A COMPARATIVE STUDY IN EVALUATING EFFECT OF NATAMYCIN AND VORICONAZOLE EYE DROPS IN MYCOTIC KERATITIS IN A TERTIARY EYE CENTRE OF EASTERN INDIA

Ophthalmology

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KEYWORDS

Introduction

Corneal disease is second only to cataracts as the most common cause of blindness worldwide, resulting in more than 1.5 million new cases of vision loss annually.¹ Ophthalmic mycosis is emerging as a major cause of vision loss and morbidity, and can be sight-threatening.^{2,3} Fungal keratitis is one of the major causes of ophthalmic mycosis,⁴ accounting for more than 50% of proven ophthalmic mycoses in some countries.⁵ In Africa and other tropical countries, about 44% of corneal ulcers are caused by fungi.⁶ Treatment of fungal keratitis is generally more difficult than that of bacterial ulcers, and resulting visual impairment is, on average, more severe.

There are only few published randomized trial of antifungal therapy for mycotic keratitis,⁷⁻¹⁰ and no new ocular antifungal medications have been approved by the Food and Drug Administration since Natamycin was approved in the 1960s. The triazole Voriconazole is active against both filamentous fungi(*Aspergillus* sp) and *Candida* species and has recently become the treatment of choice for systemic diseases such as pulmonary aspergillosis. Here, the present discussion will focus on comparing the efficacy of two topical antifungal drugs- NATAMYCIN & VORICONAZOLE in treatment of fungal corneal ulcer.

All patients who presented with a corneal ulcer at a tertiary ophthalmic government institute, Kolkata from June 1,2018 to June 30,2019, had corneal scraping, if fungal elements were present on the corneal scraping, patients were eligible for enrolment. All patients provided written, informed consent for their study participation. The treatment procedure complied with the tenets of the Declaration of Helsinki. Complete inclusion and exclusion criteria are listed below.

Inclusion Criteria:

- Presence of a corneal ulcer at presentation.
- Evidence of filamentous fungus on examination of KOH mount (confirmed by culture subsequently).
- The patient must be able to verbalize a basic understanding of the study after it is explained to the patient, as determined by physician / examiner. This understanding must include a commitment to return for follow-up visits.
- Willingness to be treated as an in-patient or to be treated as an out-patient and come back every 48-72 hours to receive fresh medication for 3 weeks.

Exclusion Criteria:

- Overlying epithelial defect < 0.5 mm at its greatest width at presentation.
- Impending perforation.
- Evidence of bacteria on Gram stain at the time of enrolment.
- Evidence suggestive of *Acanthamoeba* infection.
- Evidence of Herpetic keratitis by history or examination.
- Corneal scar not easily distinguishable from current ulcer.
- Age less than 16 years

The information of the patients was recorded in a predesigned proforma after obtaining written informed consent from the patient

and the study was conducted after having approval from Institutional Ethical Committee.

Materials and methods

All patients with a corneal ulcer presenting at the institute had corneal scrapings using a Kimura spatula for Gram stain and potassium hydroxide wet mount and had cultures plated on blood, chocolate, and potato dextrose agar. Enrolled cases were included in the study following the model of parallel assignment. The total cases were grouped into two.

Series I received 5% topical **Natamycin** [Natamet Eye Drops (United Pharmacies) (Natamycin USP) - 50mg (3mL)]

Series II received 1% topical **Voriconazole** [VORIZOLE (Aurolab) - It contains 30 mg sterile lyophilized dry Voriconazole powder. To get 1% (10 mg/ml) solution, this powder has to be reconstituted with 3 ml of Water for Injection provided along with the pack. Both the group received without repeated scraping of the corneal epithelium at 1 and 2 weeks after enrolment.

The antifungal medications were applied topically to the cornea. One drop (Natamycin (5%) or Voriconazole (1%) (which ever was chosen) every 5 minutes for first five doses followed by hourly application throughout the day, except during sleep for first 7days. Then one drop two hourly continued for another 7days. After that, one drop three hourly given & the regimen continued till complete resolution of the ulcer.

All the patients were followed up till the healing of the corneal ulcer or three months duration whichever is earlier. The date of first examination was taken into consideration while calculating time required for the ulcer to heal. All the patients were closely followed up on weekly basis at outpatient department. Patients who missed two or more consecutive follow up visit were excluded from the study. Also the patients who showed evidence of noncompliance to the treatment protocol were excluded from the study. Assessments of best spectacle-corrected visual acuity (BSCVA) and clinical characteristics (infiltrate/scar size, epithelial defect size) were performed at enrolment, then weekly until the ulcer heals and also at the end of 3rd month from date of enrolment. Visual acuity measurements were performed using Snellen's visual acuity chart from 6 meter distance. Snellen acuity is then converted to log MAR for statistical calculation. A Haag-Streit 900 slitlamp biomicroscope (Haag-Streit AG, Koeniz, Switzerland) was used to assess the size of the infiltrate/scar and epithelial defect at study visits, and ocular adverse events such as corneal perforation. Infiltrate/scar size and epithelial defect size were measured according to a protocol adapted from the Herpetic Eye Disease Study. Since the patient were repeatedly measured for consecutive 12 weeks for visual acuity and ulcer size. These gives rise to a potential Inter Observer Correlation. Here we have assumed an independent Correlation structure. So it was not possible to model either the ulcer size or the visual acuity by simple linear model. For this to remove the correlation structure, Linear Regression Model is used using Generalised Estimating Equation.

Results

Following chart shows the result of Generalised Estimating Equation with Linear Regression Model with outcome as ulcer size in mm2:

Parameter	Number	B(point estimate)	95% Wald Confidence	
			Lower	Upper
Constant		0.802		
Natamycin (5%)	14	0.623	-0.234	1.480
Voriconazole (1%)	16	0	-	-

Quasi Likelihood under Independence Model Criterion (QIC) is 1007.195 which Shows good model fitness.

By this chart we can reach following results:

For changing treatment from voriconazole to natamycin ulcer size worsens by 0.623 or in other words, healing of ulcer is prolonged. But this is not statistically significant as evident by 95% confidence interval (As confidence interval includes value 0).

Following chart shows the result of Generalised Estimating Equation with Linear Regression Model with outcome as visual acuity in log Mar:

Parameter	Number	B(point estimate)	95% Wald Confidence	
			Lower	Upper
Constant		2.148	—	—
Natamycin (5%)	14	0.483	-0.130	1.096
Voriconazole (1%)	16	0	—	—

Quasi Likelihood under Independence Model Criterion (QIC) is 316.430 which Shows good model fitness.

By this chart we can reach following results:

For changing treatment from voriconazole to natamycin visual acuity worsens by 0.483 (as in logMAR scale visual acuity worsens with increase of value). But this is not statistically significant as evident by 95% confidence interval (As confidence interval includes value 0). Visual acuity can never be accepted as criteria for healing of corneal ulcer. So as such there is no question of treatment failure or success from visual acuity point of view. So Kaplan Meir Analysis is not possible here. So the mean visual acuity was plotted for Voriconazole and Natamycin. The graphs are shown below. From the very visual impression it is clear that there is nothing to choose between Voriconazole and Natamycin with outcome measure as visual acuity.

X axis = Mean Visual Acuity in Log MAR Scale

Y axis = Time in weeks

There were 3 cases of corneal perforations requiring surgical management in Natamycin treated group. But there was no such case in

voriconazole treated group. These cases were excluded from the study and not analysed as per predesigned exclusion criteria for enrolment in study. No case of serious and significant side effect can be detected in both the treatment group.

Comparison between mean visual acuity of Natamycin & Voriconazole

Discussion

Voriconazole has been shown to be highly effective against filamentous organisms (e.g., aspergillosis) and is more potent in invasive aspergillosis than amphotericin B^{11,13}. The present study suggests that topical voriconazole may also be useful for the treatment of fungal infections of the eye. Topical and oral voriconazole are being increasingly used in clinical practice for the treatment of fungal corneal ulcers, though the superiority of these agents compared with natamycin has not been established¹⁴⁻¹⁶. In our study, topical Voriconazole was found to be a slightly better treatment option than topical Natamycin with respect to healing of ulcer. But the difference was not statistically significant. In this regard one study by Namperumalsamy V. Prajna, Jeena Mascarenhas et al available¹⁶. They also failed to demonstrate any statistically significant difference in healing time of diagnosed fungal corneal ulcer, between Natamycin and Voriconazole as primary treatment measure. In our study we also compared topical Voriconazole and topical Natamycin with respect to improvement of visual acuity. Both the groups improved on visual acuity while under treatment. Visual recoveries were faster in patients treated with topical Voriconazole than in patients treated with topical Natamycin. But again the difference was statistically not significant. Our results so obtained are in tune with study by Namperumalsamy V. Prajna; Jeena Mascarenhas et al¹⁶.

Small study population and failure to ascertain patient's compliance to treatment protocol (as they were treated on outdoor basis) is a serious limitation of our study. Strength of the study being its prospective nature, stringent inclusion and exclusion criteria, close follow up protocol. Confirmation of the study result can only be done by conducting a study on larger patient population and preferably treating them under hospital admittance.

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