in matter of predisposing factors. Among 40 patients, 87.5% (35) presented with hypopyon as anterior chamber finding on slit lamp Biomicroscopic examination. Both the Groups were statistically similar in this presentation Table-6. The results of direct films and cultures Table-7 were Aspergillum species (10 eyes in group A and 08 eyes in group B), Fusarium species (6 eyes in group A and 7 eyes in group B), Candida species (3 eyes in group A and 5 eyes in group B) and with no statistically significant difference between both groups (P>0.05).

**Table-5: Distribution of patient according to predisposing factors**

| Predisposing factors | Group A (Nos.20) | | Group B (Nos.20) | |
|---|---|---|---|---|
| | No. | % age | No. | % Age |
| **Trauma by Vegetative Matter** | 13 | 65 | 15 | 75 |
| **Diabetes mellitus** | 2 | 10 | 1 | 5 |
| **Prolonged use of topical steroids** | 2 | 10 | 1 | 5 |
| **Contact Lens wear** | 1 | 5 | 2 | 10 |
| **Risk factor more than 1** | 2 | 10 | 1 | 5 |

P-value >0.05 NS

**Table-6: Hypopyon Status at presentation**

| Hypopyon | Group A (Nos.20) | | Group B (Nos.20) | |
|---|---|---|---|---|
| | No. | % age | No. | % Age |
| **Present** | 16 | 80 | 19 | 95 |
| **Absent** | 4 | 20 | 1 | 5 |

P-value >0.05 NS

**Table-7: Distribution of type of Fungus on the basis of Culture report**

| Type of Fungus | Group A (Nos.20) | | Group B (Nos.20) | |
|---|---|---|---|---|
| | No. | % age | No. | % Age |
| **Aspergillus** | 10 | 50 | 8 | 40 |
| **Fusarium** | 6 | 30 | 7 | 35 |
| **Candida** | 5 | 15 | 5 | 25 |
| **Others** | 1 | 5 | 0 | 0 |

P-value >0.05 NS

It was noted that 65% (13) patients presented with BCVA <5/60 but after treatment only 10% (2) patients had BCVA in this range in Group A as compared to It was noted that 60% (12) patients presented with BCVA <5/60 but after treatment only 5% (1) patient had BCVA in this range in Group B. 25% (5) patients presented with BCVA ranging from 5/60 to 6/60, after treatment only 15% (3) patients improvement lied in 5/60 to 6/60 range of BCVA and 15% patients (3) improved within range of 6/60 to 6/18 as compared to 40% (8) patients presented with BCVA ranging from 5/60 to 6/60, after treatment all 40% (8) patients improved to 6/36 to 6/24 and 45% (9) patients improved within range of 6/24 to 6/18 Table 8 & 9. Thus it was observed that with treatment there was significant improvement in BCVA in Group A & B patients.

**Table-8: Distribution of patient with treatment and improvement in BCVA in Group A**

| BCVA | Group A (Nos.20) | | | |
|---|---|---|---|---|
| | Before Treatment | | After Treatment | |
| | No. | % age | No. | % Age |
| **< 5/60** | 13 | 65 | 2 | 10 |
| **5/60 - 6/60** | 5 | 25 | 3 | 15 |
| **6/60 - 6/36** | 2 | 10 | 9 | 45 |
| **6/36 - 6/24** | 0 | 0 | 4 | 20 |
| **5/24 - 6/18** | 0 | 0 | 2 | 10 |

P-value <0.05 S

**Table-9: Distribution of patient with treatment and improvement in BCVA in Group B**

| BCVA | Group B (Nos.20) | | | |
|---|---|---|---|---|
| | Before Treatment | | After Treatment | |
| | No. | % age | No. | % Age |
| **< 5/60** | 12 | 60 | 1 | 5 |
| **5/60 - 6/60** | 8 | 40 | 0 | 0 |
| **6/60 - 6/36** | 0 | 0 | 2 | 10 |
| **6/36 - 6/24** | 0 | 0 | 8 | 40 |
| **5/24 - 6/18** | 0 | 0 | 9 | 45 |

P-value < 0.05 Significant

**Table-10: Statistical trend in BCVA improvement after treatment in Group A**

| Time | Z Score | p-value | Significant |
|---|---|---|---|
| **At Presentation** | 0.000[a] | 1.0 | Not Significant |
| **1st Day** | 0.000[a] | 1.0 | Not Significant |
| **7th Day** | 0.000[a] | 1.0 | Not Significant |
| **14th Day** | -3.448[b] | 0.001 | Significant |
| **28th Day** | -3.760[b] | 0.000 | Significant |
| **42nd Day** | -3.755[b] | 0.000 | Significant |

P-value < 0.05 Significant

**Table-11: Statistical trend in BCVA improvement after treatment in Group B**

| Time | Z Score | p-value | Significant |
|---|---|---|---|
| **At Presentation** | 0.000[a] | 0.000 | Not Significant |
| **1st Day** | 0.000[a] | 1.000 | Not Significant |
| **7th Day** | -2.236[b] | 0.250 | Significant |
| **14th Day** | -3.878[b] | 0.000 | Significant |
| **28th Day** | -3.859[b] | 0.000 | Significant |
| **42nd Day** | -3.853[b] | 0.000 | Significant |

P-value < 0.05 Significant

**Table-12: Statistical comparison between Group A and Group B on the basis of improvement in BCVA**

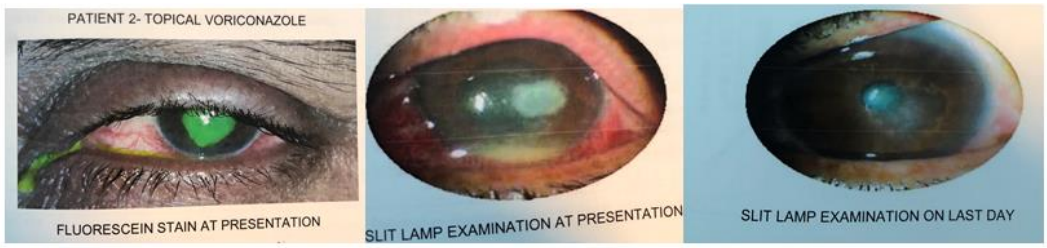
| Time | BCVA Comparison Values Group A verses Group B | | Significant |
|---|---|---|---|
| | Df | p-value | |
| **At Presentation** | 7 | 0.600 | Not Significant |
| **1st Day** | 7 | 0.600 | Not Significant |
| **7th Day** | 7 | 0.848 | Not Significant |
| **14th Day** | 8 | 0.211 | Not Significant |
| **28th Day** | 8 | 0.038 | Significant |
| **42nd Day** | 9 | 0.086 | Not Significant |

P-value < 0.05 Significant

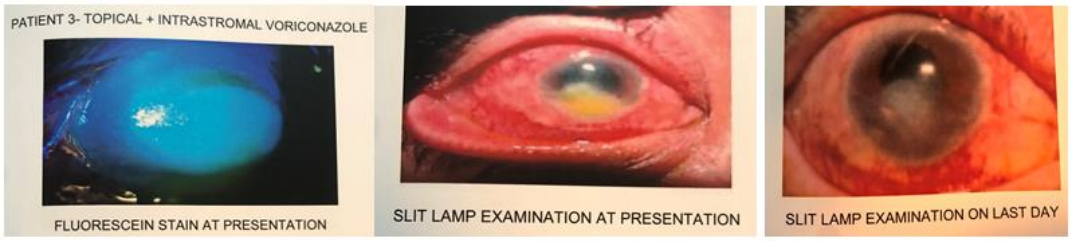
Statistically, a significant gain in BCVA was noted as compared to base value (BCVA at presentation) from 1st day onward at each follow up visit in both the groups A & B Table 11 & 12. When both the Groups compared on the basis of BCVA then both the Group were statistically similar at presentation, 1st day, 7th day, 14th day and 42nd day. There was

statistically significant in improvement of BCVA at 28th day of follow up Table-13.


**Patient 1**




**Patient 2**




**Patient 3**

The mean size of the active ulcer in Group A before treatment was 63.86 $mm^2$ which decreased to 11.48 $mm^2$ at the end of follow up period (42 days) as comparison the mean size of the active ulcer in Group B before treatment was 65.56 $mm^2$ which decreased to 3.38 $mm^2$ at the end of follow up period (42 days). Statistically speaking, a highly significant reduction in size of active ulcer in comparison to baseline value was noted from 1st day onwards at each follow up visit in both the Group A and B Table 14 & 15.

**Table-14: Trends showing reduction in size of active ulcer with treatment in Group A**

| Time | Group A (N=20) | | p-value | Signification |
|---|---|---|---|---|
| | Mean | SD | | |
| At Presentation | 63.86 | 18.21 | - | - |
| 1st Day | 63.86 | 18.21 | > 0.05 | Not Significant |
| 7th Day | 58.20 | 19.26 | 0.000 | Significant |
| 14th Day | 45.22 | 18.46 | 0.000 | Significant |
| 28th Day | 27.46 | 19.60 | 0.000 | Significant |
| 42nd day | 11.48 | 22.97 | 0.000 | Significant |

**Table-15: Trends showing reduction in size of active ulcer with treatment in Group B**

| Time | Group B (N=20) | | p-value | Signification |
|---|---|---|---|---|
| | Mean | SD | | |
| At Presentation | 65.56 | 13.70 | - | - |
| 1st Day | 65.56 | 13.70 | > 0.05 | Not Significant |
| 7th Day | 57.73 | 11.32 | 0.000 | Significant |
| 14th Day | 38.83 | 09.67 | 0.000 | Significant |
| 28th Day | 10.90 | 11.41 | 0.000 | Significant |
| 42nd day | 03.38 | 12.46 | 0.000 | Significant |

Statically significant improvement in healing was noted in both the Group A and Group B analyzed separately. When both groups compared on the basis of healing which was measured by reduction in active

ulcer size on flourescein staining then both groups were statistically similar at presentation, 1st day, 7th Day, 14th day and 42nd day. There was statistically highly significant difference in healing at 28th day visit of follow up. Thus there was more significant improvement on the basis of healing in Group B as compared to Group A on the 28th day after initial presentation Table-16.

**Table-16**: **Statistical comparison between Group A and Group B on the basis of healing which was measured by reduction in size of active ulcer**

| Time | Healing comparison: Group A Vs Group B | | | Signification |
|---|---|---|---|---|
| | Df | p-value | Std. error difference | |
| **At Presentation** | 35.30 | 0.741 | 5.09 | Not Significant |
| **1st Day** | 35.30 | 0.741 | 5.09 | Not Significant |
| **7th Day** | 30.72 | 0.927 | 4.99 | Not Significant |
| **14th Day** | 28.70 | 0.181 | 4.66 | Not Significant |
| **28th Day** | 30.56 | 0.003 | 5.07 | Significant |
| **42nd day** | 29.30 | 0.176 | 5.84 | Not Significant |

## DISCUSSION

Fungal keratitis is a common ophthalmologist problem especially in outdoor workers in tropics. It usually carries an unfavorable prognosis due to its protracted course and requirement of specific therapy [7]. Corneal ulceration is a major cause of monocular blindness in developing countries. Fungal infections of the cornea are one of the most difficult forms of the microbial keratitis to treat successfully and quite challenging [8].

To overcome these problems, modalities of targeted drugs delivery are being evaluated. Similar attempts of site directed deposit have been made in posterior segment pathologies in the form of intravitreal injections and sub tenon injections of drugs [9]. In last few years, broad spectrum antifungal agents such as voriconazole have been tried and also alternate routes of administration such as intracorneal injections of voriconazole have been used to treat resistant fungal keratitis [10-12]. Amphotericin B has been used previously to treat recalcitrant mycotic keratitis without significant improvement. Voriconazole has optimal activity against fungi that are resistant to amphotericin and itraconzole [13-15].

Our study includes 40 eyes with deep recalcitrant fungal keratitis that were randomly distributed between the two groups according to their order of presentation. Group A include 20 patients who received topical voriconzole eye drops alone and Group B include 20 patients who received intrastromal injections of voriconzole plus topical voriconzole eye drops.

There was no statistically significant difference between both the groups regarding age, sex, and residency status (demographic data). Age in Group A was 41.40 $\pm$ 9.47 years and Group B was 42.65 $\pm$ 8.10 years. The most affected age group was 3rd and 4th decade of life when presumably they are more physically active and are at higher risk of corneal injury. In our study there was male predominance as males form majority of working class [16-18]. In our study 82.5% patients were from rural area and 17.5% patients were from urban area in both the groups. The incidence was more in rural because of more chances of exposure chances of exposure to injury, lack of awareness of the problems, delay in consulting ophthalmologist, using native modalities of treatment like application of some irritants in eye and removal of foreign body with unsterile material. Deshmukh *et al.*, conducted study about epidemiology and factors affecting visual acuity in fungal keratitis. In that study 91.34% patients were from rural background similar to our study [16].

Out of 40 patients 40% (16) were farmers and 25% (10) were agriculture labourers. Both the groups were statistically similar as in both the groups majority of patients belongs to same occupations. It was similarly reported by Lixin Xie *et al.*, and M. Jayahar *et al.*, who found that maximum patients were farmers [19-21]. In a study conducted by Bharathi MJ *et al.*, 64.75% of patients with fungal keratitis were agricultural labourers which were similar with present study.

In our study, trauma by vegetative matter was the most common predisposing factor for fungal keratitis in both the groups which was similar to the studies of Solaiman *et al*., Bastola P *et al*., Reema nath *et al*., and M. Jayahar *et al*., [22, 23-27] Thus similar to other studies we noted that farmers and agricultural labourers were mainly affected because they were predisposed to trauma by vegetative matter. Our study didn't show any predilection for either eye involvement. The mean time from the onset of symptoms till start of voriconzole treatment in both study groups was 20. 20 days in group A and 20.85 days in group B. Out of 40 patients, 87.50% (35) patients presented with hypopyon as anterior finding on slit lamp biomicroscopic examination in both groups with no statistically significant difference. In the study

Ganapathy kalaiselvi *et al*., hypopyon was present in 88% [28].

The result of direct films and cultures were Aspergillus species (10 eyes in group A and 8 eyes in group B), Fusarium species (6 eyes in group A and 7 eyes in group B), Candida species (3 in group A and 5 in group in B) and Curvularia (1 in group A and nil in group B) with no statistically significant difference between both the groups similar to Solaiman *et al*., study [22]. Saha *et al.*, conducted study about mycological profile of infectious keratitis in Delhi and illustrated that Aspergillus flavus was most common fungus isolated followed by Fusarium species out of 346 corneal ulcers patients thus favoring present study [29].

In the present study it was noted that in group A 65% patient presented with BCVA <5/60 but after treatment only 10% patients remained in this range. Statistically a significant gain in BCVA was noted as compared to baseline value (BCVA at presentation) from 7$^{th}$ day onwards at each follow up visit in group A. In group B improvement in BCVA was seen earlier as there was statistical significant gain in BCVA was noted from 1$^{st}$ day onwards at each follow up visit. Thus, statistically significant difference in improvement in BCVA was noted in both groups when group A and group B analyzed separately.

In our study when we compared the group A and group B on basis of improvement in BCVA both groups were statistically similar at presentation, 1$^{st}$ day, 7$^{th}$ day, 14$^{th}$ day and 42$^{nd}$ day but there was statistically significant difference noted on 28$^{th}$ day follow up visit. Improvement in BCVA was more in group B than Group A at 28$^{th}$ day visit follow up.

In present study the mean size of active ulcer in group A before treatment was 66.86 mm$^2$ which was decreased to 11.48 mm$^2$ at the end of follow up visit. Statistically a highly significant reduction in size of active ulcer in comparison to baseline value was noted from 1$^{st}$ day onwards at each follow up visit. Whereas the mean size of active ulcer in group B before treatment was 65.56 mm$^2$ which decreased to 03.38 mm$^2$ at the end of follow up period (42 days). Statistically speaking, a highly significant reduction in size of active ulcer as compared to baseline value was noted from 1$^{st}$ day onwards. But when both groups compared on the basis of healing which was measured by reduction in size of active ulcer then both groups were statistically similar at presentation, 1$^{st}$ day, 7$^{th}$ day, 14$^{th}$ day and 42$^{nd}$ day. Whereas there was statistically significant difference in healing at 28$^{th}$ day visit of follow up. Thus healing of fungal keratitis was statistically significant higher in group A (p-value 0.003) on 28$^{th}$ day visit. The difference was noted at 28$^{th}$ day because in group A maximum healing occurred between 4 and 6 weeks whereas in group B maximum healing occurred between 2 and 4 weeks time period. Thus, the duration of maximum healing ranged between 2 and 6 week in group A and between 2 and 4 weeks in group B and healing was thus more rapid in group B than group A.

It was observed that 18 patients responded well to treatment only & 2 patients failed to respond in Group A in comparison to 19 patients responded well to treatment and one patient failed to respond adequately to treatment in Group B. In some patients when there was no improvement seen with one intrastromal injection, another injection was given with 3 successive as a maximum. No complications related to injection were recorded in the present study. No side effects caused by voriconazole eye drops were reported in this study. However, in the study by Vemulakonda *et al.*, only two patients reported a mild transient stinging sensation on installation of 1% voriconazole eye drops [30].

Earlier various studies were concluded to evaluate therapeutic efficacy of voriconazole showing the similar results as present study. Al Badriyeh *et al*., have demonstrated the clinical benefit of topical voriconazole when used alone as primary and salvage therapies in two case reports [31]. Bunya *et al*., reported that voriconazole has been successful when amphotericin B or fluconazole have been unsuccessful in case of drug resistant fungal keratitis and endophthalmitis [32]. Arora *et al*., evaluate the efficacy of topical 1% voriconzole versus 5% natamycin in treatment of 30 patients with fungal corneal ulcers [33]. They concluded that topical 1% voriconazole was a safe and effective drug in primary management of fungal keratitis. Intrastomal injection of the antifungal agent provides maximum concentration of the drug at the target site and this increases its killing effect. Intrastromal injections are easy to prepare and inject and can be repeated several times safely with no learning curve [34].

In our study voriconazole, intrastromal injection and/or eye drops, was started as soon as the diagnosis was made clinically and confirmed by smear and/or cultures. No other antifungal agent was used concurrently to detect the response to voriconazole as a single antifungal medication. However, in other studies [35, 36] the other antifungal eye drops were not stopped and were maintained after intrastomal injections of voriconazole for their patients with deep and/or resistant fungal keratitis. Thus, evaluation of the efficacy of intrastromal voriconazole as single treatment modality in their cases was doubted.

As regards to the duration of healing of fungal keratitis, healing was more rapid in group B than in group A in the present study. This proved that adding intrastromal injection to topical voriconazole eye drops shortens the duration of healing of fungal keratitis.

Jones *et al*., ported that the average length of healing by natamycin eye drops as a topical antifungal was 39 days which was longer than the mean duration of healing in this study [32].

Prakash *et al.*, evaluated the role of intrastromal injection of voriconazole in the management of deep resistant fungal keratitis. They observed that intervention, a faster reduction in the size of corneal infiltration was documented and a complete resolution of ulcers was seen within 3 weeks in all cases [35].

No complications related to intrastromal voriconazole injection were recorded during the study. Repeated intrastromal injections of voriconazole (50 µg/0.1 ml) were tolerated with no signs of ocular toxicity. No side effects caused by voriconazole eye drops were reported in this study. This matches with the clinical study by Al-Badriyeh *et al*., [31] who reported no side effects with 2% voriconazole eye drops. However, in the study by Vemulakonda *et al*., [30], only two patients reported a mild transient stinging sensation on instillation of the 1% voriconazole eye drops.

Other similar studies [37-41] concluded that voriconazole either eye drop or intrastromal injection of voriconazole could be effective for the treatment of deep or resistant fungal keratitis. Adding intrastromal injection to topical eye drops could shortens the healing time. According to the report by Jang *et al.*, voriconazole is also effective against Candida chorioretinitis.

## CONCLUSION

Fungal keratitis is especially the recalcitrant deep fungal keratitis is among the major factor of visual loss and blindness in developing countries. Fungal infections of cornea are usually difficult to treat. Moreover, the penetration of many antifungal drugs into the cornea is suboptimal, which makes the fungal keratitis difficult to treat the deep mycotic fungal keratitis. In present study we evaluated the role of voriconazole in deep recalcitrant fungal keratitis.

In conclusion, our study correlates with the other studies that voriconazole, either eye drops or intrastromal injection could be effective for treatment of deep and/or resistant fungal keratitis. Adding intrastromal injection to topical drops could significantly raise the healing rate and hasten the resolution period without significant complications related to injection. This is economically better as it shortens the period of hospitalization, reduction in the size of active ulcer and with faster return of patients to their usual activity.

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