



Natamycin Vs Voriconazole in The Treatment of Mycotic Corneal Ulcers

KEYWORDS

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ABSTRACT Fungal keratitis is a leading cause of ocular morbidity as well as mortality in developing countries. As much as 50% of corneal ulcers are proven to be of fungal etiology in developing countries. The management consists of medical in the form of topical or systemic antifungal agents or surgical in the form of therapeutic penetrating keratoplasty. In fungal corneal ulcers broad spectrum antifungal drugs are usually chosen, commonly used are Natamycin, amphotericin B, fluconazole, miconazole, & ketoconazole. Voriconazole (VRC) is a new, broad spectrum antifungal agent. This study is an attempt to compare the safety and efficacy of two drugs – Voriconazole and Natamycin for the treatment of fungal corneal ulcer, especially in terms of reduction of epithelial defect, size and depth of infiltrate, size and depth of scar and time of resolution.

INTRODUCTION

Corneal diseases are a major cause of vision loss and blindness, second only to cataract in overall importance. Scarring of the cornea as a result of suppurative keratitis is an important cause of preventable blindness¹. Suppurative keratitis may be caused by bacteria, fungi, and protozoa. Fungal keratitis is a leading cause of ocular morbidity as well as mortality in developing countries². As much as 50% of corneal ulcers are proven to be of fungal etiology in developing countries³. The management consists of medical in the form of topical or systemic antifungal agents or surgical in the form of therapeutic penetrating keratoplasty⁴. In fungal corneal ulcers broad spectrum antifungal drugs are usually chosen, commonly used are Natamycin, amphotericin B, fluconazole, miconazole, & ketoconazole⁵. Considering the scarcity of options of drugs in the management of mycotic keratitis, there has always been the search for better alternative drugs. Voriconazole (VRC) is a new, broad spectrum antifungal agent that is effective against yeasts and molds⁶⁻⁸. The present study was conducted to evaluate the efficacy of 1% Voriconazole as a primary treatment modality in proven fungal keratitis and secondly, to compare its efficacy with 5% Natamycin for fungal keratitis.

MATERIAL & METHODS

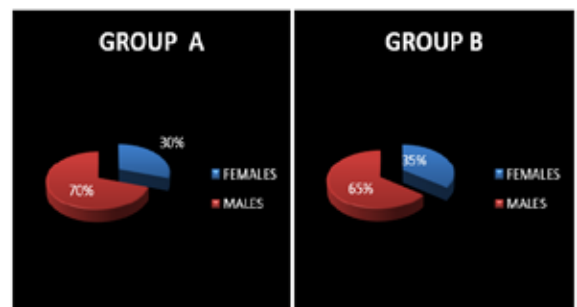
A Prospective, Randomized Comparative study was conducted with 40 patients of fungal corneal ulcers. They were divided into two groups of 20 patients each by randomization (done by computerized software) after confirmation of fungal hyphae, to receive treatment with 5% Natamycin (Group A) or 1% Voriconazole (Group B). A comprehensive history regarding systemic and ocular complaints were taken. A detailed clinical examination was carried out including visual acuity, measurements of the size of the epithelial defect, stromal infiltrate and hypopyon at presentation and different follow ups during the treatment. Each cornea was scraped and had a KOH, Gram stain and bacterial and fungal cultures were recorded. Patients were followed up everyday for 1 week / earliest sign of resolution, followed by every 3rd day for 2 weeks, every week for 2 weeks, then every two weeks till 2 months or until complete resolution of infiltrate whichever was later. The cri-

teria used for declaring treatment failure was: (1) Corneal perforation after starting of treatment. (2) Non resolving ulcer with increase in signs and symptoms. Results were compared at the end of study and data analyzed statistically by Pearson chi square test and t- test. Standard follow up visits were taken as after 1 week, 2 weeks, 4 weeks and 8 weeks for statistical analysis. $P < 0.05$ were considered statistically significant.

RESULTS

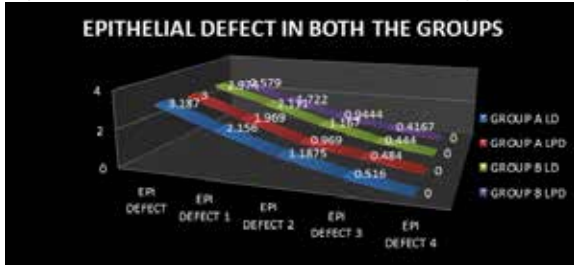
Forty patients of fungal corneal ulcers were enrolled after confirmation of fungal hyphae and randomized into two groups in this study. Out of all the patients of the present study, maximum patients belonged to 45-60 years of age. The mean age was 46.4yrs in Group A and 48.85yrs in Group B. There were 14 males in Group A and 13 males in Group B, indicating that in our study fungal corneal ulcers were more commonly found in males as seen in fig 1, on the basis that males are commonly engaged in outdoor activity rendering them more prone to trauma. Laterality was comparable in two groups. Most of the patients did not have any systemic illness prior to onset of symptoms with the exception of diabetes mellitus which was found in 5% of patients only. Of the various predisposing factors, trauma was found in 92.5% of subjects. Other factors like prior history of viral keratitis, prolonged steroid use, contact lens usage, known to be associated with occurrence of fungal keratitis were not present in our study.

Fig 1: Sex distribution in both the group



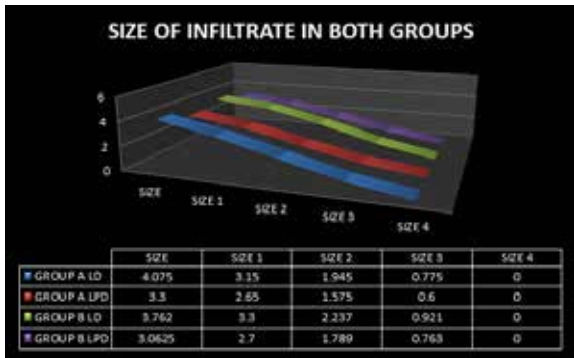
Both the epithelial defect and size of infiltrate were noted as largest diameter * largest perpendicular diameter in millimeters on every follow up. Epithelial defect resolved in most cases by 4 weeks followed by the resolution of ulcer as determined by the size of infiltrate. In Group A, epithelial defect was present in 16 cases with mean of 3.19 *3.00 and in Group B, it was present in 19 cases with mean of 2.97 *2.58. The mean size of epi defect was comparable in two groups on presentation and follow up as shown in fig 2.

Fig 2: Mean size of epithelial defect in both groups



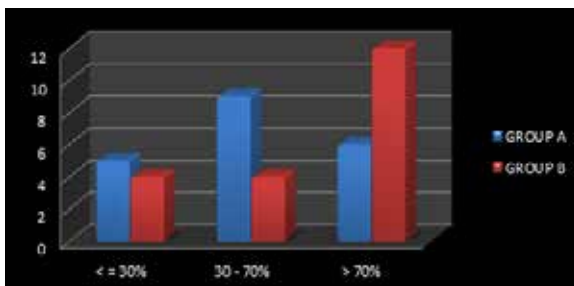
The size of infiltrate was followed up on slit lamp; it becomes well demarcated initially followed by reduction in size. Maximum number of cases had infiltrate size between 2-5 mm (13 cases in group A and 12 in Group B). Average sizes on presentation in Group A and in Group B were 4.08*3.3 and 3.76*3.06 mm respectively as seen in fig 3, it was comparable in both the groups p- value being 0.946*0.956 .

Fig 3: Size of infiltrate in both the groups



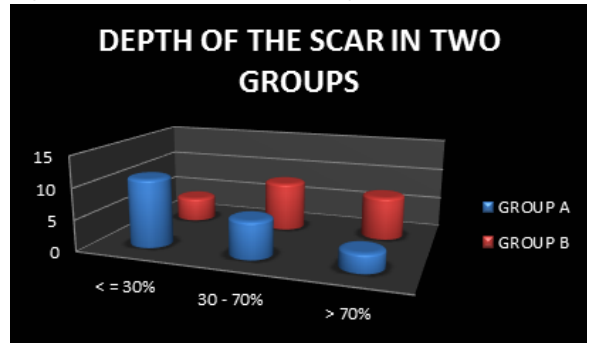
Infiltrate depth on presentation was measured by slit lamp and recorded. Depth in Group A in most of the cases (9cases) lies between 30-70%, while the Group B, most of the ulcers (12cases) are deep having depth >= 70% (as seen in fig 4). The size of hypopyon was noted in millimeters on slit lamp and it was also comparable between the two groups on presentation and follow up.

Fig 4: Depth of infiltrate in both the groups



Average time of resolution with natamycin was 24.5 days and with VRC it was 31.26 days. There was one treatment failure due to perforation in Group B making efficacy of VRC to be 95% and natamycin to be 100%. No other complications were seen in our study. Average scar size in Group A was 3.3*2.98mm and in Group B was 3.37*3.03mm which was comparable in two groups. Overall the depth of scar was decreased in both the groups and the difference was not significant in both the groups (p- value 0.076) as seen in fig 5.

Fig 5: Depth of scar in both the groups



DISCUSSION

This study is an attempt to compare the safety and efficacy of two drugs – Voriconazole and Natamycin for the treatment of fungal corneal ulcer, especially in terms of reduction of epithelial defect, size and depth of infiltrate, size and depth of scar and time of resolution after a follow up for minimum of 8 weeks after the initiation of treatment or till the resolution of infiltrate whichever was later. On comparing the two groups, the mean size of epithelial defect was comparable at presentation and at follow ups (p- value > 0.05). This is hence evident that the two groups were comparable initially in terms of average size of epithelial defect and on follow up after starting the treatment; the healing of epithelial defect had healed in all the patients Thus, indicating the efficacy of both the medications. Prajna, John et al (2003)⁹ in his study concluded that there was no significant difference at baseline in size of epithelial defect between the two arms of study. Size of infiltrate on presentation is the most important factor in determining the outcome of fungal keratitis. P. lalitha et al (2001), in their study showed that one of the predictors of treatment failure was ulcers that exceeded 14 mm(P = 0.009), inferring that large size was associated with poor outcome of the ulcer.

On starting the treatment, margins of stromal infiltrate was found to initially become well defined, followed later by the reduction of size. Resolution of infiltrate denoted by 0 size was reached in both the groups by 8 weeks. On looking at the distribution of depth of infiltrate in two groups, 45% of patients had depth more than 70%. Amongst these many of our patients had formation of deep endothelial abscess hence corroborating with the general characteristic features of fungal keratitis. It is an important confounding factor in our study as it may itself lead to delay in response to treatment. Hypopyon is another important parameter in our study. On looking at the change in hypopyon size between the groups, p- value > 0.05 which is not significant. In one of our patients in Group A and three of our patients in Group B, hypopyon initially increased in size by 0.5mm on initial follow up visits subsiding thereafter, this may indicate lack of compliance on the patient's side or slow onset of drug action. Thus, our study over-

all suggests delay in onset of action with Voriconazole as compared to Natamycin.

Complete resolution of ulcers with medication was seen in 97.5% of our patients with only one treatment failure in Group B who perforated within one week of starting treatment. In Group A, the average time of resolution of infiltrate was 24.50 days and in Group B it was 31.26 days. Hence, the average healing time was marginally better in natamycin but the difference was statistically not significant. Prajna NV et al (2013) found that topical natamycin is superior to topical voriconazole and voriconazole monotherapy is not recommended for filamentous fungal keratitis¹⁰. All the ulcers showed resolution and average time of resolution was directly proportional to the size of infiltrate and amount of hypopyon at presentation in our study.

CONCLUSION

Voriconazole 1% topical preparation is a safe and effective drug and Natamycin 5% preserved topical formulation used conventionally is highly efficacious in treatment of fungal keratitis. There was no extra advantage of Voriconazole in prompting healing than natamycin and can be used as a reserve drug in case of failure of conventional therapy.

Hence, the results of this study showed efficacy of both natamycin and Voriconazole in treatment of fungal keratitis with no added advantage over natamycin.

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