Original Research Article

Clinical study of effectiveness of intrastromal voriconazole injection in the management of deep non healing fungal corneal ulcer as an adjunctive therapy

P. Ramapathi Rao[1*], S. Deepa[1], D. Babu Rao[2]

[1]Assistant Professor, Department of Opthalmology, Dr. Patnam Mahender Reddy Institute of Medical Sciences & Hospital, Chevella, Rangareddy district, Telanagana, India

[2]Professor, Department of Opthalmology, MNR Medical College, Sangareddy, Telangana, India

Received: 28-10-2021 / Revised: 10-12-2021 / Accepted: 29-12-2021

Abstract

Aim: To study the effectiveness of intrastromal voriconazole injection in the management of deep non healing fungal corneal ulcer as an adjunctive therapy. **Study design:** Interventional case series. **Materials and methods**: Thirty eyes of thirty patients with deep stromal recalcitrant fungal keratitis not responding to topical antifungal medications. Localized injection of voriconazole may be a minimally invasive, safe, and effective adjuvant treatment modality for deep non healing fungal corneal ulcer **Results:** The study included 30 subjects. There were seventeen males and thirteen females. All patients were referred to us for management by peripheral opthalmic clinics with a history of recalcitrant microbial keratitis and corneal abscesses involving up to posterior stroma. **Conclusion:** Our study conclude that intrastromal voriconazole might be used as an adjuvant for non healing fungal ulcers and help in reducing the risk of complications.

Keywords: keratitis, voriconazole, corneal ulcer

Introduction

A fungal corneal ulcer, is an infection of the corneal stroma. It can cause rapid visual loss and pain. Fungal keratitis is one of the most serious infectious diseases of the eye that usually leads to blindness[1]. Trauma, indiscriminate use of corticosteroids and antibiotics, and prolonged contact lens use have resulted in a tremendous increase in the ocular morbidity of fungal keratitis, especially in developing countries[2].Fungal infections of the cornea are usually difficult to treat. Contemporary antifungal drugs in the treatment of mycotic keratitis are less effective than antibacterial drugs in the treatment of bacterial keratitis. 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 amphotericin B to treat fungal keratitis[3]. Fungal keratitis need to be treated as soon as possible to preserve vision. A fungal infection can lead to perforation of the cornea, loss of vision, and even loss of the eye if left untreated.

Contact lens wear, eye trauma with vegetative matter, previous ocular surgery, topical steroid use, and immunosuppression are the risk factors that can predispose to fungal corneal ulcer[4]. Patients will complain of eye pain, light sensitivity, red eyes, and possibly reduced vision. The onset and progression of symptoms is slower than symptoms and progression in bacterial keratitis. Bacterial keratitis is more common than fungal keratitis.

Materials and methods

Injection voriconazole is available as 200mg of white lyophilized powder in a glass vial. The powder was reconstituted with 19ml of lactated Ringer solution (LR) to obtain 20ml of clear concentrate containing 10mg/ml of voriconazole. A 1-ml aliquot of this solution was further diluted with 20ml of LR to a concentration of 0.5mg/ml (50µg/0.1ml). the reconsituted solution was loaded in a 1-ml tuberculin syringe with a 30-gauge needle. After adminstration of peribulbar anesthesia, the patient was shifted to the operating table. Under full aseptic conditions, the preloaded drug was adminstrated under operating microscope. With the bevel down, the needle was inserted obliquely from the uninvolved, clear area to reach just flush to the abscess at mid-stromal level (as the intended level of the drug deposit) in each case. The drug then was injected and the amount of the hydration of the cornea was used as a guide to assist the area covered. Once the desired amount of hydration was achieved, the plunger was withdrawn slightly to ensure discontinuation of the capillary column and thus prevent back leakage of the drug. Five divided doses were given around the abscess to form a deposit of the drug around the circumference of the lesion. This was done in such a manner that a centripetally directed progressive wave of fluid appeared to encompass the abscess along each meridian. Circumferential injection ensured the formation of a barrage of intrastromal voriconazole around the entire abscess. The total amount of the drug injected intrasrtomally ranged from 0.05ml to 0.1ml.Postintrastromal injection, all patients were continued 5% natamycine eye drops hourly, tablet itraconazole 100mg bd and 1% cyclopentalate hydrochloride eye drops three times day. Patients were examined every third day and response to the therapy was recorded, including best corrected visiual acuity (BCVA) and measurement of size of abscess on slit-lamp biomicroscopy. The infection was considered resolved when there was complete healing of the epithelial defect with resolution of corneal abscess and scar formation. The patients were continued to topical antifungal therapy for atleast one week after the complete resolution of the infection.[3-7]

*Correspondence

Dr. P. Ramapathi Rao

Assistant Professor, Department of Opthalmology, Dr. Patnam Mahender Reddy Institute of Medical Sciences & Hospital, Chevella, Rangareddy district, Telanagana, India.

E-mail: drramapathirao@gmail.com,

Results

Each of the thirty patients were referred to us for management by peripheral opthalmic clinics with a history of recalcitrant microbial keratitis and corneal abscesses involving up to posterior stroma. Patients had already received topical fluoroquinolone drops and antifungal agents for two to four weeks. History of vegetative trauma in twelve patients, foreign body or dust in seven patients, no history of trauma in four patients, insect trauma in two patients, industrial injury in two patients and one each with stone, sand and buffalo tale.

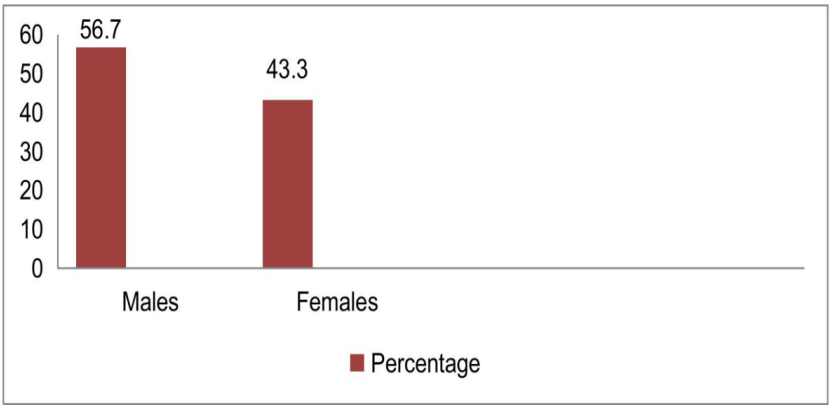

Fig 1: Distribution (%) of patients according to gender

Keratomycosis is more common in males(56.7%) than in females(43.3%) (Fig1).

Table 1: Distribution (%) of patients according to age group and gender

S.No	Age group	Males	Percentage	Females	Percentage	Total	Percentage
1.	10-20	2	11.8	3	23.1	5	16.7
2.	21-30	2	11.8	3	23.1	5	16.7
3.	31-40	2	11.8	0	0	2	6.6
4.	41-50	3	17.6	6	46.1	9	30
5.	51-60	5	29.4	1	7.7	6	20
6.	61-70	3	17.6	0	0	3	10
Total		17	100	13	100	30	100

The prevalence of keratomycosis was higher among 51-60 in males and 41- 50 in females(Table2).

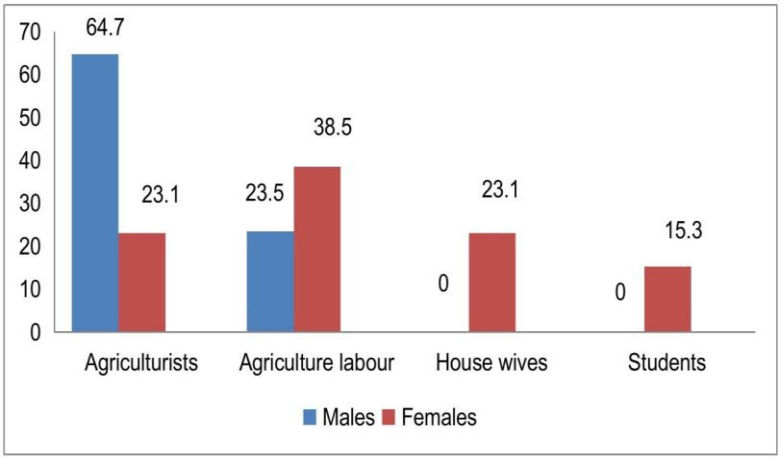

Fig 3: Distribution (%) of patients according to their occupation

This data shows that keratomycosis is seen mostly in agriculturists and agriculture labour. This could be linked to their nature of work(Fig3).

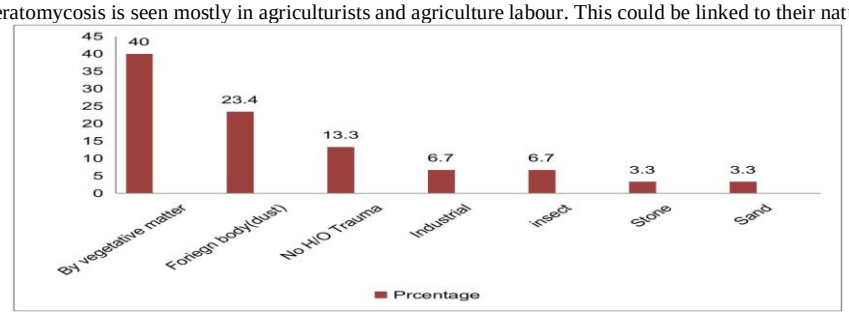

Fig 4 : Distribution (%) of patients of fungal keratomycosis by cause

In majority of the cases the cause of injury was vegetative matter(40%) followed by foreign body(23.4%)(Fig4). Table-5: Distribution (%) of patients with keratomycosis and associated with hypoyon

Table 2:Hypopyon status

S. No	Hypopyon Status	Male	Percentage	Female	Percentage
1.	Hyopopyon Present	11	64.7	8	61.5
2.	No hypopyon	6	35.3	5	38.5

Hypoyon is more common in males (64.71%)than females(61.54%)(Fig5).

Table 3: Distribution (%) of patients according to size of ulcer

S.No	Size of lesion	No.of cases	Percentage
1.	1/4th to 1/2 of cornea	21	70
2.	1/2 to 3/4th of cornea	8	26.7
3.	> 3/4th of cornea	1	3.3

In majority of the cases(70%) the ulcer size was 1/4th to 1/2 of cornea(Fig 6).

Discussion

Corneal infectons involving deeper parts of the stroma are not amenable to topical antimicrobial therapy. This is particuraly true for mycotic keratitis 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. Similar attempts of site-directed drug deposite have been made in posterior segment pathologies in the form of intravitreal injections and posterior Sub-tenon injections of drug[5]. In our series, none of thirty cases had responded to topical antifungal therapy and therefore we decided to proceed with intrastromal drug delivery[6] Intrastromal injections of amphotericin B have been used previously to treat recalcitrant mycotic keratitis without significant improvement. We used voriconazole because previous experiences with it in ocular infections, using both topical and systemic routes, have been promising[7] . Furthermore, voriconazole has optimal activity against fungi that are resistant to amphotericin B and itraconazole and has a good safety profile[8].The intrastromal injections of voriconazole helped in early and complete resolution of the ulcer with no adverse effects in twenty six out of thirty cases of our study[9].

Our series of thirty cases provides some indication of a possible therapeutic role of intrastromal antimicrobial drug delivery by intrastromal injection in the management of recalcitrant fungal keratitis. We belive that if combimed with topical therapy, a judicious use of intrastromal adminstration of antifungal drugs may be of immense benefit in such cases[10].Gaurav Prakash, Namrata Sharma have done similar study which was reported in Americal Journal Ophthalmology, where in they have injected intrastromal voriconazole in three patients and in all those patients the infection was controlled. Our study confirms the success rate of the study done by the them. Another study by Vandana Jain, Nishikant Borse one case of post operative recalcitrant fungal tunnel infection treated with intrastromal injection of voriconazole, the infection was controlled.

Advantages of intrastromal voriconazole injection:High percentage of success in healing the recalcitrant mycotic fungal keratitis. Because the drug is given as depot, the patient compliance in usage of other topical drugs is decreased in duration and dosage[10,11]

Limitations of intrastromal voriconazole: The only reason why the voriconazole is not used as first line of the drug in fungal keratitis is the huge cost of the drug(rupees 2400 per 200mg vial). There is a risk of corneal perforation while injecting the drug.

Conclusion

Targeted delivery of voriconazole by intrastromal injection may be a safe and effective way to treat the cases of deep-seated recalcitrant fungal keratitis responding poorly to conventional treatment modalities. In our view, if the cost of the drug comes down and in the centers where the load of the fungal keratitis cases are more, the drug can be used as first line of the treatment especially in deep mycotic keratitis.

References

1. Epidemiology and treatment of fungal corneal ulcers Int Ophthalmol Clin. 2007;47:7–16
2. Sharma N, Goel M, Titiyal JS, Vajpayee RB. Evaluation of intrastromal injection of voriconazole as a therapeutic adjunctive for the management of deep recalcitrant fungal keratitis Am J Ophthalmol. 2008;146:56–9
3. Kalaiselvi G, S, Krishnan T, Sengupta S. Intrastromal voriconazole for deep recalcitrant fungal keratitis: A case series Br J Ophthalmol. 2015;99:195–8
4. Ghate D, Edelhauser HF. Ocular drug delivery. Expert Opin Drug Delivery 2006;3:275-287
5. Polizzi A, Sinischalchi C – Effect of voriconazole on a corneal abscess caused by Fusarium. Acta ophthalmol Scand 2004;82:762-764
6. Breit. SM, Hariprasad SM, Mieler WF, Shah GK, Mills MD, Grand MG. Management of endogenous fungal endophthalmitis with voriconazole and caspofungin. Am J Opthalmol 2005;139:135 – 140.
7. Hariprasad. SM, Mieler WF, Lin. TK et al – Voriconazole in the treatment of fungal eye infections: a review of current literature. BR J. Opthalmol.2008;92:871-878.
8. Gao H, Pennesi M, Shah K, et al – Safety of intravitreal voriconazole: electroretinographic and histopathologic studies. Trans Am OphthalmolSoc 2003;101:183-189.
9. Diekema DJ, Messer SA, Hollis RJ, Jones RN, Pfaller MA – Activities of caspofungin, itraconazole, posaconazole, ravuconazole, voriconazole, and amphotericin B against 448 recent clinical isolates of filamentous fungi. J Clin Microbiol 2003;41:3623-3626.
10. Pfaller MA, Messer SA, Hollis RJ, Jones RN, Diekema DJ. In vitro activities of ravuconazole and voriconazole compared with those of four approved systemic antifungal agents against 6,970 clinical isolates of candida spp. Antimicrob agents chemother 2002;46:1723-1727.
11. Prakash G, Sharma N, Goel M et al .Evaluation of intrastromal injection of voriconazole as a therapeutic keratitis. Am J Ophthalmol.2008;146:56-59.

Conflict of Interest: Nil Source of support: Nil