

INTRACAMERAL AND INTRACORNEAL VORICONAZOLE IN DEEP KERATOMYCOSIS WITH ENDOTHELIAL PLAQUE

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ABSTRACT

Fungal keratitis, one of the major causes of ophthalmic mycosis is second only to cataract as the most common cause of blindness worldwide.

OBJECTIVE

The aim was to study the intracorneal and intracameral Voriconazole in deep keratomycosis with endothelial plaque.

MATERIALS AND METHODS

This was a study in the Cornea Clinic of Sarojini Devi Eye Hospital and Regional Institute of Ophthalmology, a Tertiary Care Teaching Hospital of Osmania Medical College (Govt.), Hyderabad, over a period from September 2012 to August 2014. The study group included 30 patients who were diagnosed clinically and microbiologically (+ve smear and culture) as fungal corneal ulcers with deep stromal infiltrates and endothelial plaque not responding to routine antifungal drugs and given voriconazole intracorneally and intracamerally.

Data of patient's age and sex and history of corneal trauma with type of the agents were noted. The time of healing of the ulcer with the scar formation after intracorneal and intracameral voriconazole was noted and the visual acuity was recorded after the healing of the corneal ulcer.

RESULTS

Thirty eyes of 30 patients with deep keratomycosis with endothelial plaque were evaluated; 19(63.3%) were Males and 11(36.7%) were Females. Age distribution was 4(13.3%) in >10-20 Yrs, 5(16.7%) in 21-30 Yrs, 4(13.3%) in 31-40 Yrs, 6(20.0%) in 41-50 Yrs, 5(16.7%) in 51-60 Yrs and 6(20.0%) in 61-70 Yrs. The type of trauma was the organic (Vegetative matter) in 19(63.4%), inorganic matter in 8(26.7%) and no H/o trauma with the agent not known in 3(10.0%). The causative fungi were Fusarium in 15(50.0%), Aspergillus in 12(40.0%) and Candida in 3(10.0). The time of healing of the Fungal Corneal Ulcer after Intracorneal and Intracameral Voriconazole was 4(13.3%) in 4-6 wks.; 12 (40.0%) in 6-8 wks., 5(16.7%) in 8-10 wks., and 4(13.3%) in 10-12 wks.; 25(83.3%) which were healed by corneal scarring were given 1 (One) intracorneal and intracameral injection of Voriconazole. The 5(16.7%) did not respond to 2 (Two) intracorneal and intracameral voriconazole injections, progressed to corneal perforations and were treated by Therapeutic Penetrating keratoplasty. Visual acuity was <3/60 in 18(60.0%) and 3/60 to <6/60 in 12(40.0%), and <3/60 in 3(10.0%), 3/60-<6/60 in 13(43.3%) and 6/60- <6/18 in 9(30.0%) before and after the intracorneal and intracameral voriconazole respectively.

CONCLUSIONS

Targeted delivery of Intracorneal and Intracameral Voriconazole was effective with a better visual outcome and a significant reduction in healing time in deep keratomycosis with endothelial plaque not responding to routine antifungal therapy.

KEYWORDS

Deep Keratomycosis, Endothelial Plaque, Voriconazole, Intracorneal, Intracameral.

HOW TO CITE THIS ARTICLE: Srinivas Prasad Killani, Srihari Atti, Atul Gupta, Sambasiva Reddy Pujala, Sridhar Goli, Superna Mahendra, Archana Adapala, Kranthi Budamakayala. "Intracameral and Intracorneal Voriconazole in Deep Keratomycosis with Endothelial Plaque." Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 99, December 10; Page: 16476-16480, DOI: 10.14260/jemds/2015/2446

INTRODUCTION

Ocular fungal infections or ophthalmic mycoses are common, especially in tropical countries with a poor prognosis compared to bacterial infections.

Corneal disease is second only to cataract as the most common cause of blindness worldwide with more than 1.5 million new cases of vision loss yearly.^(1,2)

It is a leading cause of monocular blindness worldwide accounting for about 50% of all cases of infectious keratitis in developing countries.⁽²⁾ Predisposing factors to the fungal infection are trauma with organic matter, long-term use of antibiotics and steroids, corneal surface disorders, refractive surgeries and contact lens disinfectant solutions.⁽³⁾ Fungi can invade Corneal stromal lamella, penetrate an intact Descemet's membrane and spread into the anterior chamber. The toxicity of fungus is related to its mycotoxin and its ability to replicate. Fungal keratitis is usually characterized by a corneal epithelial defect and inflammation of the corneal

Financial or Other, Competing Interest: None.

Submission 20-11-2015, Peer Review 21-11-2015,

Acceptance 02-12-2015, Published 10-12-2015.

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DOI:10.14260/jemds/2015/2446

stroma with endothelial plaque, hypopyon, fungal web and fungal ball in the anterior chamber. If untreated, fungal keratitis can lead to corneal scarring and vision loss.

Corneal infections involving the deeper parts of the stroma are not amenable to routine topical antifungal therapy. The currently available antifungal agents, amphotericin B, natamycin, fluconazole, ketoconazole, 5-flucytosine, itraconazole and voriconazole have limitations of poor penetration into the eye, limited spectrum of activity and surface toxicity.^(4,5) Surgical intervention in the form of therapeutic keratoplasty is required more often in fungal keratitis compared with bacterial keratitis indicating a poor response to treatment with antifungal agents. To overcome these problems, alternate routes were evaluated in fungal keratitis like intracorneal, intracameral, intravitreal, etc. Intracorneal and intracameral injections of amphotericin B,^(6,7,8,9) and Intracameral Amphotericin-B,^(6,8) were tried in fungal keratitis. But Amphotericin was associated with increased anterior chamber reactions and the risk of potential injury to the lens and toxicity to the corneal endothelium.

Marangon FB, et al.⁽¹⁰⁾ conducted a study to investigate the in vitro efficacy of voriconazole and other antifungals. Lalitha P, et al.⁽¹¹⁾ studies have suggested that voriconazole may have a broader spectrum of antifungal activity compared with amphotericin B. Gao H, et al.⁽¹²⁾ and Nehemy MB, et al.⁽¹³⁾ have reported intraocular voriconazole to be safe in vitro and in vivo and less toxic to retina than amphotericin B.

Voriconazole, a recent azole antifungal acts by inhibiting the synthesis of ergosterol in the fungal membranes and ultimately the growth of the microorganism. Voriconazole has a superior activity against fungi that are resistant to amphotericin B and itraconazole. It also has a good safety profile. It is available in the form of oral and IV formulations. Oral voriconazole is highly bio-available (96%) and has demonstrated good penetration into different parts of the eye. However, oral voriconazole can be associated with side effects as well as significant drug interactions. Topical 1% voriconazole demonstrated a good penetration through the cornea into aqueous humour without compromising intraocular safety. The intracorneal and intracameral voriconazole help in resolution of the ulcer with no adverse effects and facilitate the clearance of the nidus of infection from cornea.^(4,5) Voriconazole 50µg/0.1ml is used to inject circumferentially around the fungal abscess in the corneal stroma and in the anterior chamber as an adjunctive to topical antifungal therapy.

AIM

The aim was to study the intracorneal and intracameral Voriconazole in deep keratomycosis with endothelial plaque.

MATERIALS AND METHODS

This was a study in the Cornea Clinic of Sarojini Devi Eye Hospital and Regional Institute of Ophthalmology, a Tertiary Care Teaching Hospital of Osmania Medical College (Govt.), Hyderabad over a period from September 2012 to August 2014. The study group included 30 patients who were diagnosed clinically and microbiologically (+ve smear and culture) as fungal corneal ulcers with deep stromal infiltrates and endothelial plaque not responding to routine antifungal drugs and given voriconazole intracorneally and intracameraly. The patients with perforated fungal corneal ulcers and children <10 yrs. age were excluded. The study was approved by the Institute of Ethical Committee with the informed consent from all the patients of the study group.

Data of patient's age and sex and history of corneal trauma with type of the agents were noted. Each patient underwent a detailed clinical evaluation of recording the medical history, Snellen's visual acuity testing, slit-lamp biomicroscopy and ultrasonography to evaluate the posterior segment. Corneal scrapings obtained under topical anaesthesia were sent for microbiological investigations of Potassium Hydroxide (KOH) wet-mount preparation, Gram's stain and cultures on blood agar, chocolate agar and Sabaroud's agar.

Once the fungus was +ve for KOH and Gram stains, topical drops of 5% natamycin and 1% voriconazole eye drops every 2 hours, drops of 1% cyclopentolate hydrochloride 3 times a day and Tablet Itraconazole 100mg 2 times per day were given. When the clinical response was not seen in 2 to 3 weeks or the ulcer showed the signs of worsening, all the patients were given Voriconazole 50 micrograms in 0.1ml intracorneally as a barrage circumferentially around the fungal abscess and 50 micrograms in 0.1ml intracameraly under sterile techniques. The anterior chamber was washed thoroughly after 60 seconds contact time of intracameral voriconazole. Second injection was given when no clinical response was found after a minimum of 48 hours duration after the first injection. Totally not more than two injections of intracorneal and intracameral voriconazole were given.

Topical and systemic antifungal drugs were continued even after starting intracameral and intracorneal voriconazole injections. The topical antifungal was given for at least one week after the complete resolution of the infection. The infection was considered resolved when there was a complete healing of the ulcer with scar formation. If the patient was showing signs of worsening or if the ulcer or endothelial plaque was rapidly worsening after intracorneal and intracameral voriconazole injections, Therapeutic Penetrating Keratoplasty (TKP) was done. The time of healing of the ulcer with the scar formation after intracorneal and intracameral voriconazole was noted and the visual acuity was recorded after the healing of the corneal ulcer. The ulcer was defined as not improved if there was no change in the size of the ulcer and worsened if there was an increase in size or depth of ulcer or perforation. All the data was analyzed by simple statistical methods.

RESULTS

Thirty eyes of 30 patients with deep keratomycosis with endothelial plaque were evaluated after the intracorneal and intracameral voriconazole injection.

Sl. No	Age Group	Males	Females	Total	%
1.	10 - 20	4	0	4	13.3
2.	21- 30	2	3	5	16.7
3.	31- 40	1	3	4	13.3
4.	41-50	3	3	6	20.0
5.	51- 60	3	2	5	16.7
6.	61 - 70	6	0	6	20.0
Total		19	11	30	100.0
%		63.3	36.7		

Table 1: Age group and Gender

Sex distribution was 19(63.3%) Males and 11(36.7%) Females. Age distribution was 4(13.3%) in >10-20 yrs, 5(16.7%) in 21-30 yrs, 4(13.3%) in 31-40 yrs, 6(20.0%) in 41-50 yrs, 5(16.7%) in 51-60 yrs, and 6(20.0%) in 61-70 yrs.

Sl. No.	Type of Trauma	Type of Agent	No. of Cases	%
1.	Organic (Vegetative)	Paddy Husk	19	63.4
		Thorns	9	30.0
		Leaves	4	13.3
		Insects	2	6.7
		Animal Tail	2	6.7
2.	Inorganic	Stone	8	26.7
		Sand	2	6.7
		Foreign Body	4	13.3
3.	No H/o Trauma	Agent not Known	2	6.7
Total			30	100.0

Table 2: Type of the Trauma

The type of the trauma was the organic (Vegetative matter) in 19(63.4%), inorganic matter in 8(26.7%) and no H/o Trauma with the agent not known in 3(10.0%).

Sl. No	Type of Fungus	Males	Females	Total	%
1.	Fusarium species	7	8	15	50.0
2.	Aspergillus species	7	5	12	40.0
3.	Candida species	3	0	3	10.0
Total		17	13	30	100.0

Table 3: Type of Causative Fungi

The type of causative fungi were Fusarium species in 15(50.0%), Aspergillus species in 12(40.0%) and Candida species in 3(10.0%).

Sl. No	Time of Healing in Weeks	No. of Cases	%
1.	4 - 6 weeks	4	13.3
2.	6 - 8 weeks	12	40.0
3.	8 - 10 weeks	5	16.7
4.	10 - 12 weeks	4	13.3
5.	Progressed to Corneal Perforation after 2 - 3 weeks of treatment of intracorneal and intracameral Voriconazole	5	16.7
Total		30	100.0

Table 4: Time of Healing after intracorneal and intracameral voriconazole

The time of healing of the Fungal Corneal Ulcer after Intracorneal and Intracameral Voriconazole was 4(13.3%) in 4-6 wks., 12(40.0%) in 6 - 8 wks., 5(16.7%) in 8-10 wks., and 4(13.3%) in 10-12 wks.

Sl. No	Clinical Outcome	Males	Females	Total	%
1	Corneal Scar formation	15	10	25	83.3
2	Corneal Perforations	4	1	5	16.7
Total		19	11	30	100.0

Table 5: Clinical Outcome after intracorneal and intracameral voriconazole

25(83.3%) healed with Corneal scar and 5(16.7%) progressed to corneal perforations after intracorneal and intracameral voriconazole.

Sl. No	Visual Acuity	Before		After	
		No. of Cases	%	No. of Cases	%
1.	< 3/60	18	60.0	3	10.0
2.	3/60- <6/60	12	40.0	13	43.3
3.	6/60- <6/18	0	0.0	9	30.0
4.	>6/18	0	0.0	0	0.0
Total		30	100.0	25	83.3
5.	Progressed to Corneal Perforation			5	16.7
Total				30	100.0

Table 6: Visual acuity before and after Intracorneal and Intracameral Voriconazole

Visual acuity was <3/60 in 18(60.0%) and 3/60 to <6/60 in 12(40.0%), and <3/60 in 3(10.0%), 3/60- <6/60 in 13 (43.3%) and 6/60- <6/18 in 9(30.0%) before and after the intracorneal and intracameral voriconazole respectively.



Fig. 1: Deep Keratomycosis before Intracorneal and Intracameral Voriconazole



Fig. 2: Healed Keratomycosis after Intracorneal and Intracameral Voriconazole

The 25(83.3%) cases which were healed by corneal scarring were given 1 (One) intracorneal and intracameral injection of Voriconazole. The 5(16.7%) cases, which did not respond to 2 (Two) intracorneal and intracameral voriconazole injections, progressed to corneal perforations and were treated by therapeutic penetrating keratoplasty.

DISCUSSION

Ophthalmic mycosis is emerging as a major cause of vision loss and morbidity. Fungal keratitis is one of the major causes of ophthalmic mycosis.^(4,5) It is known that fungi are destroyed by a humoral and cellular host defence mechanism, but the large size of the hyphae of filamentous fungi precludes ingestion by neutrophils. Fungal hyphae tend to multiply extensively without inducing much cellular infiltration leading to a disease process that may be indolent.

Fungi can penetrate the intact Descemet membrane and enter the anterior chamber resulting in endothelial plaque and hypopyon, which is difficult to treat with antifungal agents because of their poor ocular penetration or

bioavailability and toxicity.^(6,8) Generally, prolonged and intensive topical and systemic antifungal therapy is required to eradicate the fungal infections. Contemporary antifungal drugs in the treatment of mycotic keratitis are less effective than contemporary antibacterial drugs in the treatment of bacterial keratitis. Moreover, the penetration of many antifungal drugs into the cornea is suboptimal, which makes it difficult to treat cases of deep keratomycosis. Hence, to overcome these problems targeted drug delivery to achieve adequate drug levels at the site of infection by intracorneal and intracameral injections of antifungals are being evaluated. Voriconazole has optimal activity against fungi that are resistant to amphotericin B and itraconazole.^(6,7,8)

Our study Causative fungi were *Fusarium* in 50.0%, *Aspergillus* in 40.0% and *Candida* in 10.0% correlates with the studies of Bharathi MJ, et al.⁽¹⁴⁾ of *Fusarium* 42.82% followed by *Aspergillus* of 26.0%. and Gopinathan U, et al.⁽¹⁵⁾ of *Fusarium* 37.2% followed by *Aspergillus* of 30.7%. Our study vegetative matter trauma 50.0% was compared to 61.28% in Bharathi MJ, et al.⁽¹⁴⁾ and of 22.97% in Suman Saha, et al.⁽¹⁶⁾ Our study Age distribution of 4(13.3%) in >10-20 Yrs; 5(16.7%) in 21-30 Yrs; 4(13.3%) in 31-40 Yrs; 6(20.0%) in 41-50 Yrs; 5(16.7%) in 51-60 Yrs; and 6(20.0%) in 61-70 Yrs showing higher incidence with increasing age and with 63.3% of males compared to 36.7% of females correlating with the studies of Bharathi MJ, et al.⁽¹⁴⁾ Gopinathan U, et al.⁽¹⁵⁾ and Suman Saha, et al.⁽¹⁶⁾ So, our study and other studies show that the fungal keratitis was commonly caused by *Fusarium* and *Aspergillus* with Vegetative matter trauma in males, as they are the most working class with more exposure to risk factors due to their more outdoor activities as compared to females and common with increasing age with a significant burden of visual impairment.

In our study, the time of healing after Intracorneal and Intracameral Voriconazole was 13.3% in 4-6 wks.; 40.0% in 6-8 wks.; 16.7% in 8-10 wks; and 13.3% in 10-12 wks. Visual acuity was <3/60 in 18(60.0%) and 3/60 to <6/60 in 12(40.0%), and <3/60 in 3(10.0%), 3/60- <6/60 in 13 (43.3%) and 6/60- <6/18 in 9(30.0%) before and after the intracorneal and intracameral voriconazole respectively; 83.3% healed with Corneal scar and 16.7% progressed to corneal perforations after intracorneal and intracameral voriconazole; 83.3% which were healed by corneal scarring were given 1 (One) intracorneal and intracameral injection of Voriconazole; 16.7% did not respond to 2 (Two) intracorneal and intracameral voriconazole injections, progressed to corneal perforations and were treated by Therapeutic Penetrating keratoplasty. So, in our study the intracorneal and intracameral Voriconazole helped in the resolution of the deep keratomycosis with endothelial plaque with a good visual outcome with the surgical intervention only in 16.7%.

Hariprasad SM, et al.⁽¹⁷⁾ reviewed over 40 clinical case reports of treatment with voriconazole and suggested that it may be used safely and effectively against a broad range of fungal pathogens. Perfect JR, et al.⁽¹⁸⁾ observed that voriconazole is an effective and well tolerated treatment for refractory or less-common invasive fungal infections.

Sharma N, et al.⁽¹⁹⁾ conducted a study on 12 patients and concluded that intrastromal injection of voriconazole may be used as a modality of treatment for managing cases of recalcitrant fungal keratitis. Prakash G, et al.⁽²⁰⁾ observed that targeted delivery of voriconazole by intracorneal injection may be a safe and effective way to treat cases of deep seated recalcitrant fungal keratitis responding poorly to conventional treatment modalities.

In Ganapathy Kalaiselvi, et al.⁽²¹⁾ 25 patients with culture proven fungal keratitis, not responding to a combination of topical 5% natamycin and 1% voriconazole

were treated with intrastromal voriconazole and concluded that targeted delivery of voriconazole by intrastromal injection was a safe and effective way to treat deep recalcitrant fungal keratitis.

Jain V, et al.⁽²²⁾ concluded that topical therapy along with a judicious use of intrastromal administration of voriconazole may be of immense benefit in refractory fungal keratitis.

Singh PK, et al.⁽²³⁾ in a case report observed that intrastromal injections of voriconazole helped in early and complete resolution of the ulcers and it is a new promising therapy for fungal keratitis refractory to standard antifungal agents. So, intracorneal voriconazole was reported to be safe and effective in deep recalcitrant fungal keratitis in the studies of Namrata Sharma, et al.⁽¹⁹⁾ Gaurav Prakash, et al.⁽²⁰⁾ Ganapathy Kalaiselvi, et al.⁽²¹⁾ Jain V, et al.⁽²²⁾ and Singh PK, et al.⁽²³⁾

Shen YC, et al.⁽²⁴⁾ conducted a retrospective, consecutive case series of 10 patients to report the therapeutic efficacy of intracameral voriconazole in the treatment of fungal endophthalmitis resulting from keratitis and concluded that intracameral voriconazole may be an effective treatment for fungal endophthalmitis contiguously spreading from keratitis. Gupta et al.⁽²⁵⁾ reported that intracameral Voriconazole injection to be a safe and effective treatment in intracameral extension following penetrating keratoplasty for fungal keratitis.

Haddad RS, et al.⁽²⁶⁾ observed that combination of intracameral and intrastromal voriconazole in the treatment of recalcitrant *Acremonium* fungal keratitis was cost-effective treatment in impeding the progression of keratitis.

So our study correlate with the above studies that the intracorneal and intracameral Voriconazole has a therapeutic role in the clinical resolution of the deep keratomycosis with endothelial plaque with a good visual outcome. In all cases reported in the literature so far, intracorneal and intracameral injections of antifungal agents were used as a last resort to treat cases of non-healing deep fungal keratitis not responding to conventional therapy. In our study also intracorneal and intracameral voriconazole were given to 30 patient's refractory to conventional antifungal therapy with 83.3% resolving completely and 16.7% developing corneal perforations indicating treatment failure requiring therapeutic penetrating keratoplasty, i.e. surgical intervention was required only in 16.7%.

In summary, intracorneal and intracameral voriconazole injections may be effective in the treatment of deep keratomycosis. None of our patients developed any toxic effects with the drug after the injection. It was observed that judicious and timely use of intracorneal and intracameral voriconazole injections as an adjunctive therapy may be undertaken in selected patients who are unresponsive to other forms of antifungal therapy. The major advantage of this treatment modality is that it delivers the drug at the site of infection, achieving a high intracorneal and aqueous concentration, which may not be possible with topical and systemic antifungal therapy. So, a combination of Intracorneal and Intracameral voriconazole is a new promising therapy for fungal keratitis refractory to standard antifungal agents. Further studies and randomised controlled trials with larger sample size are recommended before this choice of treatment assumes a standard approach.

CONCLUSIONS

Targeted delivery of Intracorneal and Intracameral Voriconazole had a therapeutic role with a better visual routine antifungal therapy. Less number of therapeutic keratoplasties was performed in patients of deep

keratomycosis with endothelial plaque, who received voriconazole injection intracorneally or intracamerally.

To give more number of injections and to wait for a longer time before deciding about Therapeutic Keratoplasty may be a better option to bring about healing.

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