IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 22, Issue 4 Ser.9 (April. 2023), PP 35-40
www.iosrjournals.org

Intrastromal Voriconazole for Recalcitrant Fungal Keratitis – A Prospective Study

C. S. Sandhya, P. Sree Lakshmi, B. Swetha
Department of ophthalmology, S V medical college, Tirupati, Andhra Pradesh, India.

ABSTRACT
AIM:
To study the effectiveness of intrastromal voriconazole in recalcitrant fungal keratitis.
MATERIALS AND METHODS:
The study was conducted over a period of one year, from November 2019 to October 2020. 30 eyes of 30 patients with a microbiologically proven fungal corneal ulcer that did not respond to topical antifungal therapy were included in the study. Patient satisfying inclusion and exclusion criteria were included in the study. Intrastromal voriconazole injection at a dosage of 50 µg/0.1 ml in divided doses with 30G or 25 G needle around the infiltrate
RESULTS:
Of the 30 patients enrolled in the study, intrastromal injections of voriconazole helped resolve the infection in 23 (76.6%) patients, of which 20 cases resolved without any additional intervention while three patients had impending perforation during follow-up and were managed successfully using cyanoacrylate glue with bandage contact lens. Overall, 18 patients required more than one injection, with eleven requiring more than two injections. Out of the 20 successfully treated patients, 12 patients received a single injection, 7 received the injection twice, and 1 had three injections
CONCLUSION:
Intrastromal voriconazole has a definitive role in the management of recalcitrant fungal keratitis as an adjuvant to topical therapy with a high success rate.

Date of Submission: 10-04-2023 Date of Acceptance: 23-04-2023

I. INTRODUCTION:

Microbial keratitis is a common vision-threatening disease occurring in all parts of the world. In South India, several studies showed that fungal keratitis is more common than bacterial keratitis[1]. Microbial keratitis not responding to medical treatment is a clinical challenge as it can progress to perforation. Deep fungal keratitis is difficult to manage due to poor penetration of drug and limited spectrum of available topical antifungal agents. Deep fungal keratitis can be managed by modalities aimed at targeted drug delivery.[2 3]The purpose of the present study was to evaluate the role of intrastromal voriconazole in recalcitrant fungal keratitis. Intrastromal voriconazole can be an effective and adjuvant treatment modality in selected patients who are unresponsive to other forms of antifungal therapy, as it delivers high intra corneal drug concentration at the site of infection which is usually not possible with topical antifungals. It might reduce the risk of complications of corneal ulcer like perforation of cornea and its sequalae.

II. MATERIALS AND METHODS:

The present study was a prospective interventional study conducted on patients presenting to the Ophthalmology Outpatient Department at SVRRGG Hospital in Tirupati. The study was approved by the institutional ethical committee. The study was conducted over a period of one year, from November 2019 to October 2020. 30 eyes of 30 patients with a microbiologically proven fungal corneal ulcer that did not respond to topical antifungal therapy for at least 1-2 weeks were included in the study. The diagnosis of fungal keratitis was made based on clinical evaluation, positive smear, and cultures for the fungus. All the patients were explained in detail regarding the procedure, and informed consent was obtained from all subjects.

Patients with total corneal ulcer, with impending corneal perforation and fungal keratitis associated with endophthalmitis are excluded from the study. At initial presentation, all the patients fulfilling the inclusion criteria were evaluated with a detailed history, which included the mode of injury, occupation, duration of symptoms, history of treatment taken, systemic illness, and clinical evaluation, including best-corrected Snellen visual acuity testing. Slit-lamp bio microscopy was performed with documentation of ulcer characteristics like the location of

ulcer, size of the ulcer, size of infiltrate, depth of the infiltrate, presence of satellite lesions, presence of an endothelial plaque and height of the hypopyon. The area of the ulcer was calculated by measuring the maximum diameter and the dimension perpendicular to the maximum diameter.

Corneal scrapings were taken with no.15 surgical blade from the base and edges of the ulcer after application of topical proparacaine eye drops or 4% lignocaine hydrochloride eyedrops. The scrapings were sent for gram's stain, potassium hydroxide (KOH) wet mount preparation and for cultures on blood agar, chocolate agar, and sabouraud dextrose agar.[4]

After confirmation of diagnosis, the patients were started on topical anti-fungal treatment with Topical natamycin sulphate (5%), and/or topical voriconazole 1% eye drops instilled hourly and the treatment response was monitored. If there was no improvement or response to therapy after 7-14 days or if the infection showed signs of worsening, the patients received an intrastromal injection of voriconazole (50 mg/0.1 mL) around the infiltrate in five divided doses to form a depot of the drug around the circumference of the lesion.
Circumferential injection ensured the formation of a barrage of intrastromal voriconazole around the entire infiltrate. Intraoperative complications, if any, were recorded.

III. Follow-up

After the intrastromal injection, all patients were continued on the topical antifungal regimen. Patients were examined every day, and the response to therapy was recorded on the slit lamp examination, and the need for repeat injection was assessed. The size of the infiltrate, the height of the hypopyon, and the occurrence of any complications were noted by a slit lamp bio microscopy. The response to therapy was noted on slit-lamp examination and defined as 'not improved' if there was no change in the size and area of the ulcer or infiltrates and described as 'worsened' if there was an increase in area, size, or depth of the ulcer or infiltrate by 20% or perforation. The ulcer was defined as 'healing' if the area and size of the epithelial defect and the infiltrate reduced by more than 20% from that at presentation. The infection was considered resolved when there was complete healing of the epithelial defect with the resolution of corneal infiltrate and scar formation. The patients were continued on topical antifungal therapy for at least two weeks after the complete resolution of the infection.

In case of worsening or no response to the previous injection within 2 to 3 days, the intrastromal injection of voriconazole was repeated. Patients with impending perforation underwent application of cyanoacrylate glue with bandage contact lens along with the continuation of the topical antifungal regimen.

IV. RESULTS:

The study included thirty eyes of thirty patients with fungal corneal ulcer with or without hypopyon and endothelial plaque. The depth of corneal involvement in all these cases extended up to or deeper than the mid-stromal level. A history of trauma with agricultural agents was elicited from 23 patients (76.7%). Systemic disease was present in 14 (46.6%) patients, including diabetes in six, asthma in one, and hypertension in seven.

The age of the patients in this study ranged from 25 years to 77 years, with the mean being 35.73 years majority of the subjects were within the age group of 41-60 years (64.0%) followed by 61-77 years (23.0%). There was slight male preponderance with17 male patients (56.7%) and 13 female patients (43.3%). Most of the patients were agricultural laborers (33.3%), followed by farmers (30.0%) and homemakers (26.7%). Nearly three-fourths of the participants had trauma with vegetative matter (76.7%), 13.3% of the patients were on topical steroids and 6.7% and 3.3% of the subjects had chronic dacryocystitis and lagophthalmos respectively.

Almost half of the subjects had a central corneal ulcer (46.7%) while 33.3% had paracentral ulcer and in 20% of the patients, the ulcer was located in the peripheral cornea. Majority of patients had hypopyon (83.33%), endothelial plaques were seen in 23.0% and satellite lesions in 21.0%. Nearly half of the subjects diagnosed microscopically for Fusarium species (50%), followed by Aspergillus species (23.3%) and other fungi (13.33%), included candida species, Acremonium species.

Table 1: Particulars of microbiological diagnosis

Fungal Species	Frequency	Percentage
Fusarium species	15	50%
Aspergillus species	7	23.33%
Other fungi	4	13.33%
Unidentified fungi	4	13.33%
Total	30	100

The mean age of the subjects in this study was 53.20±12.1 years. The minimum and maximum ages of the participants were 25.0 and 77.0, respectively. The mean size (in mm2) of the ulcer and infiltrate was 10.78 and 23.40, respectively. The mean height of the hypopyon (in mm) was 1.68 ranging from 1-3 mm. Unpaired t-test was used to determine the association of quantitative data with the outcome. Healing depended on the size of the ulcer. There was a statistically significant difference in the mean value of the size of ulcer between the

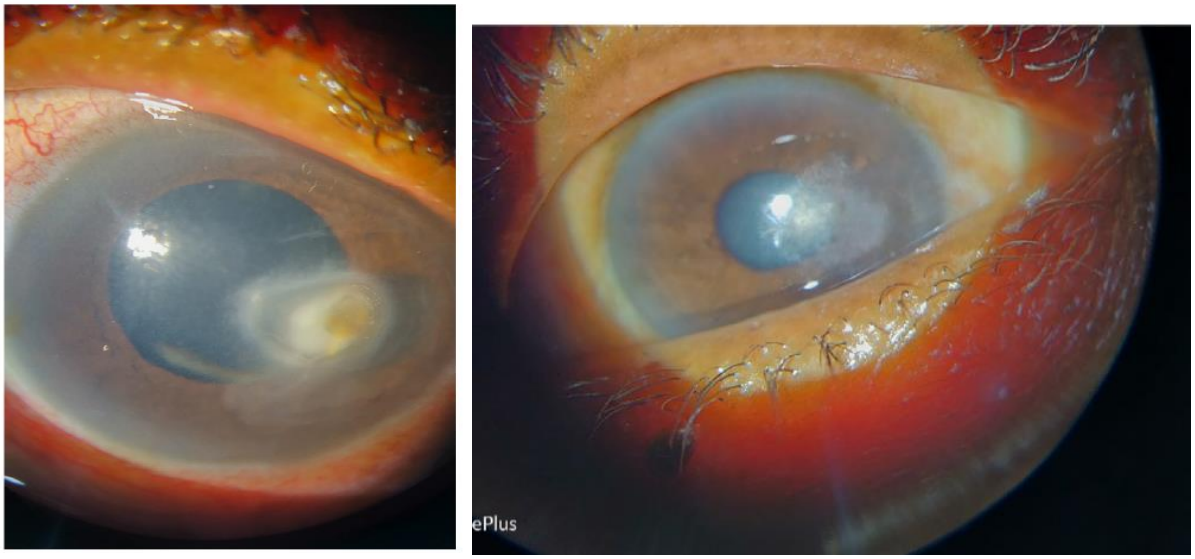
healed and perforated groups (P<0.05). Healing was better in small ulcers, and this difference was found to be statistically significant (P<0.05).

Table 2: Comparison of quantitative variables with the outcome

Characteristics	Epithelial outcome	N	Mean	SD	P value
Age (in years)	Healed	27	53.43	12.20	0.85
	Perforated	3	52.42	12.68	
Size of the ulcer (in mm²)	Healed	27	6.97	3.59	**0.02***
	Perforated	3	23.28	14.47	
Size of the infiltrate (in mm²)	Healed	27	18.30	8.30	**0.02***
	Perforated	3	40.14	18.65	
Number of injections	Healed	27	1.70	0.87	**0.007***
	Perforated	3	2.71	0.48	
Size of hypopyon	Healed	27	1.66	0.68	0.86
	Perforated	3	1.71	0.48	

***Statistically significant**

Of the 30 patients enrolled in the study, intrastromal injections of voriconazole helped resolve the infection in 23 (76.6%) patients, of which 20 cases resolved without any additional intervention while three patients had impending perforation during follow-up and were managed successfully using cyanoacrylate glue with bandage contact lens.



Left eye fungal corneal ulcer at presentation and at 3 months follow up showing healed corneal ulcer with scar formation.

Out of the 20 successfully treated patients, 12 patients received a single injection, 7 received the injection twice, and 1 had three injections. Deep ulcers required more number of injections, whereas the superficial ones required a lesser number of injections. No procedure-related complications or drug related systemic or local adverse effects were noted in the present study.

In seven (23.3%) patients, treatment with intrastromal injections failed. In these seven patients, the ulcer progressed despite injections of intrastromal voriconazole and finally underwent therapeutic penetrating keratoplasty. The organism was identified as Fusarium in five of the seven patients that failed to respond to treatment, and one was Candida, and one was an unidentified fungus. Of these seven patients, three were diabetic, with inadequate control of blood sugar levels, and one patient had used topical steroid drops prior to presenting to us, and one had lagophthalmos.

Chi-square test was used to determine the association of qualitative data with the outcome. Healing of the ulcer depended on the systemic illness. The proportion of subjects without systemic illness had better healing than those with systemic illness. This difference between the proportions was found to be significant statistically.

The size of the ulcer at presentation significantly affected the treatment outcome. Larger ulcers were associated with an increased risk of treatment failure.

Paracentral and peripheral ulcers responded better when compared to central ulcers, and this difference in proportions was found statistically significant. The size of the ulcer, depth of the ulcer, and size of the infiltrate were important factors associated with treatment success. The presence of endothelial plaques and corneal vascularization had a bad prognosis on the outcome. Though there was no statistical significance, the percentage of perforations was more in infection with Fusarium species (35.7%).

A paired t-test was used to compare the mean BCVA of an affected eye before treatment and after three months of treatment. The mean BCVA of the affected eye showed there is an improvement of vision after three months of intervention. This difference in the mean value was found to be having a high, statistically significant difference.

V. DISCUSSION:

In South India, several studies showed that fungal keratitis is more common than bacterial keratitis. Deep fungal keratitis is difficult to manage due to poor penetration of drug, drug toxicity, and limited spectrum of available topical antifungal agents can be managed by modalities aimed at targeted drug delivery. The purpose of the present study was to evaluate the role of intrastromal voriconazole in recalcitrant fungal keratitis.

Fungal keratitis can present as superficial keratitis, corneal abscess, and endothelial plaque and may be associated with hypopyon. The commonly available antifungal agents are amphotericin B, Natamycin, fluconazole, ketoconazole, and voriconazole. Amphotericin B is effective against yeasts, and its fungistatic activity is limited against filamentous fungi, and its systemic use is associated with various side effects[5]. Natamycin has relatively poor corneal penetration and precipitates on the corneal surface[6]. In vitro susceptibility data show that voriconazole has the best efficacy against pathogenic fungi compared with other agents.[7 8]

It is evident from previous studies that oral and topical antifungal agents have poor ocular penetration, thereby achieving suboptimal drug levels at the site of infection. Hence, targeted drug delivery is required to achieve adequate drug levels at the site of infection, and to achieve an adequate intracorneal concentration of antifungals, intrastromal injections of antifungals have been tried.[9]

In this study, the drug was injected around the ulcer to form a drug deposit around the circumference of the lesion, thus creating a barrage of intrastromal voriconazole around the entire infiltrate.

Regarding risk factors for corneal ulcers, three-fourths of the participants had trauma with vegetative matter (76.7%). Agricultural trauma is an important cause of ocular injury in India as most of the Indian population live in rural areas.

Farming is a common occupation in rural India. Ocular injuries are more commonly seen in adult men who are engaged in agricultural work.

In the present study, 76.7% of cases were due to injury with the vegetative matter. While 13.3% of the patients were on topical steroids and 6.7% and 3.3% of the patients had chronic dacryocystitis and lagophthalmos, respectively.

In a study done by Kalaiselvi G et al., a history of trauma with agricultural agents was seen in 18 patients (72%) of the cases.[10]

In a study done by Namratha Sharma et al., a history of trauma with agricultural agents was seen in 58.3% of the cases and in a study done by Piyali Konar, it was 75%.[11]

Various studies that were done in western and southern India have documented Fusarium as the most common fungal pathogen causing keratitis.[12]

In the present study also, Fusarium was the most common pathogen identified in 50% of the cases. In a study done by Kalaiselvi G et al., in South India, the most common pathogen isolated was Fusarium, i.e., 13 (52%), which was similar to this study. In a study done by Piyali Konar et al. in North India, Fusarium was the most common pathogen to be isolated, i.e., 6(30%).[13]

Lalitha et al have also shown that an ulcer area of more than 14 mm^2, the presence of a hypopyon, and infection with Aspergillus species are important risk factors for treatment failure.[14] In the present study, out of seven failures, Fusarium species was responsible for six cases (86%). Overall, it was found that only about half the eyes (9/15 – 60%) with Fusarium keratitis responded to the treatment regimen, illustrating the fact that Fusarium species may be resistant to many of the antifungal drugs that are currently used to treat fungal infections.

In the present study, in seven (23.3%) patients, treatment with intrastromal injections failed. The ulcers progressed despite the injections and finally underwent therapeutic penetrating keratoplasty. Among these seven eyes that failed, five received three injections, and two received two injections. The average number of injections given to the patients was 1.86, with a minimum of one to a maximum of four injections required. Overall, 18 patients required more than one injection, with eleven requiring more than two injections. Out of the 20 successfully treated patients, 12 patients received a single injection, 7 received the injection twice, and 1 had three injections. The mean value of number of injections required in healed ulcers was 1.70±0.87, and in perforated ulcers was 2.71±0.48.

In a study done by Kalaiselvi G et al. the mean value of number of injections required in healed ulcers was 1.38 and in perforated ulcers was 1.57, which was similar to the present study.

There is insufficient knowledge of the pharmacokinetics of voriconazole when injected into the corneal stroma. Hence the need for reinjection and the interval between injections needs to be determined on clinical grounds and may differ from case to case. Based on the present study, and from the literature, a considerable number of patients with deep fungal corneal ulcer required repeated injection.

Although intrastromal voriconazole has good success rate, the dosage and frequency of injections is yet to be determined. Large clinical trials with long‑term follow‑up might be required in determining the frequency of injections required.

Previous case series have reported success with intrastromal voriconazole in recalcitrant deep mycotic keratitis.

Prakash et al. demonstrated successful healing in all three patients with deep non-healing fungal ulcers.[15]

Sharma N et al. did a prospective study on twelve eyes and have reported a success rate of 83.33% (10 of 12 eyes).[16]

Similarly, Kalaiselvi et al. reported a treatment success rate of 72% in Tamil Nadu, India. They found successful healing in eighteen out of twenty-five eyes.[17]

Piyali Konar et al. did a prospective study on 20 eyes and had a success rate of 70%(14/20).

In the present study, 23 out of the 30 patients responded to intrastromal treatment, with success rate of 76.66%. We recommend randomized control trials (RCTs) with a larger sample size for establishing the benefit and success rate of the treatment.65

VI. COMPLICATIONS

No procedure-related complications were noted in this study similar to other studies.

Complications due to toxicity of voriconazole leading to possible endothelial damage, the formation of new infective foci, and micro-perforations during injection should be borne in mind while using this modality of treatment.

Further studies are recommended before this choice of therapy assumes a standard approach. 66

VII. STRENGTH OF THE STUDY

The present study had sufficient sample size to assess the efficacy of the intrastromal voriconazole in fungal corneal ulcers.

There was good clinical and microbiological correlation of the fungal corneal ulcers.

VIII. LIMITATIONS

There was no control group in the present study to compare with fungal corneal ulcers treated with topical medication alone. Intrastromal voriconazole was given as an adjuvant to topical therapy, so effectiveness of intrastromal voriconazole per se cannot be assessed.

IX. SUMMARY

Intrastromal voriconazole can be an effective and adjuvant treatment modality in selected patients who are unresponsive to other forms of antifungal therapy, as it delivers high intra corneal drug concentration at the site of infection which is usually not possible with topical antifungals. It might reduce the risk of complications like

perforation of cornea which further requires therapeutic penetrating keratoplasty.

Hence this study shows that judicious and timely usage of intrastromal voriconazole as an adjunctive therapy can be given in cases of recalcitrant fungal keratitis.

X. CONCLUSION

1. Intrastromal voriconazole has a definitive role in the management of recalcitrant fungal keratitis as an adjuvant to topical therapy with a high success rate.
2. Therapeutic success was achieved in 76.6% of cases
3. The most common age group was 4th-6th decade with male preponderance.
4. Most common isolated pathogen was Fusarium.
5. Progression of ulcer with perforation was more with large sized ulcers and deeper ulcers and more common in ulcers caused by Fusarium species.

Although injection of intrastromal voriconazole has shown promising effects,the frequency of injections, associated complications are yet to be determined by larger clinical trials with long term follow up.

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