

## CLINICAL STUDY OF VORICONAZOLE VS. NATAMYCIN IN TREATMENT OF MYCOTIC CORNEAL ULCERS

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### ABSTRACT

#### BACKGROUND

The main cause of ocular morbidity and mortality in developing countries is fungal keratitis. In developing countries, approximately 50% of corneal ulcers are proven to be fungal. Following trauma with vegetative matter, filamentous fungi is responsible for a large proportion of corneal infections in tropical climate than temperate climate. Fungal keratitis is best managed by timely diagnosis of infection and appropriate administration of antifungal therapy.

The aim of the study is to evaluate the efficacy of topical 5% natamycin and 1% voriconazole in treatment of mycotic corneal ulcers. The fungal corneal ulcer was treated with 1% VRC and 5% natamycin and their efficacy was compared with respect to resolution of infiltrate viz adverse events, example non-healing ulcer perforation.

#### MATERIALS AND METHODS

Two groups were formed, each group constituted of minimum 15 patients and each were treated topically with either 5% natamycin (group A) or 1% VRC as main primary treatment for mycotic keratitis. Comparison was done in both groups on basis of depth of infiltrate, mean size and LogMAR visual acuity at presentation. There was minimum 8 weeks follow up or till complete resolution of infiltrate, whichever event occurred later. The culture was performed to identify the causative organisms.

#### RESULTS

Fungal keratitis was found to be more common in males, 60% in group A and 66.7% in group B. Major predisposing factor was trauma, which was present in 17 (56.7%) patients. Twenty-nine of total 30 patients showed complete resolution. 25.86 days and 1.05 in group A and 28 days and 0.58 in group B was the average time of resolution and gain in LogMAR visual acuity. They were compared in two groups ( $p > 0.05\%$ ). The most common isolates found were *Curvularia* spp. (38%) and *Aspergillus* spp. (38%).

#### CONCLUSION

Both 1% voriconazole and 5% natamycin were found to be efficacious agents in primary fungal keratitis management. Average healing time was marginally better with natamycin. Hence, 5% natamycin was more efficacious than 1% VRC in treatment of fungal keratitis curing from 1 to 5 mm of infiltrate in our study.

#### KEYWORDS

Fungal Keratitis, Natamycin, Voriconazole.

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#### BACKGROUND

According to WHO, corneal diseases are a major cause of vision loss and blindness second only to cataract in overall importance.<sup>1</sup> 50% of keratitis is constituted of fungal keratitis in tropical region and in developing countries.<sup>2</sup> In developed countries, fungal keratitis accounts for 1-5% of

keratitis.<sup>1-8</sup> In south India, fungal keratitis accounts for about 44% of corneal ulcers.

Appropriate antifungal medication and timely diagnosis of infection is required for the management and treatment of fungal keratitis. In general, fungal keratitis is more difficult to treat than bacterial one causing more severe visual impairment.<sup>1</sup> The agent's ability to penetrate the aqueous and achieve therapeutic levels defines the success of the antifungal agents as the antifungal agents are the main therapeutic option in fungal keratitis.<sup>9</sup> Natamycin is a fungicidal polyene antibiotic and is the only FDA approved drug for the treatment of fungal keratitis.<sup>10</sup> Natamycin is believed to be effective only in superficial infections because of its poor penetration. There have been reported 45.2% treatment success with natamycin as a primary treatment for fungal keratitis.<sup>11</sup>

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Considering the scarcity of options of drugs in the management of mycotic keratitis, there has always been the search for better alternative drugs in combating the existing problem in management.

The newer triazoles are more effective in vitro against filamentous fungal keratitis has been indicated in studies such as *Aspergillus* species topical 1% VRC administration has been mentioned in numerous case reports and small case series for the treatment of fungal corneal ulcers.<sup>12-17</sup>

In the recent past, the use of newer triazoles has been suggested in the treatment of fungal keratitis not responding to conventional antifungals. Voriconazole (VRC) is a broad-spectrum fungistatic antifungal agent that is effective against yeasts and moulds. Excellent results have been reported following VRC off-label use in case of fungal keratitis. For the corneal ulcers present deep in stroma, the superior in vitro susceptibility profile and increased penetration of VRC in comparison to natamycin could be an advantage.<sup>18</sup>

An attempt has been made in this study to evaluate the efficacy of 1% VRC as a primary treatment modality in proven fungal keratitis and secondly to compare its efficacy with 5% natamycin (only FDA approved agent) for fungal keratitis.

#### Aims and Objectives

1. To determine the efficacy of 1% VRC in the management of fungal corneal ulcer as a primary treatment.
2. To compare the efficacy of 1% VRC vs. 5% natamycin as primary treatment in fungal corneal ulcer with respect to resolution of infiltrate viz a viz adverse events, e.g. perforation, non-healing ulcer.

#### MATERIALS AND METHODS

The study was conducted at the outpatient Department of Ophthalmology, Santosh Medical College and Hospital, Ghaziabad, during a period from January 2016 to June 2017. Two groups of minimum of 15 patients each of isolated fungal keratitis were taken. One group received 5% natamycin (group A) and other received 1% VRC (group B). Patients with presence of corneal ulcer with evidence of filamentous fungus on KOH or Giemsa stain or Gram stain at the presentation who gave a written informed consent for the study participation were included in the study. Patients with previous corneal scars, impending perforation and prior usage of antifungal drugs were excluded. A detailed history of any systemic illness, trauma, contact lens use and usage of topical steroid was also taken. Complete ophthalmological examination was done including LogMAR visual acuity, slit-lamp biomicroscopy for measuring infiltrate size, epithelial defect and hypopyon, if present. Intraocular pressure was assessed digitally. Corneal scrapings were taken after instilling lignocaine 2% with blunt Kimura's spatula or #15 sterile surgical blade. Material obtained was used for direct microscopic examination using Gram stain and 10% KOH mount. Material was also directly inoculated into Sabouraud's dextrose agar and brain heart infusion broth for

transportation to laboratory and culture. Patients who were positive for fungal hyphae and negative for bacteria were included in our study.

For medication, 1% VRC eye drops were prepared by reconstituting lyophilised powder available as 200 mg vials with sterile deionised water to make 1% solution of VRC that was stored in refrigerator for 48 hours. The drug was reconstituted every 24-48 hours for continued use. A 5% natamycin topical formulation is available commercially. One drop of randomised medication was applied 1 hourly to the affected eye at least till 2 weeks. Further dosage titrated according to patient's response. Adjunctive therapy included topical ofloxacin q.i.d., 0.5% Timolol b.i.d. if needed, 2% homatropine q.i.d.

Patients were followed up every day for 1 week/earliest sign of resolution. Subsequently, they were followed every third day for 2 weeks, then every week for 2 weeks, then every 2 weeks till 2 months or until complete resolution of infiltrate, whichever was later. All the parameters of corneal infiltrate, epithelial defect and hypopyon were recorded on each follow up. Standard follow up visits were taken as after 1, 2, 4 and 8 weeks for statistical analysis. Results were compared at the end of study and data analysed statistically.

**Inclusion Criteria-** Patients with corneal ulcer presenting to Santosh Medical College and Hospitals, Ghaziabad, irrespective of their age and sex.

1. Presence of a corneal ulcer with evidence of filamentous fungus on KOH or Giemsa stain or Gram stain at the time of presentation.
2. Informed consent for the treatment.

**Exclusion Criteria-** Patients who are not available for follow up for a required period of time and patients with any of the following-

1. Evidence of bacteria on Gram stain at the time of presentation.
2. Evidence of *Acanthamoeba* or herpetic keratitis on stain or history or examination.
3. Impending perforation.
4. Bilateral ulcers.
5. Previous PK.
6. No light perception in the affected eye.
7. History of corneal scar in affected eye (except pterygium).
8. Use of antifungal drop.
9. Pregnancy or breastfeeding.
10. Known allergy to study medication (antifungal or preservatives).

#### RESULTS

The following observations were made during the study- Corneal infections caused by fungus are common and represent 30-40% of all cases of culture-positive infectious keratitis in India.

Fungal keratitis was found to be more common in males, 60% in group A and 66.7% in group B. The difference was statistically not significant ( $p$  value 0.386). This maybe

explained on the basis that males are commonly engaged in outdoor activity rendering them more prone to trauma. The age distribution in group A was 38.13 years and in group B 48.60 years, p-value being 0.789 (nonsignificant).

The major predisposing factor for fungal keratitis has been trauma and contact lens usage. Trauma has been reported to be associated with 55-65% of fungal ulcers in various studies.<sup>19,20</sup> In our study, trauma was present in 17 (56.7%) patients. Trauma was due to prior injury with vegetative matter in 10 (33.33%) patients, cattle tail in 3 (10%) patients and unidentifiable object in the rest. None of the patient had history of contact lens usage.

Mean size of ulcer in millimetres in terms of longest diameter\*longest perpendicular diameter was 3.96\*3.28 in

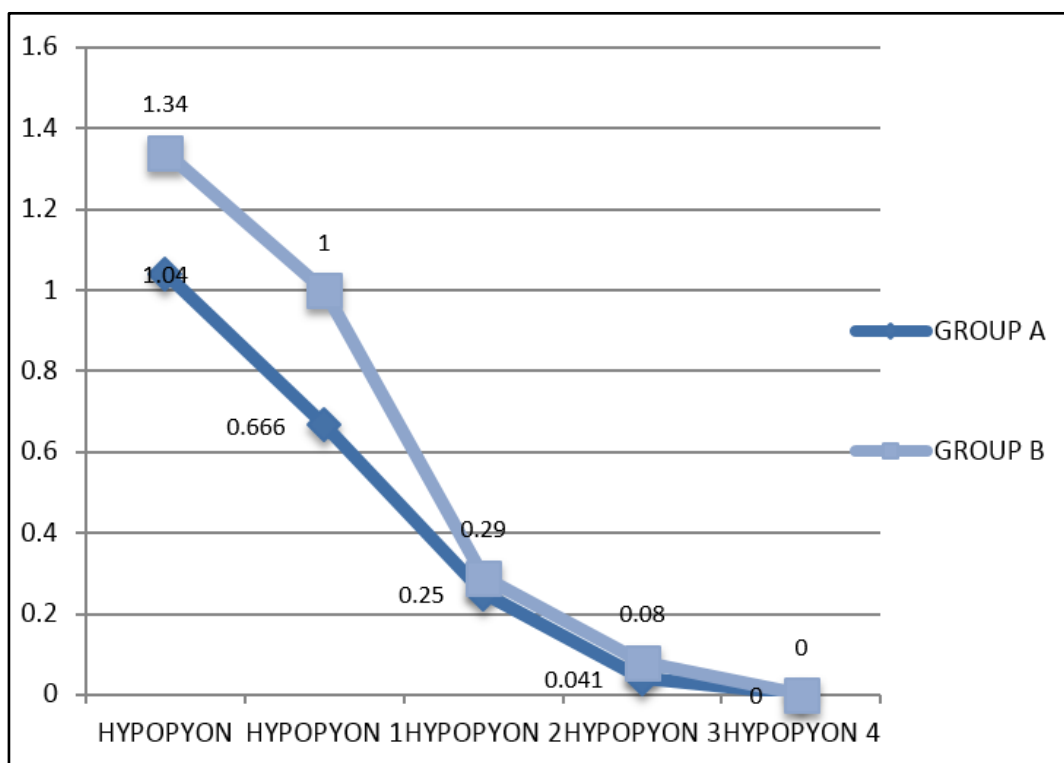
group A and 3.71\*3.01 in group B. The distribution was comparable. Based on the depth of infiltrate noted at presentation, patients were distributed into three groups- <30%, 30-70% and >70%. Seventeen patients (56.7%) had depth >70%, 9 (30%) had depth 30-70% and 4 (13.3%) had depth <30%. Distribution was comparable between both the groups (p value 0.116). Hypopyon was present in 23 (76.66%) of patients ranging from 0.5 to 4 mm. The height and distribution was comparable in both the groups (p value = 0.696). In group A, change was nonsignificant on all follow-ups, and in group B, it was significant only at last follow-up.

	Size	Size 1	Size 2	Size 3	Size 4
Group A	3.96*3.28	3.16*2.53	1.86*1.50	0.233*0.20	00
Group B	3.71*3.01	3.33*2.66	2.25*1.75	0.571*0.428	00
P value	0.354*0.298	0.771*0.410	0.566*0.593	0.928*0.937	1.00
Significance	NS	NS	NS	NS	NS

**Table 1. Mean Size on Comparison in Between Two Groups**

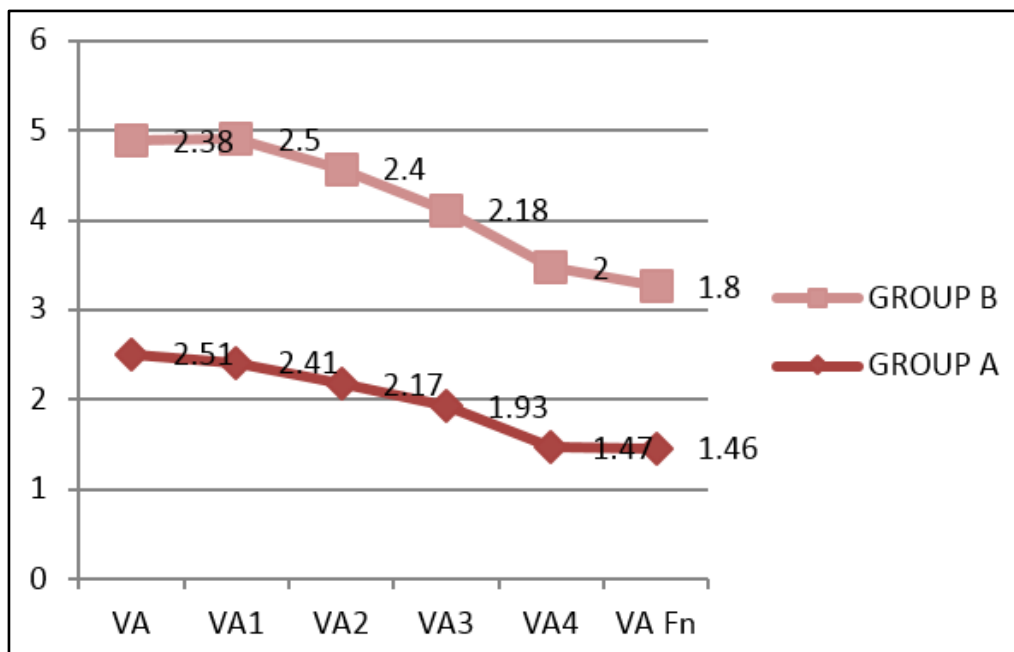
The average time of complete resolution of corneal infiltrate in group A was 25.86 days, and in group B, it was 28 days. It ranged from minimum of 12 days to a maximum of 60 days. Hence, the average healing time was marginally better with natamycin and the difference was statistically significant, p value being 0.0007. Hence, natamycin was more efficacious in treatment of fungal keratitis curing from 1 to 5 mm of infiltrate in our study. Study by P. Lalitha et al

have described the efficacy of natamycin to be about 45.6% in their series with 23.6% slow healing ulcers.<sup>11</sup> One patient in group B had treatment failure with perforated corneal ulcer, who was referred to a higher centre for keratoplasty. The average scar size was found to be 3.6\*3.33 mm in group A and 3.63\*3.43 in group B. Depth of scar was comparable in both the groups (p value = 0.360).



**Figure 1. Mean Size (in mm) of Hypopyon on Follow Up in Both the Groups**

The visual acuity in terms of mean LogMAR at presentation was 2.51 in group A and 2.38 in group B. The best corrected visual acuity at the last follow up in each group was 1.46 in group A and 1.80 in group B. Difference was not significant statistically (p value 0.749).



**Figure 2. Change in LogMAR Best Corrected Visual Acuity on Followup in Both the Groups**

IOP was measured digitally and was high in 3 patients in group A and 4 patients in group B. It was comparable in both the groups (p value = 0.694).

Filamentous fungi have been reported as causative agent in large proportions of mycotic corneal ulcers in tropical climates than in temperate climates.<sup>1</sup> In our study, *Aspergillus* spp. and *Curvularia* spp. were most common isolates. On direct microscopy, 28 patients showed evidence of hyphae on direct microscopy. There were no definite accompanying systemic factors except diabetes mellitus that was found only in 4 patients.

The scar size was found to be comparable in two groups. There was reduction in depth of scar when compared with depth of infiltrate in both the groups after the treatment.

Microorganism	Group A	Group B
<i>Aspergillus fumigatus</i>	2 (13.33%)	2 (13.33%)
<i>Aspergillus niger</i>	1 (6.66%)	0
<i>Fusarium</i> spp.	1 (6.66%)	1 (6.66%)
<i>Curvularia</i> spp.	1 (6.66%)	4 (26.66%)
<i>Aureobasidium pullans</i>	1 (6.66%)	0

**Table 2. Identification of Fungi Isolated From Corneal Scrapings of Patients in Both The Groups**

**DISCUSSION**

Fungal keratitis is difficult to treat and carries a significant risk of intraocular involvement. Natamycin has been reported as the most effective medication against *Fusarium* and *Aspergillus*.<sup>21</sup>

In monotherapy with topical 5% natamycin, poor outcome have been reported due to large ulcer size *Aspergillus* as causative organism and hypopyon. They have been thought to be predictors of poor outcome.<sup>11</sup> All the 15 patients in the study healed well with topical natamycin alone.

Of the newer antifungal agents, VRC has been reported as highly potent triazole with 100% in vitro susceptibility against common ocular fungal pathogens compared with only 60-84% for fluconazole, amphotericin B and ketoconazole.<sup>22</sup>

Topical 5% natamycin was comparable to 1% VRC in terms of efficacy. Average time of resolution of corneal ulcer was more with VRC than natamycin and the difference was statistically significant. Hence, natamycin was more efficacious in treatment of fungal keratitis curing from 1 to 5 mm of infiltrate in our study. Complete healing in both the groups with topical therapy alone shows effective penetration of both the drugs through the cornea effectively.

**CONCLUSION**

Both the drugs were found to be efficacious agents in primary fungal keratitis management. Average healing time was marginally better with natamycin. Hence, 5% natamycin was more efficacious than 1% VRC in treatment of fungal keratitis curing from 1 to 5 mm of infiltrate in our study. Considering the cost, the shelf life and the variable bioavailability of topical VRC, it may be maintained as second line of treatment in the management of fungal keratitis, refractory to topical natamycin or other conventional antifungal agents. Further, larger randomised comparative studies with a larger number of patients may be required to substantiate the result of this study along with culture and sensitivity of fungal isolates.

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