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Original Research Article

Intrastromal voriconazole injection as a primary treatment of deep seated fungal corneal ulcer versus conventional treatment

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ABSTRACT

Purpose: To compare efficacy of intrastromal Voriconazole as a primary treatment of deep seated fungal corneal ulcer versus conventional treatment in form of 5% topical Natamycinin Northern India.
Materials and Methods: A prospective, hospital based, interventional study was done between Jan 2022 to Jan 2023 in all deep seated fungal corneal ulcers involving half or more of corneal stromal depth.
Results: A total 30 patients (15 patients in each group) were studied. Groups were comparable in terms of age, gender, laterality, causative organism and size and depth of infiltrate. Mean age in intrastromal Voriconazole group was 40.5±19.2 and in topical 5% Natamycin group was 40.8±16. Out of the 15 patients in Natamycin group, 6(40%) patients did not show any improvement, worsening seen in 4(27%), improvement was noted in 3(20%) and 2(13%) patients were cured of fungal corneal ulcer. Out of 15 patients in intrastromal Voriconazole group, 7(47%) patients showed improvement, 6(40%) patients were cured and worsening of ulcer was noted in 2(13%) patients. On comparison, outcome between two groups was found to be statistically significant ($p<0.006$).
Conclusion: 5% Natamycin is a drug of choice for fungal corneal ulcer, however, due to poor penetration of topical antifungal drugs, in deep seated fungal corneal ulceration and abscesses it was not found to be very effective. In these cases, due to broader spectrum of activity, higher achieved concentration at infection site and lower complication rate, intrastromal Voriconazole could be considered as a primary therapy. Further prospective studies with larger sample size are needed toestablish the outcome.

1. Introduction

Fungal keratitis is very common in India due to the tropical climate and large agricultural population. In India, about 50% of culture-positive keratitis is due to mycotic infections.[1] Microbial keratitis constitutes a majority of cases of ocular morbidity and monocular blindness. Trauma by vegetative matter, injudicious use of topical antibiotics and corticosteroids are various risk factors for fungal corneal ulcers.[2,3] Mycotic infections are also more common in rural than urban population and they are also common in low socioeconomic conditions.

In North India, Aspergillus is the most common organism causing fungal keratitis, followed by Fusarium and Curvularia whereas in South India Fusarium is the most common organism responsible for fungal keratitis followed by Aspergillus.[4–6] Overall, Aspergillus is the commonest organism responsible for causing fungal keratitis worldwide.

Fungal keratitis may involve deep stromal layer of the cornea and its treatment is more difficult than bacterial ulcers because topical antifungal medications are larger molecules and have poor penetration. Poor bioavailability, surface toxicity, limited spectrum are other limitations of

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currently available topical antifungal medications.[6,7]

Topical 5% Natamycin is the drug of choice for treatment of fungal corneal ulcers. It is a fungistatic drug and belongs to the polyene group. It is the only antifungal approved by the Food and Drug Administration (FDA). It has a higher probability of clinical cure and prevents chances of corneal perforation and therefore the need to perform therapeutic keratoplasty. Ketoconazole, Fluconazole, Itraconazole and Voriconazole are commonly used as systemic antifungals or in combination with Natamycin as topical therapy. Voriconazole is an azole (2^{nd} generation triazole). It acts on fungal cytochrome P 450 enzyme and block the synthesis of ergosterol in the plasma membrane thus inhibiting fungal growth. It has a greater light and temperature stability.

Natamycin has been a primary treatment for fungal corneal ulcer but in deep seated and larger corneal ulcer, there is always a need for adding systemic medication that may have various side effects. Standard treatment protocol includes topical, systemic and targeted drug delivery (TST).[8] Refractory fungal corneal ulcers not responding to medical therapy are treated by targeted drug delivery system in the form of intracameral or Intrastromal injections.[9,10] Therapeutic keratoplasty is done in patients of deep seated ulcers not responding to conventional treatment.[11,12]

Although Voriconazole has a broader spectrum of activity than Natamycin and is effective against most of the filamentous fungi as well as candida,[13] it has no added advantage over topical 5% Natamycin in the treatment of fungal corneal ulcer as a primary therapy in topical form.[14] Intrastromal Voriconazole, however, with its higher achievable concentration at the infection site, was found to be efficacious in the management of recalcitrant, deep fungal corneal ulcers in previous studies,[9,15–19] and therefore risk of complications such as corneal perforation and need for therapeutic keratoplasty is reduced.

Here in our study, we assessed the efficacy and complications of intrastromal Voriconazole as primary therapy for deep seated fungal corneal ulcer versus conventional treatment in form of topical 5% Natamycin. No other study is available from this part of the world where intrastromal Voriconazole is used as a primary therapy and where the fungal keratitis related ocular morbidity is very common.

2. Materials and Methods

This prospective, interventional, single centre study was carried out at a tertiary care centre in Northern India, between Jan 2022 to Jan 2023. The study adhered to the tenets of the declaration of Helsinki and was approved by the institutional ethical committee.

The patients of fungal corneal ulcer were diagnosed clinically and by Gram stain, KOH mounting and culture sensitivity of the corneal swab. All the investigations and surgical procedures were carried out after seeking informed written consent from the patient or legal guardian (in case of children).

2.1. Inclusion criteria

A patient of microbiologically proven fungal corneal ulcer size >2mm involving half or more of stromal depth in all age groups.

2.2. Exclusion criteria

1) Any suspected case of bacterial or viral corneal ulcer 2) Patients with corneal thinning, perforation or descemetocele 3) Pregnant or breastfeeding females 4) Patients on immune modulating agents

Socio-demographic data of the cases and the relevant information related to risk factors was noted like history of any trauma, treatment history, etc.

Patients presented with corneal ulcer were subjected to detailed examination including visual acuity, slit- lamp biomicroscopy. The findings noted on slit lamp included: the size, density and depth of infiltration, size of epithelial defect, degree of stromal edema, hypopyon and scleral involvement, if any.

Routine smear under sterile conditions on precleaned glass slides, one for 10% KOH mount to look for fungal elements and other for Gram stain to look for bacterial pathogens was done. Additionally, the corneal scraping was inoculated in Sabouraud's agar for culture and sensitivity. Random blood sugar testing was done to rule out diabetes mellitus.

30 Patients of proven fungal corneal ulcer of size >2mm covering more than half of the stromal depth were recruited from the OPD and randomly categorized into two groups of 15 each. Conventional treatment in form of topical 5% Natamycin was started in one group, given 1 hourly at daytime and 2 hourly at bedtime. Depending upon the clinical response, the dose was tapered over 4-7 days interval. Patients were followed up for a minimum of 10 weeks or complete resolution of the ulcer, whichever was earlier. If no response to treatment was noted, systemic antifungal (oral Itraconazole)/topical VCZ/ targeted drug delivery was considered in the same order of priority..

Intrastromal Voriconazole was started in next group of patients (50μg/0.1ml). Patients were examined for 3 days and the response to treatment was noted along with the need for repeat injection. If signs of healing were noted, patients were further kept on conventional treatment in form of topical Natamycin and systemic Itraconazole and reviewed after one week and then once every 2 weeks for 3 months and thereafter till the ulcer healed completely. The criteria for healing were as follows:-

2.3. Cured corneal ulcer

A completely healed ulcer with fluorescein negative staining and completely resolved stromal infiltration.

2.4. Improved corneal ulcer

Non-progression or decrease in epithelial defect and stromal infiltration size by at least 20%.

2.5. No change (Ulcer remained same)

Size and depth of the infiltrate remained same.

2.6. Worsened corneal ulcer

Size and depth of the infiltrate increased by at least 20% or if the ulcer perforated or any untoward drug reactions were noted.

2.7. Procedure of intrastromal voriconazole injection

Voriconazole injection is available as a lyophilized powder (200mg). The powder was reconstituted with 19ml of ringer lactate solution (RL) to obtain 20ml of clear concentrate containing 10 mg/ml of Voriconazole. 1 ml of this solution was diluted with 20 ml of RL to make a final concentration of 0.5 mg/ml(50ug/0.1ml). This reconstituted solution was filled in a 1 ml tuberculin syringe with a 26-gauge needle.

Peribulbar anesthesia is administered and the patient was shifted to the operating table. The preloaded drug was administered under operating microscope under full aseptic condition. The needle was inserted from the uninvolved and clear area to reach the abscess at the mid-stromal level (the intended level for the drug deposit) in each case. After injecting the drug the amount of hydration of the cornea was used as a guide to assess the area covered. The plunger was withdrawn slightly to ensure discontinuation of the capillary column once the desired amount of hydration was achieved.

To form a deposit of the drug, five divided doses were given around the abscess. Circumferential injections form of a barrage of Intrastromal Voriconazole around the entire abscess. The total amount of drug injected ranged from 0.05 ml to 0.1 ml.

3. Results

15 patients in each group were studied with mean age in topical Natamycin group was 40.8±16 years and in Intrastromal Voriconazole group was 40.5±19.2 years. The keratitis was more common in males as compared to females in both the groups (12:3 and 11:4 respectively). Both the groups were comparable in laterality, etiology, isolated organism, ulcer size and ulcer site (Table 1).

Out of the 15 patients in Natamycin group, 6(40%) patients did not show any improvement, worsening of the ulcer was noted in 4(27%). Improvement was noted in 3 (20%) patients and 2(13%) patients werecured of fungal corneal ulcer. (Table 2) (Chart 1)

Out of the 15 patients in intrastromal group, 7(47%) patientsshowed improvement. 6(40%) patients were cured and worseningof the ulcer was noted in 2 (13%) patients. (Table 2) (Figures 1 and 2, Chart 1)

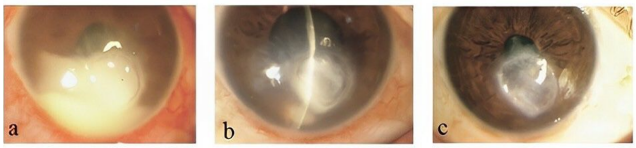

Figure 1: A 21 years old male with Fusarium fungal keratitis **a**) Deep corneal abscess with hypopyon **b**) 7 days post intrastromal Voriconazole injection with resolving abscess **c**) completely resolved abscess 3 week post injection

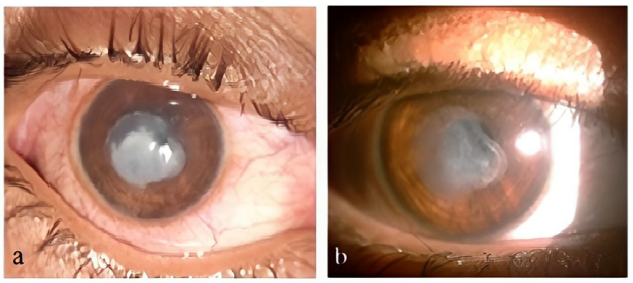

Figure 2: A 50 year old female with Aspergillus fungal keratitis **a)** Fungal corneal abscess **b)** 7^{th} week post intrastromal injection

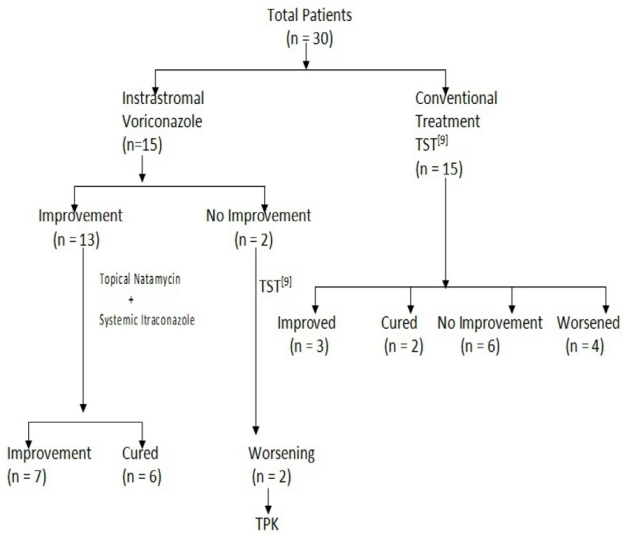

Chart 1: Flowchart of response to treatment

On comparison of Outcome between Groups by Pearson's Chi-Square test a highly statistically significant difference in outcome between two groups was found ($p<0.006$). (Table 2)

Table 1: Demographic and clinical characteristics of study patients

Features	Topical Natamycin 5%(n=15)	Intrastromal Voriconazole (n=15)	Total (n=30)	P value
Mean age	40±16	40.5±19.2	36.8±8.96	0.9388
Male: Female	12:3	11:4	23:7	0.6659
Laterality (Right:Left)	8:7	8:7	16:14	1.00
Trauma with vegetative matter	11(73%)	10(66.6%)	21(70%)	0.6903
Duration of symptoms(days)	9.5±4.6	10.1±3.4	8.96±4.09	0.6876
Infilrate size mean (height×width) in mm	4.2×3.1	5.6×4.3	5.0×3.8	0.5324
Epithelial Defect size mean(mm)	6.3×4.2	7.3×8.2	6.8×6.2	0.4932
Hypopyon	10(66.6%)	11(73%)	21(70%)	0.6903
Isolated organism (Aspergillus: Fusarium: others)	11:3:1	10:3:2	21:6:3	0.8265

Table 2: Treatment outcome at 10^{th} week of both 5% Topical Natamycin (A) and injection Intrastromal Voriconazole (B) treated patients (A n=15, B n=15)

Treatment response	No Change	Improved	Cured	Worse	P value at 10^{th} week (A&B)
I st week					
A	13(87%)	2(13%)	0	0	
B	6(40%)	9(60%)	0	0	
3rd week					
A	11(73%)	3(20%)	0	1(6%)	
B	3(20%)	11(73%)	0	1(6%)	
5th week					
A	9(60%)	3(20%)	1(6%)	2(13%)	
B	3(20%)	8(53%)	3(20%)	1(6%)	**<0.006**
7th week					
A	7(46%)	3(20%)	2(13%)	3(20%)	
B	1(6%)	8(53%)	4(26%)	2(13%)	
9th week					
A	6(40%)	3(20%)	2(13%)	4(26%)	
B	1(6%)	7(46%)	5(33%)	2(13%)	
10th week					
A	6(40%)	3(20%)	2(13%)	4(22%)	
B	0	7(47%)	6(40%)	2(13%)	

Pretreatment visual acuity better than 6/60 was found in 1 patient (6%) in Natamycin group while 3 patients (20%) in Voriconazole group whereas post-treatment 4 patients (27%) of Natamycin group and 6 patients (40%)of Intrastromal Voriconazole group showed visual acuity of greater than 6/60. (Table 3)

3 Patients (20%) in topical Natamycin group and 2 patients (13.3%) in Intrastromal Voriconazole group developed severe corneal thinning while 1 patient (6.66%) in Topical Natamycin group developed corneal perforation. In all 5 patients therapeutic keratoplasty was performed.

4. Discussion

Managing a case of fungal keratitis is difficult as the penetration of topical antifungal agents commonly available, remains inadequate at the deeper layers of cornea. In severe and deep seated fungal corneal ulcer, systemic antifungals have been used but the systemic medications have poorer penetration and have their own side effects. MUTT-II trial did not show any additional benefit of adding oral Voriconazole to topical antifungal agents in the treatment of severe fungal keratitis.[12] American Academy of Ophthalmology (AAO) has recommended topical 5% Natamycin as the drug of choice in filamentous fungal keratitis and in deep seated or severe fungal corneal infections (due to lower penetration of Natamycin) it is recommended to jointly use 5% topical Natamycin with topical 1% Voriconazole.[20] Still, in deeper lesions they have limitations of poor bioavailability and limited ocular penetration.[21]

Sufficient drug concentrations can be achieved at the site of infection by targeted drug delivery and it serves as an additive treatment in eyes with deep seated fungal corneal ulcers. Intrastromal Voriconazole in recalcitrant

Table 3: Pretreatment and post treatment visual acuity in both groups

Visual acuity	Natamycin Group(n=15)		Voriconazole Group(n=15)	
	Pretreatment	Posttreatment	Pretreatment	Posttreatment
PL+ to <=1/60	3 (20%)	6(40%)	2 (13%)	2(13%)
1/60 to <=3/60	4 (27%)	4(27%)	6 (60%)	3(20%)
3/60 to <=6/60	7 (47%)	1(7%)	4 (27%)	4(27%)
>6/60	1 (6%)	4(27%)	3 (20%)	6(40%)

corneal ulcer cases have shown 72% and 80% success rate respectively in studies done by Sharma N et al and Kalaiselvi Get al.[9,15] On this background, we further studied the role of intrastromal Voriconazole as a primary therapy in deep seated fungal corneal ulcers hypothesizing that timely intervention may stop the disease progression earlier and halt the perforation related complications.

In this study, we took 30 patients of microbiologically proven, deep seated fungal corneal ulcers and divided these patients in two groups of 15 each. One group of 15 patients were given 5% Topical Natamycin and the other group of 15 patients were given injection Intrastromal Voriconazole as the primary treatment either in single or multiple injections. These Patients were kept on follow up for 10 weeks and response to the treatment was assessed in terms of change in the ulcer size, reduction in stromal infiltration and changes in best corrected visual acuity (BCVA) etc.

Voriconazole is a second-generation triazole. It is a broad-spectrum antifungal agent. It primarily inhibits the cytochrome P450 14-alpha demethylase and 24-methylene dihydrolanosterol demethylation essential for synthesis of ergosterol, which adversely affects the permeability of the fungal cell membranes. It has a molecular mass of 349.32 Da which allows better corneal penetration and ocular bioavailability. Its systemic form has good intraocular penetration but it is costly and can cause systemic side effects. Topical Voriconazole has a good corneal epithelial penetration. Previous studies, however, showed no additional benefit of topical Voriconazole over topical Natamycin as primary therapy.[14] Therefore, a more effective way of using Voriconazole in the management of fungal keratitis is needed which can be achieved by the Intrastromal route which is employed in this study.

In our study, out of 30 cases 23(76.6%) were males and 7 (23.3%) cases were females. This slight male preponderance could be due to males more involvement in outdoor activities making them more prone to injury. Similar to our study, Whitcher et al also observed higher male preponderance in fungal corneal ulcers.[22] Gonzales CA et al also reported male: female ratio as 1.6:1 in the Madurai study.[23] In our study, the male female ratio was 3:1.

With respect to the age, 18 (60%) cases were in the age group <40years, 10 (33%) cases in the age group 40-60 years and 2(7%) cases in the age group>60 years. Similar to our study, in a study done by Gopinathan et al in South India, 64.4% of cases were male in the younger age group (16 – 49 years).[24] While another study by Laspina et al found highest incidence in the age group of 30-59 years.[25]

History of Vegetative matter injury was present in 20(67%) cases in our study. As per study by Upadhyay MP et al vegetative matter injury was the major causative agent in fungal corneal ulcers.[26] Vegetative matter injury has been reported in many other studies like one study by Bharathi et al.[6]

Aspergillus was the most common species identified in 21(70%) patients in our study. This result was similar to study done by Chowdhary et al in North India where the spectrum of fungi isolated were Aspergillus in 41% followed by Curvulariain 29%.[27] In South India Fusarium was reported to be the most frequent cause of fungal keratitis, causing upto 42.1% of these infections as per study by Srinivasan M et al, and in our study, it was found in6(20%) cases only.[5]

We have found that in the Intrastromal Voriconazole group, 13(86.7%) patients improved, healed or were cured after Intrastromal Voriconazole therapy. This was significantly higher than 5% topical Natamycin group where only 5(33.3%) patients improved, healed or were cured after 10 weeks.

In 5% topical Natamycin treated group, 4(27%) patients showed worsening after therapy while in Intrastromal Voriconazole group, 2(13%) patients showed worsening which was significantly higher in Natamycin group. Even the BCVA better than 6/60 was found in more number of patients in Voriconazole group 6(40%) compared to Natamycin group 4(27%) in deep seated fungal corneal ulcers.

Contrary to our study, a study done by Masanoori N et al had also used Intrastromal Voriconazole as primary therapy but with topical Natamycin and they had found that Intrastromal Voriconazole was successful in treating yeast keratitis but not in the cases of filamentous fungal keratitis.[28] However, it was a case series and only three patients were of filamentous fungi out of which two were of Fusarium species and only one was of Aspergillus. Since Voriconazole has been found to be highly effective against Candida and Aspergillus but is less effective against Fusarium so their results cannot be generalized to a population where Aspergillus species is more prevalent as in our study population of North India.[29] Another study done by Sharma N et al[30] compared intrastromal Voriconazole

injection of 50 μg/0.1 ml versus topical 1% Voriconazole as an adjunct to Natamycin in recalcitrant cases in a randomized control trial and found that Intrastromal injections did not offer any additional benefit over topical therapy but in their study, they took the depth limit of fungal corneal ulcer up to $2/3^{rd}$ of the stroma.

We did not find any complications with injection Intrastromal Voriconazole except in 1(7%) case where intrastromal hemorrhage was noted. There was no difference between superficial vascularization between the two groups.

A limitation of our study was its small sample size, citing the importance of further prospective studies in larger groups of subjects. This would help in analyzing the response to Intrastromal Voriconazole injection as a primary treatment in deep seated fungal corneal ulcers, as early interventions are needed in these cases to reduce the rate of complications and avert the eye from undergoing therapeutic keratoplasty which has its own failure rate.

5. Conclusion

Intrastromal injection of Voriconazole has emerged as a novel technique for the treatment of microbial keratitis. Intrastromal Voriconazole injection is an easy procedure to perform, which shows early healing of the cornea and better visual acuity outcomes. We also observed that Intrastromal injection of Voriconazole as a primary treatment works better than 5% topical Natamycin in deep seated fungal corneal ulcers. It could be a real boon, in cases those respond poorly to conventional treatment.

Lack of uniformity in presentation of patients with corneal ulcer makes it difficult to devise fixed criteria for treatment of corneal ulcers. Randomized controlled studies are required to establish the criteria for patient selection for better outcomes and low complication rates. These will also establish the efficacy of Intrastromal Voriconazole as a sole therapy and also as the initial treatment in the deep seated fungal corneal ulcers.

6. Source of Funding

None.

7. Conflict of Interest

None.

References

1. Thomas PA. Current perspectives on ophthalmic mycoses. *Clin Microbiol Rev*. 2003;16(4):730–97.
2. Castano G, Elnahry AG, Mada PK, : . Fungal Keratitis. Treasure Island (FL): StatPearls Publishing; 2022.
3. Mahmoudi S, Masoomia, Ahmadikia K, Tabatabaei SA, Soleimani M, Rezaie S, et al. Fungal keratitis: An overview of clinical and laboratory aspects. *Mycoses*. 2018;61(12):916–30.
4. Chander J, Sharma A. Prevalence of fungal corneal ulcers in Northern India. *Infection*. 1994;22(3):207–9.
5. Srinivasan M, Gonzales CA, George C, Cevallos V, Mascarenhas JM, Asokan B, et al. Epidemiology and aetiological diagnosis of corneal ulceration in Madurai, south India. *Br J Ophthalmol*. 1997;81(11):965–71.
6. Bharathi MJ, Ramakrishnan R, Vasu S, Meenakshi R, Palaniappan R. Epidemiological characteristics and laboratory diagnosis of fungal keratitis. A three-year study. *Indian J Ophthalmol*. 2003;51(4):315–21.
7. Kaur IP, Rana C, Singh H. Development of effective ocular preparations of antifungal agents. *J Ocul Pharmacol Ther*. 2008;24(5):481–93.
8. Sharma N, Sahay P, Maharana PK, Singhal D, Saluja G. Management algorithm for Fungal Keratitis: The TST(Topical , Systemic and Targeted therapy) protocol. *Cornea*. 2019;38(2):141–5.
9. Sharma N, Agarwal P, Sinha R, Titiyal JS, Velpandian T, Vajpayee RB. Evaluation of intrastromal voriconazole injection in recalcitrant deep fungal keratitis: Case series. *Br J Ophthalmol*. 2011;95(12):1735–7.
10. Hu J, Zhang J, Li Y, Han X, Zheng W, Yang J, et al. A Combination of Intrastromal and Intracameral Injections of Amphotericin B in the Treatment of Severe Fungal Keratitis. *J Ophthalmol*. 2016;2016:3436415.
11. Saha S, Sengupta J, Banerjee D, Saha S, Khetan A, Mandal SM. Systemic Evaluation on Antifungal Susceptibility of Keratitis Associated Fungal Pathogens in Eastern India. *J Med Microbiol Diagn*. 2014;3(1):1000134.
12. Prajna NV, Krishnan T, Rajaraman R, Patel S, Srinivasan M. Effect of Oral Voriconazole on Fungal Keratitis in the Mycotic Ulcer Treatment Trial II (MUTT II): A Randomized Clinical Trial. *JAMA Ophthalmol*. 2016;134(12):1365–72.
13. Nett JE, Andes DR. Antifungal Agents: Spectrum of Activity, Pharmacology, and Clinical Indications. *Infect Dis Clin North Am*. 2016;30(1):51–83.
14. Prajna NV, Krishnan T, Mascarenhas J, Rajaraman R, Prajna L, Srinivasan M, et al. The mycotic ulcer treatment trial: A randomized trial comparing natamycin vs voriconazole. *JAMA Ophthalmol*. 2013;131(4):422–9.
15. Kalaiselvi G, Narayana S, Krishnan T. Intrastromal voriconazole for deep recalcitrant fungal keratitis: a case series. *Br J Ophthalmol*. 2015;99(2):195–8.
16. Siatiri H, Daneshgar F, Siatiri N, Khodabande A. The effects of Intrastromal Voriconazole injection and topical Voriconazole in the treatment of recalcitrant fusarium keratitis. *Cornea*. 2011;30(8):872–5.
17. Singh P. The role of intrastromal voriconazole in deep resistant fungal keratitis. *Asian J Ophthalmol*. 2014;13(3):121–4.
18. Saluja G, Sharma N, Agarwal R, Sharma HP, Singhal D, Maharana PK, et al. Comparison of Safety and Efficacy of Intrastromal Injections of Voriconazole, Amphotericin B and Natamycin in Cases of Recalcitrant Fungal Keratitis: A Randomized Controlled Trial. *Clin Ophthalmol*. 2021;15:2437–2446.
19. Konar P, Joshi S, Mandhare SJ, Thakur R, Deshpande M, Dayal A. Intrastromal voriconazole: An adjuvant approach for recalcitrant mycotic keratitis. *Indian J Ophthalmol*. 2020;68(1):35–8.
20. Retamal J, Ordenes-Cavieres G, Grau-Diez A. Natamycin versus voriconazole for fungal keratitis.: Natamycin versus Voriconazole for fungal keratitis. *Medwave*. 2018;18(8):e7388.
21. Thomas PA. Fungal infections of the cornea. *Eye (Lond)*. 2003;17(8):852–62.
22. Whitcher JP, Srinivasan M, Upadhyay MP. Corneal blindness: a globalperspective. *Bull World Health Organ*. 2001;79:214–21.
23. Gonzales CA, Srinivasan M, Whitcher JP, Smolin G. Incidence of corneal ulceration in Madurai district, South India. *Ophthalmic Epidemiol*. 1996;3(3):159–66.
24. Gopinathan U, Garg P, Fernandes M, Sharma S, Athmanathan S, Rao GN. The epidemiological features and laboratory results of fungal keratitis: a 10-year review at a referral eye care center in South India. *Cornea*. 2002;21(6):555–9.

25. Laspina F, Samudio M, Cibilis D, Ta CN, Farina N, Sanabria R, et al. Epidemiological characteristics of microbiological results on patients with infectious corneal ulcers: a 13-year survey in Paraguay. *Graefes Arch Clin Exp Ophthalmol*. 2004;242(3):204–9.
26. Upadhyay MP, Karmacharya PC, Koirala S, Tuladhar NR, Bryan LE, Smolin G, et al. Epidemiologic characteristics, predisposing factors, and etiologic diagnosis of corneal ulceration in Nepal. *Am J Ophthalmol*. 1991;111(1):92–9.
27. Choudhary A, Singh K. Spectrum of fungal keratitis in North India. *Cornea*. 2005;24(1):8–15.
28. Masanori N, Eguchi H, Hayashi Y, Miyamoto T, Hotta F, Mitamura Y. Ineffectiveness of Intrastromal Voriconazole for filamentous fungal keratitis. *Clin Ophthalmol*. 2014;8:1075–9.
29. Marangon FB, Miller D, Giaconi JA, Alfonso EC. In vitro investigation of voriconazole susceptibility for keratitis and endophthalmitis fungal pathogens. *Am J Ophthalmol*. 2004;137(5):820–5.
30. Sharma N, Chaco J, Velpandian T, Titiyal JS, Sinha R, Satpathy G, et al. Comparative Evaluation of Topical Versus Intrastromal Voriconazole as an Adjunct to Natamycin in Recalcitrant Fungal Keratitis. *Ophthalmology*. 2013;120(4):677–81.

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