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To compare the safety and efficacy of intrastromal voriconazole alone and in combination with intracameral voriconazole in intractable cases of fungal keratitis

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ABSTRACT

Background: Mycotic keratitis is a potential sight-threatening infection and a leading cause of ocular morbidity worldwide. It is inherently difficult to treat due to the delayed diagnosis and fungistatic nature of available topical medications. **Aims and Objectives:** The aim is to compare the safety and efficacy of intrastromal voriconazole alone and in combination with intracameral voriconazole in recalcitrant fungal keratitis cases. **Materials and Methods:** A prospective, hospital-based, interventional study was conducted in 40 cases of fungal keratitis involving >50% stromal thickness and not showing a good response to conventional antifungal treatment even after 4 weeks. Cases were randomly divided into two groups: group A and group B of 20 each; group A patients received intrastromal voriconazole, while group B patients were given intrastromal + intracameral voriconazole combination in 50 mg/0.1 mL dose. Cases were examined daily for 1 week and then every week for 4 weeks to monitor progression. **Results:** Out of 20 cases in group A, 14 (70%) patients got improved, while 18 (90%) patients in group B showed significant improvement after 4 weeks, and the difference was statistically significant (P = 0.02). In group A, the average number of injections given to the patients was 3.65 ± 1.56 for 15.2 ± 8.79 days, while in group B, the average number of injections given to the patients was 2.65 ± 1.44 for 13.2 ± 7.768 days, with a statistically significant difference (P = 0.033). **Conclusion:** Intrastromal and intracameral voriconazole combination is a cost-effective and highly efficacious modality in managing recalcitrant cases of fungal keratitis. It should be recommended in cases with thick hypopyon and *Aspergillus* as the causative fungi that do not respond to conventional treatment.

Key words: Contact lenses; Mycoses; Voriconazole

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INTRODUCTION

India is a third-world country where 70% of the population relies on agriculture, resulting in a higher incidence of vegetative trauma and instigating fungal keratitis. Triad of lack of awareness, delayed presentation to ophthalmologist, and use of over-the-counter antibiotic-steroid drops in developing countries make the situation even more troublesome, resulting in an increased number of intractable cases. Microbial keratitis is a nightmare for ophthalmologists due to its myriad presentations, overlapping symptoms, expeditious progression, diagnostic dilemma, and potential complications resulting in significant ocular morbidity. A fungal corneal ulcer is a sight-threatening infection and is responsible for almost 1–44% of cases of microbial keratitis, depending on the geographic location.[1] It is more common in outdoor workers.[2]

There is an uphill trend noticed in fungal keratitis cases globally, secondary to an increase in contact lens (CL)

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usage not only for refractive correction but also for cosmetic purposes, non-judiciary use of corticosteroids, vegetative trauma, and diabetes mellitus. In developing countries, ocular trauma by vegetative material and objects contaminated with sand or soil particles are the most common causes of fungal keratitis, while CL use is the leading cause in developed countries.[2,3] CL users are at increased risk of microbial keratitis secondary to unhygienic CL behavior, wearing lenses during sleep, and a higher chance of microbe adherence to the cornea.[1] In addition to CL wear and vegetative trauma, ocular surface disease (OSD) is the third-leading cause, accounting for almost 29% of cases.[4,5] Due to favorable conditions in tropical and subtropical areas, mycotic keratitis is more prevalent, and common causative organisms include *Fusarium*, *Aspergillus*, *Candida*, *Curvularia,* and *Bipolaris*.[3]

A tremendous amount of research has been done in the pharmaceutical field, but till date, all available antifungal medications are fungistatic in nature with poor bioavailability and limited ocular penetration, leading to less potency, especially in cases of deep-seated stromal infiltration (Figure 1). These factors lead to slow resolution of fungal infection, causing a higher number of recalcitrant fungal keratitis cases, which ultimately require therapeutic penetrating keratoplasty.[4-6]

Topical antifungal agents are the gold standard treatment for fungal keratitis, with natamycin (5%) being the main cornerstone of management. However due to the deep penetration of fungi, and moreover, the fungistatic nature of available drugs, a significant number of patients do not improve even after frequent instillations of drugs, especially if deeper stroma is involved. In recent times, voriconazole has gained a lot of popularity among ophthalmologists for the management of intractable cases of fungal keratitis. It is a triazole drug acting against the enzyme 14-alpha-lanosterol demethylase, leading to a lower ergosterol level, which is an extremely important component of the fungal cell wall. It is available and prescribed in various forms, like tablet form, topical reconstituted 1% drops, intrastromal, and intracameral injections, to achieve its higher concentration in deeper corneal layers, thus helping in early healing, visual recovery, and less number of patients requiring therapeutic penetrating keratoplasty.[7]

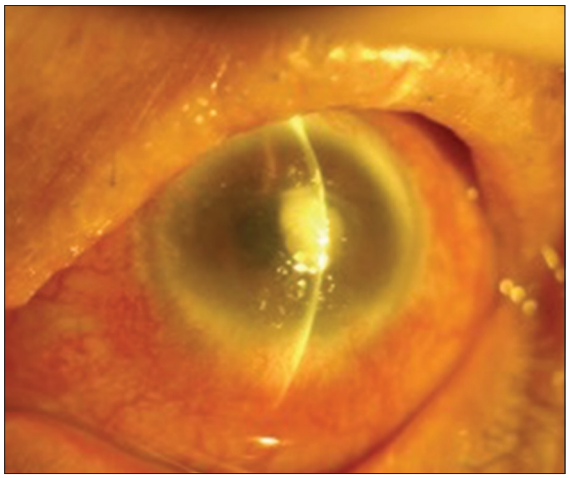

Figure 1: Left eye paracentral fungal keratitis with deep stromal abscess

On a detailed literature search, there were only a few case reports available on the use of intracameral voriconazole in deep fungal keratitis, and no comparative study is available on the use of intrastromal voriconazole alone and in combination with intracameral voriconazole. With this background, we conducted this study to compare the efficacy and safety of intrastromal voriconazole alone and in combination with intracameral voriconazole in intractable cases of fungal keratitis that were not showing a good response to conventional anti-fungal treatment.

Aims and objectives

To compare the efficacy and safety of intrastromal voriconazole alone and in combination with intracameral voriconazole in recalcitrant fungal keratitis cases, not showing a good response to oral and topical antifungal medications.

MATERIALS AND METHODS

A prospective, hospital-based interventional study was conducted for 6 months in 40 cases of recalcitrant fungal keratitis involving >50% stromal thickness and not showing good response to oral fluconazole, topical Natamycin (5%) and topical Voriconazole (1%) eye drops after 4 weeks of treatment, after taking ethical clearance from the Institutional Ethics Committee. Cases were included in the study after taking informed written consent. Patients with impending or frank perforation, scleral involvement, and endophthalmitis were excluded from the study. Cases were randomly divided into two groups: group A and group B of 20 each; group A patients received intrastromal voriconazole, while group B patients were given an intrastromal+intracameral voriconazole combination in 50 mg/0.1 mL dose. Cases were examined daily for 1 week and then every week for 4 weeks to monitor the progression of fungal keratitis. All cases were kept on regular follow-up for 6 months to monitor the signs of ocular toxicity like endothelial damage and retinal toxicity.

Procedure

30 min before the procedure, the patient was given tablet acetazolamide 250 mg stat to lower the intraocular pressure. Injection voriconazole (VOZOLE PF; Aurolab, India) is available as 1 mg white, lyophilized powder in a transparent glass vial. The powder was reconstituted with

2 mL of distilled water to a concentration of 0.5 mg/mL (50 μg/0.1 mL). The reconstituted solution was loaded into a 1 ml tuberculin syringe with a 30-gauge needle. Then, under the operating microscope, preloaded drugs were given in a bevel-up manner, and the needle was inserted obliquely from the uninvolved, clear area to reach the infiltrate at the mid-stroma level in each case. The drug was then injected, and the amount of hydration of the cornea was used as a guide to assess the area covered. On achieving the desired amount of hydration, the plunger was withdrawn slightly to prevent any back-leakage of the drug. This was repeated all around the infiltration in a circumferential manner to barrage the lesion. Then, in group B, 0.05 mL intracameral injection of voriconazole was also given in the same sitting with a 30G needle by direct paracentesis at the 9 o'clock position. After injection, corneal debridement was also performed in every case to remove necrotic tissue, which ensures better blood circulation, thus helping in decreasing microbial load and speedy recovery. After injection, topical 1% voriconazole eye drops were also continued. Cases were examined daily for 1 week and then every week for 4 weeks.

Then, data were compiled and analyzed using SPSS version 21.0 statistical software. The continuous variables were presented as mean±standard deviation, and the paired t-test was used to compare differences between two groups, and $P<0.05$ was considered statistically significant.

RESULTS

This study was conducted in 40 cases of recalcitrant fungal keratitis that showed no improvement after 4 weeks of intensive treatment. Out of 40 patients, 30 were male (75%) and 10 were female (25%), with a significant male preponderance with an M: F ratio of 3:1. The age of patients ranged from 28 years to 85 years, with the mean age being 48.94±15.87 years. The majority of patients (70%) belonged to rural backgrounds, with agriculture being their main profession. A detailed history was also recorded in every case to identify the associated risk factor. Thirty (75%) patients had a preceding history of vegetative trauma, while five patients were CL users. However, in five patients, there was no associated risk factor (Figure 2).

The mean time interval between the onset of symptoms and presentation to the hospital was 16.8±8.46 days. Out of 40 cases, 16 patients used an over-the-counter antibiotic-steroid combination before presenting to an ophthalmologist.

On slit lamp examination, all patients had more than 50% stromal thickness involvement, with typical satellite lesions in 70% (28/40) cases and hypopyon in 45% (18/40) cases. On examination, the mean infiltrate size was 49.5 mm^2±15.63 in group A and 52.8±16.36 in group B, which was comparable in both groups. In all cases, on 10% KOH mount and Gram's staining, septate or non-septate fungal hyphae were seen. However, in only 60% (24/40) cases, causative fungi could be identified on culture. The predominant pathogen isolated was *Fusarium*, found in 12 (30%) patients (Figure 3).

Out of 20 cases in group A, 14 (70%) patients showed significant improvement after 4 weeks, while 18 (90%) patients in group B showed significant improvement after 4 weeks, and this difference was statistically significant ($P=0.02$). In group A, the average number of injections given to the patients was 3.65±1.56 for 15.2±8.79 days, with a minimum of one to a maximum of seven injections required, while in group B, the average number of injections given to the patients was 2.65±1.44 for 13.2±7.768 days, with a minimum of one to a maximum of five injections required, and this difference was statistically significant ($P=0.033$). In fungal keratitis cases with thick hypopyon and *Aspergillus* as the causative organism, intracameral voriconazole had shown encouraging results compared to group A, but a statistical correlation could not be established

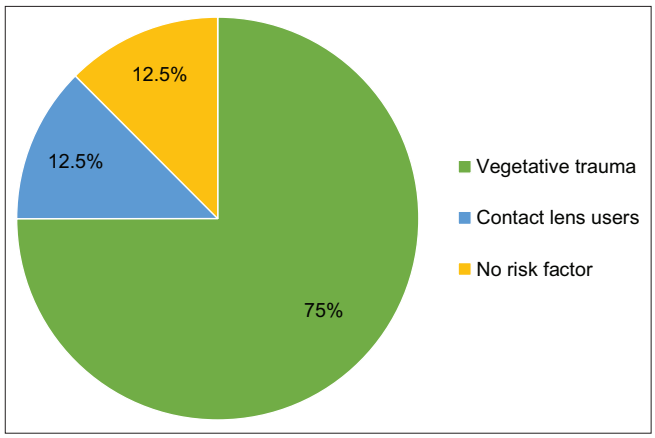

Figure 2: Risk factors for fungal keratitis

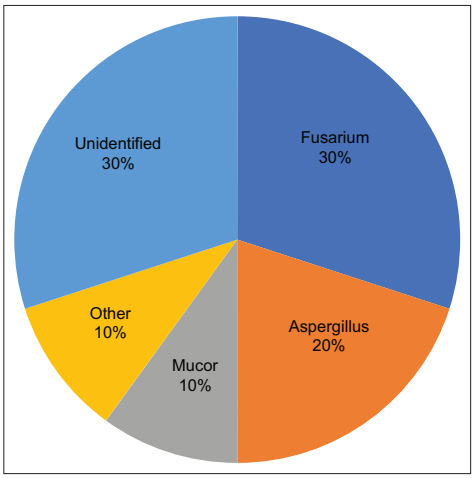

Figure 3: Identified fungal species on culture

because of the small sample size. The average resolution time was 35.5±9.22 days in group A and 28.6±8.14 days in group B, which was statistically significant (P=0.015). In group A, 3 patients required therapeutic penetrating keratoplasty, while in group B, only 1 patient ultimately required therapeutic penetrating keratoplasty, but this difference was statistically insignificant (P=0.067) (Figure 4).

No procedure-related complications, such as iatrogenic infective foci and micro-perforations and no signs of ocular toxicity like endothelial damage and retinal toxicity, were noted in our study for 6 months follow-up.

DISCUSSION

In recent times, there has been a dramatic increase in mycotic keratitis cases, especially in developed countries, due to the increased use of CL, not only for refractive error correction but also for cosmetic use. The majority of mycotic keratitis cases are due to unhygienic CL use in the Western world, while in developing countries, vegetative trauma is the leading cause, followed by injudicious use of an antibiotic-steroid combination.[8] A large number of cases of fungal keratitis become recalcitrant secondary to factors like deep penetration of fungal hyphae, the fungistatic nature of available antifungal medication, and poor penetration, leading to slower recovery and significant ocular morbidity.[2]

Natamycin is the main cornerstone of the management of fungal keratitis cases, but it has several limitations, like a limited antifungal spectrum and poor penetration;moreover, it precipitates on a corneal surface, further limiting the drug's penetration.[7] Therefore, there has always been constant research for other anti-fungal drugs with broad-spectrum and better penetration. Recently, voriconazole has been reported to have broad-spectrum anti-fungal activity and has been found to be effective against both *Fusarium* and *Aspergillus*.[9] To overcome the poor penetration, targeted drug delivery has been tried for many years. Initially, intrastromal amphotericin B was tried to attain optimal concentration, but it led to severe complications such as corneal surface toxicity and retinal toxicity, and hence was withdrawn.[10] In the past few years, a lot of research has been done on the topical and intrastromal use of voriconazole for nonhealing fungal keratitis, and it has been found to be efficacious with fewer side effects.[11-13] However, to the best of our knowledge, very few studies have been published on the intracameral use of voriconazole for nonhealing mycotic keratitis; therefore, we conducted this study to compare the efficacy and safety of intrastromal voriconazole alone and in combination with intracameral voriconazole for intractable fungal keratitis.

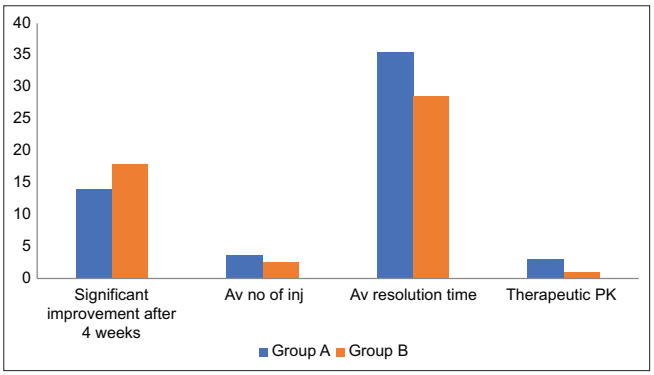

Figure 4: Comparative analysis of Group A and B efficacy parameters

In our study, there was a significant male preponderance with an M: F ratio of 3:1, and the age of patients ranged from 26 years to 85 years, with the mean age being 50.94±15.87 years, which is supported by many studies conducted in the past.[2,4,14] In our study, the mean time interval between the onset of symptoms and presentation to the hospital was 14.8±8.46 days, which was in accordance with previous studies done in India.[12,15] The most common fungi isolated in our study was *Fusarium* in 30% of cases, which further supports the numerous studies conducted on mycotic keratitis.[2,9,12]

Then, as per protocol and the allotted group, patients were given intrastromal and intracameral voriconazole (50 μg/0.1 mL) under all aseptic conditions, and injections were repeated as per their response to treatment. Out of 20 cases in group A, 14 (70%) patients showed significant improvement after 4 weeks, while 18 (90%) patients in group B showed significant improvement after 4 weeks, and this difference was statistically significant (P=0.02). The number of injections required, average resolution time, and patients requiring therapeutic penetrating keratoplasty are significantly less in mycotic keratitis cases treated with intrastromal and intracameral voriconazole combinations. In present study, there were no complications seen with the intracameral use of voriconazole like new iatrogenic mycotic foci, micro-perforations or retinal toxicity signs. Our study further supported the safety and efficacy of intracameral voriconazole in intractable cases of fungal keratitis.[16,17]

Limitations of the study

Our study showed promising results but small sample size and short follow up period were its limitations.

CONCLUSION

The intrastromal and intracameral voriconazole combination is an effective adjuvant modality for recalcitrant cases of fungal keratitis, which are very frequently encountered in daily practice. It is an easy procedure with a short learning curve. It will not only shorten the disease course but also reduce the number of patients who require therapeutic

keratoplasty. Our study showed promising results, but a small sample size and short follow-up period are its limitations. Moreover, it is an intraocular procedure that will require an OT setup. Therefore, it should be judiciously used in cases that do not improve significantly even after intensive treatment with oral and topical antifungals, and it should be considered as an add-on therapy, especially in cases with thick hypopyon and *Aspergillus* as the causative fungi.

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Authors' Contributions:
MD- Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article; **MR-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **MohD-** Design of study, statistical Analysis and Interpretation; **SS-** Review Manuscript; **RD-** Review Manuscript; **JP-** Literature survey and preparation of Figures.

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