Original Research Article

Impaction of interventional study with intrastromal voriconazole in recalcitrant deep fungal keratitis

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Abstract

Aim: To evaluate the efficacy and outcome of intrastromal voriconazole, as treatment for management of recalcitrant fungal keratitis. **Methods:** Thirty patients with fungal keratitis, not responding to a topical antifungal medications, were treated with intrastromal voriconazole (50 µg/0.1 mL) injected around the circumference of the lesion. **Results:** The mean area of the infiltrate was 30.41±17.2 mm(2), hypopyon was present in 88% and all cases had infiltrates that extended beyond the mid-stromal level. Intrastromal voriconazole helped to resolve the infection in 30 patients. The improvement of BCVA in twenty six patients from PL+,PR+ to CF-1mt group to 6/60 to 6/24 group maximum upto 6/18 to 6/9. This shows great significance of intrastromal voriconazole injection. In some patients there was a minimal improvement in BCVA atributtable to involvment of the abscesses and the resultant scar in the central cornea. **Conclusions:** Management of recalcitrant fungal keratitis with voriconazole by intrastromal injection (50 µg/0.1 mL) is a safe and effective way to treat deep recalcitrant fungal keratitis, though some may need repeated injections.

Keywords: Fungal keratitis; intrastromal; voriconazole, recalcitrant.

Introduction

Mycotic keratitis is a vision-threatening infectious disease and one of the leading causes of ocular morbidity. Mycotic infections are most common in developing countries. The fungal keratitis are usually difficult to treat. The number of effective antifungal drugs is less than those of antibacterial drugs and they are less tissue-permeable[1]. Moreover, the penetration of many antifungal drugs into cornea is suboptimal, which makes it difficult to treat cases of deep mycotic keratitis. To overcome these problems, investigators have evaluated alternative routes such as intracameral and intrastromal injections of voriconazole to treat fungal keratitis[2].

We here in report a series of 30 cases in which intrastromal voriconazole was used in conjunction with topical treatment to treat successfully deep-seated, recalcitrant, fungal keratitis.

Materials and methods

In this interventional case series, thirty cases OF mycotic keratitis involving deep corneal stroma that were unresponsive to topical antifungal therapy underwent intrastromal injection of voriconazole 50 micrograms/0.1 ml. Each of the participating patients gave informed written consent for participation in the study and for the surgical and medical management. All patients who met the inclusion criteria were injected voriconazole once via TCSI procedure within one week after enrollment, in addition to receiving treatment with conventional antifungal treatment, and these patients were classified as TCSI. The TCSI group consisted of 30 patients, while the control group consisted of 10 patients.

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The inclusion criteria for this study were as follows: (1) patients who tested positive on corneal smear examination (2) corneal infiltration area measuring less than 9-10 mm in diameter; and (3) follow-up for 3 months or more after discharge. The exclusion criteria for this study were as follows: (1) mixed keratitis; (2) corneal perforation (3) concomitant endophthalmitis; (4) presence of other ocular diseases, and (5) history of corneal transplantation.The cornea was divided into three circular areas: zone 1, zone 2, and zone 3 area for tricyclic corneal stroma injection procedure. Zone 1(the needle-entry area). The annular area adjacent to the corneal limbus measuring 1- 2 mm in width. Zone 3(needle-entry prohibited" area):The area with a diameter of 4–5 mm at the center of the cornea was designated as zone 3, while the area between zones 1 and 3 was designated as zone 2 (injection area). Preparation of a 0.5 mg/mL solution of voriconazole with the bent needle was inserted slowly to 50% of the depth of the corneal stroma at an angle of 15° to the corneal surface in the needle-entry area and cautiously inserted parallel to the cornea lamella in injection area followed by slow injection of the drug solution into the corneal stroma, until the corneal stroma around the lesion appeared to be swollen and cloudy. The procedure should be performed in the 4–6 different regions with 0.1–0.15 mL administered at each point to ensure that the entire corneal stroma around the lesion was swollen and cloudy. For eccentric lesions, the needle-entry point selected was close to the lesion, and the surgeon appropriately increased the injection pressure to make sure that the entire corneal stroma around the lesion was swollen and cloudy. TCSI was performed after surface infiltration anesthesia in the operating room by the same operator.

The control group was treated by topical voriconazole 10 mg/mL (every 2 h)) and topical natamycin 50 mg/mL (every 2 h). The TCSI was treated by conventional methods in addition to TCSI with voriconazole once within one week after enrollment. The healing of keratitis was considered the complete re-epithelialization with the complete resolution of the corneal infiltrates and no hyphae growth in

IVCM examination at the same time. And topical antifungal therapy was continued 4 times a day for 2 weeks after the healing.

Results

During the study 30 patients were included, out of which 20 were males and 10 were females. Age of the patients ranged from 40 to 65 years, mean being 52.75 years. All patients had anterior to mid stromal involvement of cornea on slit lamp examination and smears were positive for fungus and on cultures Fusarium species was identified in eighteen patients, Aspergillus species in nine patients and Candida species in three patients(Table 1).

As poor response was seen following two weeks of therapy with topical eye drops of 5% natamycin and tablet itraconazole 100mg bd, voriconazole was injected intrastromally around the infected area and 5% natamycin eye drops and tablet itraconazole 100mg bd were continued till the healing of the ulcer. In each of the thirty patients the procedure was performed successfully and no intraoperative or postoperative complications were observed, perforation of the ulcer was noticed in two patients in the second week of follow up and ulcer was progressive in third week of follow up in one diabetic patient who under went TKP, one patient did not come for follow up and the infection was resolved completely in the remaining twenty six patients after voriconazole injection. The mean healing duration was five weeks ± one week. The improvement of BCVA in twenty six patients from PL+,PR+ to CF-1mt group to 6/60 to 6/24 group maximum upto 6/18 to 6/9 group. This shows great significance of intrastromal voriconazole injection. In some patients there was a minimal improvement in BCVA atributtable to involvment of the abscesses and the resultant scar in the central cornea.

Table 1: Distribution (%) of patients with keratomycosis & type of fungi

S. No	Types of fungus	Males	Percentage	Females	Percentage
1.	Fusarium species	10	41.2	8	61.5
2.	Aspergillus Species	7	41.2	2	38.5
3.	Candida species	3	17.6	0	0

In majority of keratomycosis the Fusarium species was observed followed by Aspergillus species (Table 1).

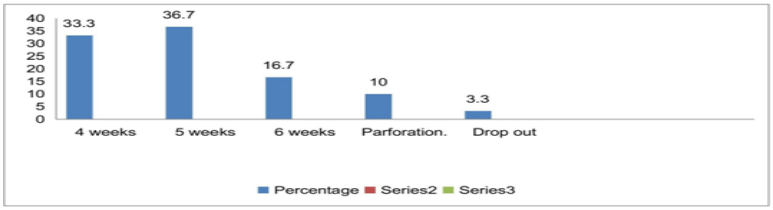

Fig 1: Distribution (%) of patients according to the time of (weeks)healing of ulcer after intrastromal voriconazole injection

Most of the cases started improving from 1st, 2nd week on words and healed with in 4-5weeks after intrastromal voriconazole(Fig 1)

Table -2: Distribution (%) of patients with Residual manifestations

S. No	Residual Manifestations	Males	Percentage	Females	Percentage
1.	Nebula	4	20	1	9.1
2.	Macula	11	53.3	8	81.8
3.	Leucoma	4	20	1	9.1
4.	Adherent Leucoma	1	6.7	0	0

Since most of the cases of keratomycosis involve the stroma a gross opacity in the form of macula was observed in most of the cases (Table 2).

Table 3: Distribution (%) of patients (keratomycosis) with treatment and improvement in Visual acuity (BCVA)

S .No	Visual acuity	Intrastromal voriconazole			
		Before		After	
		No. ofcases	Percentage	No. of cases	Percentage
1.	PL+, PR+ to CF-1mt	27	90	2	7.7
2.	CF-2mts toCF-4mts	1	3.3	10	33.3
3.	6/60 to 6/24	2	7.7	9	30
4.	6/18 to 6/9	0	0	5	16.7
5.	Under wentTKP	0	0	3	10
6.	Drop out	0	0	1	3.3
7.	P value < 0.001				

The above table shows visual acuity is improved in 10 cases of PL+, PR+ to CF-1mt group to CF-2mts to CF-4mts group and another 9 cases of same group improved to 6/6o to 6/24 group and 5 case to 6/18 to 6/9 group. This was the most significant advantage of Intrastromal Voriconazole injection.

Table 4: Distribution (%) of patients with Clinical improvement of ulcer

S. No	1st week	2nd week	3rd week	4th week	5th week	6th week
1.Reduction ofinflammation	0	10	14	2	0	-
2. Absorption ofhypopyon	2	5	7	2	0	-

Most of the inflammatory signs and hypopyon disappeared in 2nd and 3rd weeks (Table-3 & 4).

Table 5: Coefficients

Model	Unstandardizedcoefficients		Standardizedcoefficients	t	P value significance
	B	Std. Error	Beta		
Age	-.041	.014	-5.44	-2.924	.009
Sex	-.217	.520	-.090	-.417	.682
Eye	-.633	.407	-.259	-1.555	.138
Occupaton	-.089	.252	-.086	-.351	.730

Predisposingfactors	-.124	.098	-.198	-.272	.220
Ulcer site	.290	.359	.121	.808	.430
Size	-.274	.392	-.121	-.700	.494
Hypopyon	-.081	.462	-.033	-.176	.862
Culture	-.468	.343	-.259	-1.363	.191
Reduction ofinflammation	.338	.308	.322	1.091	.290
Absorptionof hypoyon	.161	.146	.227	1.102	.286
Healing ofulcer	.221	.361	.201	.613	.548

It was observed that the improvement of ulcer was associated with age of the patient, younger the patient earlier the ulcer healing.

Table-6: Impaction of interventional study with intrastromal voriconazole

Mean ± S.D value of BCVA by two time points					
BCVA					
	N	Mean	S.D	't'	P value
Before	30	1.2	0.53	8.3	0.000
After	30	3.0	1.22	-	-

The intervention shows significant impact (P value <0.001) on the improvement of keratomycosis(Table 6).

Discussion

Mycotic keratitis is an infection of the corneal stroma and becomes important cause of corneal blindness. The incidence of recalcitrant deep fungal keratitis varies around the world and is more prevalent in areas with hot humid climatic regions. Many species of fungi exist as commensals as a part of the normal ocular surface. However, under certain circumstances such as steroid treatment and injury to eye ball, these fungi might invade the eyeball and cause fungal infections[3].

Fusarium species can cause severe types of mycotic keratitis because of its high virulence and its resistance to antifungal drugs. In our study majority of keratomycosis the Fusarium species was observed followed by Aspergillus species.These species may lead to serious complications such as endophthalmitis, perforation and blindness. Several drugs have been used to treat filamentous mycotic ulcers[4]. The commonly available antifungal agents are natamycin, amphotericin-B, itraconazole. Few studies found that all fusarium species were sensitive to natamycin invitro but that did not convert to good clinical outcome irrespective of early or late presentation. The spectrum of common antifungal drugs available for fungal eye infections are limited and is associated with poor outcome[5]. However, resistance to amphotericin - B is increasing.

Management of deep fungal corneal ulcers is difficult with topical antimicrobial drugs because of limited spectrum of topical antifungal agents, poor penetration of the currently available drugs. Previous studies have shown that oral and topical antifungal agents have poor ocular penetration and hence suboptimal drug level are achieved at the site of infection. Current treatment options are far from optimal. Voriconazole is a triazole antifungal agent that induces fungal death by inhibiting lanosterol 14α-demethylase in the fungal cell membrane, which interrupts the conversion of lanosterol to ergosterol, thereby affecting the stability of the fungal cell membrane. This data showed that voriconazole has the best efficacy against pathogenic fungi compared with other drugs[6].It is used to treat several fungal infections caused by Aspergillus, Candida, and Fusarium and fungi resistant to fluconazole, itraconazole, or amphotericin B.

Some studies suggested that intrastromal injections may increase the risk of corneal perforation in fungal keratitis[7]. To overcome this dilemma.Thus, the tricyclic corneal stroma injection (TCSI) procedure was designed for intrastromal injection of voriconazole.

Studies have reported that voriconazole entered aqueous humor circulation after intrastromal injection . We were worried that it would produce adverse reactions in the aqueous humor circulation, resulting in abnormal IOP of patients after TCSI of voriconazole[8]. The preoperative IOP and post-TCSI IOP of the treated eye were compared with those of the respective contralateral eye. This difference was not statistically significant, which proved that this method was safe and would not impact the IOP.

The intrastromal injection of antifungal drugs could better control infection by increasing drug concentration at the ulcer site. Kalaiselvi et al. reported a success rate of 72 % in Tamilnadu, India[9]. Sharma N et al. study reported a success rate more than 70 %. The sensitivity of intrastromal voriconazole to different fungal species is yet to be determined[10].

Conclusion

Management of recalcitrant fungal keratitis with voriconazole by intrastromal injection is a safe and effective way to treat deep recalcitrant fungal keratitis.

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