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Original Research Article

Intrastromal and intracameral voriconazole combination: An adjuvant therapy in intractable mycotic keratitis

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ABSTRACT

Aim: To study role of intrastromal and intracameral voriconazole combination in recalcitrant fungal Keratitis.

Materials and Methods: 20 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 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. 30 min before the procedure, patient was given Tab acetazolamide 250mg stat to lower the intraocular pressure (IOP). Then under all aseptic conditions, 50 microgram/0.1 ml dose of intrastromal and intracameral voriconazole was given with 30G needle. Cases were examined daily for 1 week and then every week for 4 weeks for monitoring progression of fungal keratitis.

Results: Out of 20 cases, 18 (90%) patients showed significant improvement after 4 weeks. Depending on the response after 1 week, patients were planned for repeat injection and only 1 patient required >3 injections in whom Lasiodiplodia theobromae was the causative organism. Only 1 patient got worsened and was ultimately managed with therapeutic keratoplasty.

Conclusion: Intrastromal and intracameral voriconazole combination is an easy procedure with short learning curve which is highly efficacious and cost effective in recalcitrant fungal keratitis.

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1. Introduction

Microbial keratitis possesses a myriad clinical challenge for ophthalmologists due to its overlapping symptoms, variable presentation, rapid progression, diagnostic difficulty and potential complications leading to significant ocular morbidity. Fungal corneal ulcer is a common yet tenacious infection causing vision loss in young productive population of country leading to socioeconomic burden. Depending on the geographic location, mycotic or fungal keratitis, is responsible for almost 1-44% cases of microbial keratitis.[1] There is an uphill trend noticed in fungal keratitis cases secondary to increase in contact lens usage, non-judiciary use of corticosteroids, vegetative trauma and diabetes mellitus. In developing countries, ocular trauma by vegetative material and objects contaminated with sand particles are the most common causes of fungal keratitis while contact lens (CL) use is the leading cause in developed countries.[2–4] The contact lens associated microbial keratitis is secondary to higher chance of adherence to cornea, wearing lens during sleep, smoking history and unhygienic contact lens behaviour. In addition to CL wear and vegetative trauma, ocular surface disease (OSD) is the third leading cause accounting for almost 29% of cases.[5,6]

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Mycotic keratitis is more common in tropical and subtropical areas secondary to favourable climatic conditions and the common causative fungi include Fusarium, Aspergillus, Candida, Curvularia and Bipolaris.[3] In vegetative trauma cases, filamentous fungi are found while yeast like fungi are commonly seen in ocular surface disorders and steroid use.[7]

Most of currently 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. These factors are responsible for slow resolution of fungal infection resulting into more number of recalcitrant fungal keratitis cases which ultimately require therapeutic penetrating keratoplasty.[5–7]

Topical antifungal agents are the gold standard treatment in fungal keratitis, with natamycin (5%) being the main cornerstone. But due to ability of fungi to penetrate deeper layers and fungistatic nature of available anti-fungal medications, large number of patients don't improve even after frequent instillation of drugs; specially if deeper stroma is involved. In recent times, voriconazole has gained a lot of popularity among ophthalmologists for management of recalcitrant fungal keratitis. It is a triazole antifungal drug which act against enzyme 14-alpha- lanosterol demethylase resulting into lower ergosterol level, which is an important fungal cell wall component. It is prescribed in various forms like orally in tablet form, topical reconstituted 1% drops, intrastromal and intracameral injection to ensure higher drug concentration deeper corneal layers leading to early healing, visual recovery and less number of patients requiring therapeutic penetrating keratoplasty.[8]

With this background, we conducted this study to study role of intrastromal and intracameral voriconazole combination in intractable cases of fungal keratitis which were not showing good response to oral fluconazole, topical natamycin and topical voriconazole combination.

Aim of the study was to assess efficacy and safety of intrastromal and intracameral voriconazole combination in recalcitrant fungal keratitis, not showing good response to oral and topical antifungal medications.

2. Materials and Methods

20 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 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.

2.1. Procedure

30 min before the procedure, patient was given Tab acetazolamide 250mg stat to lower the intraocular pressure (IOP). Injection voriconazole (VOZOLE PF; Aurolab, India) is available as 1 mg white, lyophilized powder in a 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 in a 1 ml tuberculin syringe with a 30-gauge needle. Then the preloaded drug was administered under the operating microscope. With the bevel up, the needle was inserted obliquely from the uninvolved, clear area to reach the infiltrate at the mid-stroma level in each case (Figure 1). 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. 0.05 ml intracameral injection voriconazole was also given in the same sitting with 30 G needle by direct paracentesis at 9 o'clock position. After injection, corneal debridement was also done to remove dead tissue which helps in decreasing microbial load and leads to better blood circulation ; thus helping in speedy recovery.1% Voriconazole eye drops were also continued following intrastromal and intracameral injection. Cases were examined daily for 1 week and then every week for 4 weeks.

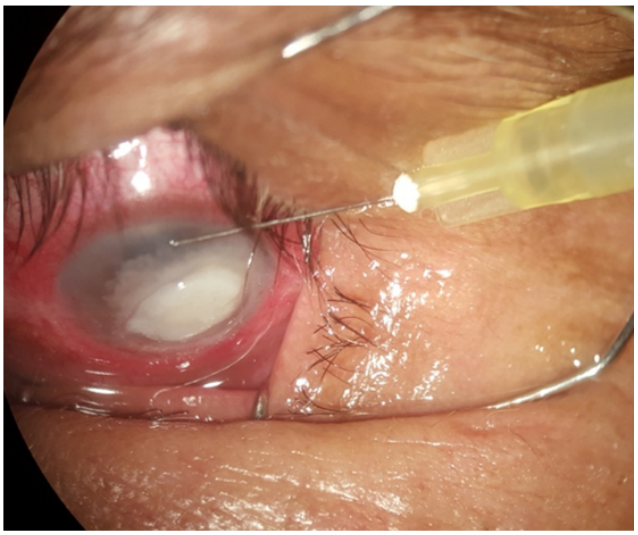

Fig. 1: Intrastromal injection at mid-stroma level with bevel up

The data was compiled and analysed using SPSS 21.0 statistical software. The continuous variables were presented as mean ± standard deviation, and the pair t-test was used to compare differences between pre and post-treatment. A p value of less than 0.05 was considered statistically significant.

3. Results

This study was conducted in 20 cases of recalcitrant fungal keratitis which were not showing any improvement after 4 weeks of intensive treatment. Out of 20 patients, fifteen were males (75%) and five were females (25%) with a significant male preponderance with M:F ratio 3:1. The age of patients ranged from 28 years to 85 years, mean age being 48.94 ± 15.87 years. Majority of patients (70%) belonged to rural background with agriculture being their main profession. Detailed history was taken in every case to identify the associated risk factor. Fifteen patients (75%) had a preceding history of vegetative trauma, while 2 patients were contact lens users. However, in 3 patients, there was no associated risk factor. The mean time interval between onset of symptoms and presentation to the hospital was 14.8 ± 8.46 days. Out of 20 cases, 6 patients used over the counter antibiotic-steroid combination before presenting to ophthalmologist.

On slit lamp examination, all patients had anterior (anterior one third) to mid-stroma (anterior two thirds) involvement on slit lamp examination. Typical satellite lesions were present in 70% (14/20) cases on slit lamp biomicroscopy. On examination, the mean infiltrate size was 49.5 mm2 ± 15.63 with hypopyon present in nine patients (45%). In all cases, on 10% KOH mount and Gram's staining, a septate or non-septate fungal hyphae were seen. However, in only 60% of the cases, causative fungi could be identified on culture. The predominant pathogen isolated was Fusarium, found in six (30%) patients (Table 1).

Table 1: Identified fungal species on culture

Fungal Species	Total number n(%)
Fusarium	6 (30%)
Aspergillus	2 (10%)
Mucor	2 (10%)
Other fungi	2 (10%)
Unidentified	8 (40%)

Then under all aseptic conditions, all patients were administered intrastromal and intracameral voriconazole combination as per their response to treatment. The average number of injections given to the patients was 2.65 ± 1.56 over a period of 13.2 ± 9.79 days, with minimum of one to maximum of five injections required. Overall 15 patients required more than one injection, with nine requiring more than two injections. Only 1 patient required >3 injections in whom Lasiodiplodia theobromae was the causative organism. After injection, corneal infiltration size was decreased significantly from 49.5 mm^2 ± 15.63 to 14.32mm^2 ± 1.10 (p = 0.001), but there was no significant change in ulcer size from 4.38± 1.32 mm to 3.13 ± 0.72 mm (p = 0.092). Out of 20 enrolled patients, 18 resolved after intrastromal + intracameral injections with 90% success rate, whereas 2 patients did not respond to the treatment. Only 1 patient got worsened and was ultimately managed with therapeutic keratoplasty in which causative fungi was unidentified. The average resolution time was 35.5 ± 9.22 days.

4. Discussion

In recent times, there has been a uphill trend noticed in cases of mycotic keratitis, especially in developed countries due to increased use of contact lens for refractive error correction, and even for cosmetic use. Most cases of mycotic keratitis are secondary to unhygienic contact lens use in western world; while in developing countries it is secondary to vegetative trauma followed by injudicious use of antibiotic-steroid combination.[9] A large number of cases of fungal keratitis become intractable owing to the factors like deep penetration of fungal hyphae, fungistatic nature of available antifungal medication and poor penetration leading to slower recovery and a significant ocular morbidity.[2]

Natamycin is the only topical antifungal drug which is available commercially but it has several drawbacks like limited spectrum, poor corneal penetration and moreover it precipitates on corneal surface; further limiting the drug penetration.[8] Therefore, there has always been a constant research going on for other anti-fungal drugs with broad-spectrum and better penetration. Recently, voriconazole is reported to have broad spectrum anti-fungal activity and is found to be effective against Fusarium and Aspergillus both.[10] To overcome the poor penetration, targeted drug delivery approach is tried for last many years. Initially intrastromal amphotericin B was tried to attain optimal concentration but it led to severe complications like corneal surface toxicity and retinal toxicity and hence was withdrawn.[11] In past few years, a lot of research has been done on topical and intrastromal use of voriconazole for nonhealing fungal keratitis and is found to be efficacious with less side effects.[12,13] But to the best of our knowledge, very few studies are published on intracameral use of voriconazole for nonhealing mycotic keratitis, therefore we conducted this study to analyse the efficacy and safety of intrastromal and intracameral voriconazole combination for intractable fungal keratitis.

In our study, there was significant male preponderance with M:F ratio 3:1 and the age of patients ranged from 28 years to 85 years, mean age being 48.94 ± 15.87 years which is supported by many studies conducted in past.[2,5,14] In our study, The mean time interval between onset of symptoms and presentation to the hospital was 14.8 ± 8.46 days which was in accordance with previous studies done in India.[13] The most common fungi isolated in our study was Fusarium in 30% cases which further supports the numerous studies conducted on mycotic keratits.[2,10,13]

Then as per protocol, 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. The average number of injections given to the patients was 2.65 ± 1.56 over a period of 13.2 ± 9.79 days, with minimum of one to maximum of five injections required. After injection, corneal infiltration size was decreased significantly from 49.5 mm^2 ± 15.63 to 14.32mm^2 ± 1.10 (p = 0.001). Out of 20 enrolled patients, 18 resolved after intrastromal + intracameral injections with 90% success rate which is significantly higher than the documented success rate of intrastromal voriconazole injection.[13,15] The average healing time was 35.5 ± 9.22 days, which is significantly less than studies using intrastromal voriconazole only.[15,16] We concluded that patients with early presentation to hospital and small size of infiltration required less number of injections, but statistical correlation could not be established due to small sample size. No procedure related complications like iatrogenic infective foci and micro-perforations and no signs of ocular toxicity like endothelial damage and retinal toxicity were noted in our study. Cases with non-healing fungal keratitis with thick hypopyon, which don't show good response to intensive treatment of topical and oral antifungals, should be considered for intrastromal + intracameral voriconazole combination as it's a cost-effective modality which will not only shorten the disease course, but also less number of cases will require therapeutic penetrating keratoplasty, reducing the burden on hospital.

5. Conclusion

Intrastromal and intracameral voriconazole combination is an effective adjuvant treatment modality for intractable cases of fungal keratitis. It is a cost-effective, easy procedure with short learning curve. Our study showed promising results but small sample size and short follow up period are its limitations. Moreover, it is an intraocular procedure which will require an OT set up. Therefore, its use should be limited to those cases which do not show significant improvement even after intensive treatment with oral and topical antifungals and it should be taken as an adjuvant therapy.

6. Source of Funding

None.

7. Conflict of Interest

None.

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