

CLINICAL EVALUATION OF INTRASTROMAL VORICONAZOLE IN RECALCITRANT FUNGAL KERATITIS A PROSPECTIVE STUDY AT SAROJINI DEVI EYE HOSPITAL, HYDERABAD

K. Srinivas Prasad¹, S. Ravinder², B. Ananda Kumar³, P. Satyavani⁴, P. Venkata Ratnam⁵, P. Padmavathi⁶, T. Sai Shreya⁷, Doli Anitha Sri⁸

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ABSTRACT: BACKGROUND: Recalcitrant Fungal keratitis is a common ocular infection leading to visual impairment. **OBJECTIVES:** To evaluate the efficacy of intrastromal Voriconazole in Recalcitrant Fungal keratitis. **MATERIALS AND METHODS:** This was an interventional study in department of Cornea, Sarojini Devi Eye Hospital, Osmania Medical College, Hyderabad over a period from Feb.2013 Feb.2014. 30 Patients of Fungal Keratitis not responding to routine topical and systemic antifungal therapy in 7 to 14 days, which were diagnosed as Recalcitrant fungal keratitis were given 5µgms/0.1ml of voriconazole intrastroml injections around the fungal infiltrates in a grid pattern. Details of patients age and sex, type of causative fungal and traumatic agents, size of corneal ulcer, presence of Hypopyon or not, and time taken for hypopyon absorption, and clinical improvement and resolution of the ulcer and visual acuity were noted. **RESULTS:** This study group of 30 patients diagnosed as Recalcitrant fungal keratitis showed Causative Fungi as Fusarium in 19(63.0%), Aspergillus in 11(37.0%). Causative Traumatic Agents were vegetative matter in 19 (63.3%), other agents in 8(26.7%) and not known in 3(10.0). 17(56.7%) were Males with 13(43.3%) Females. Age wise distribution was 3(10.0%) in >10-20yrs, 11(36.7%) in 20-40 yrs, 15(50.0%) in 40-60 yrs, and 1(3.3%) in >60 yrs. The size of the ulcer showed <1/2 of the cornea in 21(70.0%) and >1/2 of the cornea in 9(30.0%). 19 (63.3%) were with hypopyon and 11(36.7%) without hypopyon. After Intrastromal Voriconazole, the absorption of Hypopyon in 12 (63.2%) was in 2to 4 wks. and in 2(10.5%) in > 4 wks. Clinical improvement of the Fungal Corneal Ulcer was seen in no case (0.0%) in <1st wk., in 24(80.0%) in 2 to 4wks and in 2(6.7%) in > 4 wks. Time (wks.) of healing of the Fungal Corneal Ulcer was in 4-6wks in 21 (70.0%) and in >6wks in 5(16.7%). Visual Acuity was <3/60 in 2(7.7%), 3/60-<6/60 in 10(33.3%), 6/60-<6/18 in 9(30.0%) and 6/18-6/9 in 5(16.7%). **CONCLUSION:** Common causes of fungal keratitis in Recalcitrant Fungal keratitis were Fusarium in 15(50.0%), Aspergillus in 12(40.0%) and Candida in 3(10.0). Intrastromal Voriconazole has a therapeutic role in resolving recalcitrant fungal keratitis not responding to routine antifungal therapy within 4-6 wks.

KEYWORDS: Fungal keratitis, Voriconazole, Hypopyon, Recalcitrant, intrastromal.

INTRODUCTION: Ocular fungal infections or ophthalmic mycoses are being increasingly recognized as important causes of morbidity and blindness, especially in tropical countries although fungi are recognized as opportunistic pathogens. Keratitis is by far the most frequent fungal infection of eye. Fungal infections of the cornea are usually difficult to treat and pose several therapeutic challenges. Only limited numbers of drugs are commercially available for ophthalmic use. Most of the drugs are fungi static with limited spectrum of activity and poor penetration through ocular structures, which

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makes it difficult to treat deep mycotic keratitis. The pharmacological properties, in-vitro susceptibility, as well as the anecdotal reports suggest superiority of voriconazole over other antifungal agents. More recently, clinicians have tried alternative route of intrastromal injection of water-soluble molecules such as amphotericin B and voriconazole. Voriconazole has a superior activity against fungi that are resistant to amphotericin B and itraconazole and also as a good safety profile.^{1,2} Recalcitrant Fungal keratitis is a common ocular infection leading to visual impairment. So, our study was to know the efficacy of Intrastromal Voriconazole in Recalcitrant Fungal keratitis.

AIM: To study the efficacy of intrastromal voriconazole injection in Recalcitrant Fungal Keratitis

METHODS: Setting: Dept. of Cornea, Sarojini Devi Eye Hospital & Regional Institute of Ophthalmology, a Tertiary Care Teaching Hospital of Osmania Medical College (Govt.), Hyderabad, Telangana State. Number of Patients: 30 patients.

Duration of the Study: Feb. 2013 to Feb. 2014.

Inclusion Criteria: Smear and Culture +ve fungal corneal ulcers not responding routine antifungal.

Exclusion Criteria: children below the age of 10 yrs.

Main Outcome Measures: This was a resolution of the infection with complete healing of the epithelial defect with resolution of corneal abscess with scar formation, the time taken for healing and the best spectacle-corrected visual acuity (BSCVA) improvement after intrastromal Voriconazole. Study design: Interventional case series of Voriconazole 50 micrograms/0.1 ml injected in a grid pattern circumferentially around the infiltration in the corneal stroma in recalcitrant fungal keratitis.

METHODOLOGY: The study was approved by the institute ethical committee with the informed consent from all the patients. A detailed clinical history was obtained with a complete ophthalmic examination for all the patients. Epidemiological data of patient's age and sex, and history of corneal trauma with type of the agents were noted. Each patient underwent Snellen's visual acuity testing, and slit-lamp bio microscopy. Patients were screened for diabetes and hypertension and were excluded. The diagnosis of the fungal infection was made on the basis of clinical evaluation, positive smear and culture of the fungus. The size of the corneal ulcer, the presence of Hypopyon or not, and the visual Acuity at the time of clinical presentation were noted.

As soon as fungus was identified by KOH wet-mount preparation, routine antifungal therapy of 5% Natamycin eye drops every 2hrs, 1% Cyclopentalate hydrochloride eye drops 3times a day and tablet Itraconazole 100mg bd was started. When, objectively demonstrable clinical response to antifungal therapy was not seen in 7 to 14 days or the infection showed the signs of worsening, 5µgms/0.1ml of voriconazole was injected intracorneally around the fungal infiltrate in a grid pattern in five divided doses to form a barrage of voriconazole around the entire infiltrate. The total amount of the drug injected intra stromally ranged from 0.05ml to 0.1ml. After intrastromal injection, all the patients were continued on 5% Natamycin eye drops hourly, tablet Itraconazole 100mgbd and 1% Cyclopentalate hydrochloride eye drops 3 times a day.

Patients were examined at regular intervals and response to the therapy was noted. The infection was considered resolved when there was a complete healing of the epithelial defect with resolution of corneal infiltration with scar formation. The patients were continued on topical

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antifungal therapy for at least 1 wk. after the complete resolution of the infection. The details of time taken for clinical improvement, Hypopyon absorption and the healing of the corneal ulcer were noted with the type of the corneal opacity (Scar) formed and the Visual acuity. All the data was analyzed by simple statistical methods.

RESULTS: The study includes 30 patients of fungal corneal ulcer diagnosed as recalcitrant Fungal Keratitis.

Sl. No.	Gender	No. of Cases	%
1.	Males	17	56.7
2.	Females	13	43.3
Total		30	

Table 1: Distribution of patients according to gender

This table showed 17 (56.7%) Males and 13(43.3%) Females.

Sl. No.	Age Group	Males	Females	Total	%
1.	10-20	2	1	3	10.0
2.	20-40	6	5	11	36.7
3.	40- 60	8	7	15	50.0
4.	>60	1	0	1	3.3
Total		17	13	30	

Table 2: Distribution of patients according to age group and gender

This Table showed 3(10.0%) in>10-20yrs, 11(36.7%) in 20–40 yrs, 15(50.0%) in 40 - 60 yrs, and 1(3.3%) in >60 yrs.

Sl. No.	Types of Fungus	Males	Females	Total	%
1.	Fusarium species	11	8	19	63.0
2.	Aspergillus species	7	4	11	37.0
Total		17	13	30	

Table 3: Distribution of patients according to the type of Causative fungi

This Table showed Fusarium species in 19(63.0%), Aspergillus species in 11(37.0%).

Sl. No.	Type of Trauma	No. of Cases	%
1.	By vegetative matter	19	63.3
2.	Others	8	26.7
3	Agent not known	3	10.0
Total		30	

Table 4: Distribution of patients by the Causative Traumatic agent

This Table showed the vegetative matter in 19 (63.3%) and the other agents in 8 (26.7%). The type of traumatic agent was not known in 3(10.0%).

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Total	30	
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Table 5: Distribution of patients according to size of the ulcer

This Table of distribution of patients according to the size of the ulcer showed 21(70.0%) with < 1/2 of the cornea and 9(30.0%) with >1/2 of the cornea.

Sl. No.	Hypopyon Status	Males	Females	Total	%
1.	Present	11	8	19	63.3
2.	Not present	6	5	11	36.7
Total		17	13	30	

Table 6: Distribution of patients with Hypopyon status

This Table showed 19(63.3%) with hypopyon and 11(36.7%) without hypopyon.

Sl. No.	Weeks	Total	%
1	<1	2	10.5
2	2 to 4	12	63.2%
4	>4	2	10.5%
Total		16	84.2%
Lost Follow UP 3 15.8%			

Table 7: Distribution of patients with Absorption time of Hypopyon after intrastromal Voriconazole

This Table showed the Absorption time of Hypopyon after intrastromal Voriconazole, 2to 4 wks. in 12 (63.2%) and > 4 wks in 2(10.5%). 3 (15.8%) of Hypopyon cases lost follow up.

Sl. No.	Weeks	Total	%
1	<1	0	0.0%
2	2 to 4	24	80.0%
3	>4	2	6.7%
Total		26	86.7%
4 (13.3%) of patients lost follow up.			

Table 8: Distribution of patients with Clinical improvement after Intrastromal Voriconazole

This Table of clinical improvement of the Fungal Corneal Ulcer after Intrastromal Voriconazol showed no cases (0.0%) in <1st wk., 24(80.0%) in 2 to 4wks and only 2(6.7%) in > 4 wks.. 4 (13.3%) patients lost follow up.

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Sl. No	Weeks	No. of cases	%
1.	<4 wks.	Nil	0.0%
2.	4 to 6	21	70.0
3.	>6	5	16.7
Total		26	86.7
Lost Follow Up		4	13.3
Total		30	

Table 9: Distribution according to the time (wks) of healing after intrastromal voriconazole

This Table of time (wks.) of healing of the Fungal Corneal Ulcer after Intrastromal Voriconazole showed 4-6 wks in 21(70.0%) and >6 wks. in 5(16.7%). 4 (13.3%) of patients lost follow up.

Sl. No.	Visual Acuity	Before		After	
		No. of cases	%	No. of cases	%
1.	< 3/60	27	90.0	2	7.7
2.	3/60 - <6/60	1	3.3	10	33.3
3.	6/60 - <6/18	2	7.7	9	30.0
4.	6/18 - 6/9	0	0	5	16.7
Total		30	100.0	26	86.7
5.	Lost follow Up			4	13.3
Total				30	100.0

Table 10: Distribution of patients Visual acuity (BCVA) before and after Intrastromal Voriconazole

This Table of Visual acuity (BCVA) before Intrastromal Voriconazole showed <3/60 in 27(90.0%), 3/60 to <6/60 in 1(3.3%), 6/60 to <6/18 in 2(7.7%) patients and 6/18 to 6/9 in no (0.0%) patient. After the Intrastromal Voriconazole the Visual Acuity was <3/60 in 2(7.7%), 3/60 - <6/60 in 10 (33.3%), 6/60 - <6/18 in 9(30.0%) and 6/18-6/9 in 5(16.7%). 4(13.3%) patients lost follow up after intrastromal Voriconazole.

DISCUSSION: Fungal Infections of the cornea is one of the most difficult forms of microbial keratitis to treat successfully and quite challenging. Generally prolonged and intensive topical and systemic antifungal therapy is required to eradicate the fungal infections. Corneal infections involving the deeper parts of the stroma are not amenable to topical antifungal therapy because none of the present-day antifungal agents can optimally penetrates the deeper layers of cornea. To overcome these problems, modalities of targeted drug delivery are being evaluated. 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 B and itraconazole.^{1,2}

Each of the 30 patients of the study group with a diagnosis of recalcitrant microbial keratitis and corneal infiltrates involving up to posterior stroma were given antifungal therapy of topical 5%

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Natamycin eye drops and tablet Itraconazole 100 mg bd. As poor response was seen following 7 to 14 days of this therapy, intrastromal Voriconazole was given around the corneal abscess. 5% Natamycin eye drops and tablet Itraconazole 100mg bd were continued till the healing of the ulcer. In each of the 30 patients the procedure was performed successfully. 4 patients did not come for follow up. The infection was resolved completely in the remaining 26 patients after intrastromal voriconazole.

Causative fungi showed *Fusarium* species in 63.0%, *Aspergillus* species in 37.0%. In the study of Bharathi M J et al³ *Fusarium* species was 42.82% followed by *Aspergillus* species 26.0%. In the study of Gopinathan U et al⁴ *Fusarium* Species was 37.2% followed by *Aspergillus* species in 30.7%. In our study the common cause was the vegetative matter trauma (63.3%) linked to their nature of work. In other studies it was 61.28% of Bharathi M J et al³ and 22.97% of Suman Saha et al.⁵ So, our study correlate with the above studies that the common causes of Recalcitrant fungal keratitis were, *Fusarium* species, followed by *Aspergillus* species and that the vegetative matter was the most common agent.

Our study of age wise distribution showed higher incidence (86.7%) among the age group of 20-60 yrs with 36.7% in 20–40 yrs and 50.0% in 40-60 yrs. In the study of Bharathi MJ et al³ 66.84% were between 21 and 50 years old. In the study of Gopinathan U et al,⁴ 64.4% were in the age group 16-49 years. In the study of Suman Saha et al,⁵ 60.81% were in the age group >50 years. Our study of Sex distribution was 56.7% of males compared to 43.3% of females. In the study of Gopinathan U et al⁴ 72.0% were the Males compared to 28.8% of females. In the study of Suman Saha et al⁵ Males were more commonly affected. So, our study and other studies show that the fungal keratitis was common in males, as they form the most working class and more exposed to risk factors frequently due to their more outdoor activities as compared to females and common with increasing age with a significant burden of visual impairment in this working productive age group.

Our study showed the ulcer size of <1/2 of cornea in 70.0% and >1/2 of the cornea in 30.0%, Hypopyon in 63.3% and not in 36.7% patients. In the study of Ganapathy Kalaiselvi et al⁶ hypopyon was present in 88%.

Our study showed the absorption of Hypopyon after intrastromal Voriconazole, in 2 to 4 wks. In 63.2% and in >4 wks. in 10.5% patients. Clinical improvement of the Fungal Corneal Ulcer after Intrastromal Voriconazole showed no improvement in <1st wk., but 80.0% improved in 2 to 4 wks. and only 6.7% in >4 wks.

Our study showed the time (wks.) of healing of the Fungal Corneal Ulcer after Intrastromal Voriconazole 4-6 wks. In 70.0% and >6 wks. In 16.7%. In the study of Gaurav Prakash et al⁷, a complete resolution of all the ulcers was seen within 3 wks. In the study of Namrata Sharma et al^{8,9} resolution time was 4-6 wks. In 83.3% cases. In the study of Ganapathy Kalaiselvi et al⁶, it was in 72.0% patients.

Our study showed that the visual Acuity before intrastromal Voriconazole of <3/60 in 90.0%, 3/60 to <6/60 in 3.3% and 6/60 to <6/18 in 7.7% patients, improved to < 3/60 in 7.7%, 3/60 - <6/60 in 33.3%, 6/60 - <6/18 in 30.0% and 6/18 - 6/9 in 16.7% after intrastromal Voriconazole. In the study of Namrata Sharma et al,^{8,9} the best-corrected visual acuity of < 20/1200 in all patients at the time of presentation, improved to better than 20/400(6/60) in 83.3% eyes. In the study of Namperumalsamy et al,¹⁰ with a baseline BSCVA of 20/40 (6/12) to 20/400 (6/60) showed a trend toward a 2-line improvement in visual acuity with voriconazole.

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So, our study correlate with the other studies that the intrastromal Voriconazole has a therapeutic role in the clinical resolution of the recalcitrant fungal keratitis within 4–6 wks in terms of hypopyon absorption and visual acuity improvement.

CONCLUSIONS: The most frequent causes of fungal keratitis in Recalcitrant Fungal keratitis were *Fusarium* species in 63.0% followed by *Aspergillus* species in 37.0%. Intrastromal Voriconazole has a therapeutic role in resolving the recalcitrant fungal keratitis not responding to routine antifungal therapy within 4–6 wks. Targeted depot delivery of voriconazole may be a safe and effective way to treat recalcitrant fungal keratitis responding poorly to conventional treatment modalities.

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AUTHORS:

1. K. Srinivas Prasad
2. S. Ravinder
3. B. Ananda Kumar
4. P. Satyavani
5. P. Venkata Ratnam
6. P. Padmavathi
7. T. Sai Shreya
8. Doli Anitha Sri

PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Ophthalmology, Osmania Medical College, Sorojini Devi Eye Hospital, Hyderabad.
2. Associate Professor, Department of Ophthalmology, Osmania Medical College, Sorojini Devi Eye Hospital, Hyderabad.
3. Assistant Professor, Department of Ophthalmology, Osmania Medical College, Sorojini Devi Eye Hospital, Hyderabad.
4. Assistant Professor, Department of Ophthalmology, Osmania Medical College, Sorojini Devi Eye Hospital, Hyderabad.

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COMPETING INTERESTS: None

5. Assistant Professor, Department of Ophthalmology, Osmania Medical College, Sorojini Devi Eye Hospital, Hyderabad.
6. Assistant Professor, Department of Ophthalmology, Osmania Medical College, Sorojini Devi Eye Hospital, Hyderabad.
7. Post Graduate, Department of Ophthalmology, Osmania Medical College, Sorojini Devi Eye Hospital, Hyderabad.
8. Post Graduate, Department of Ophthalmology, Osmania Medical College, Sorojini Devi Eye Hospital, Hyderabad.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. K. Srinivas Prasad,
Dept. of Cornea,
Sarojini Devi Eye Hospital,
Humayun Nagar, Hyderabad-500028.
E-mail: drkallani@gmail.com

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