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Original Article

Comparison of the Efficacy of Topical Natamycin 5% and Fluconazole 0.3% Eye Drop Therapy versus Topical Natamycin 5% Alone in Deep Fungal Keratitis in Garhwal Region of Uttarakhand, India

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Abstract

Aims: The study aims to compare the efficacy of topical natamycin 5% and fluconazole 0.3% eye drop therapy versus topical natamycin 5% alone in deep fungal keratitis.

Study Design: A prospective, randomized, clinical study was conducted on patients.

Place and Duration of Study: This study was conducted at the Department of Ophthalmology, VCGS Government Medical College, Srinagar, Uttarakhand, between October 2017 and September 2018.

Materials and Methods: This study included two groups of 50 patients each. 50 patients in Group 1 were randomly started on combined therapy of natamycin 5% and fluconazole 0.3% and another 50 patients in Group 2 were randomly started on just natamycin 5% drops. Response to the therapy was recorded after a minimum of 10–14 days on the parameters of healing, efficacious, or inefficacious, and the results were compared.

Results: In the group receiving combined therapy of natamycin 5% and fluconazole 0.3%, that is, Group 1: 21 of 50 patients were healed (42%), 20 of 50 patients showed treatment efficacy (40%), and 9 of 50 patients showed inefficacious results to the therapy (18%), whereas in the group receiving monotherapy with natamycin 5% alone, that is, Group 2: Three patients of 50 were healed (6%), 14 of 50 patients showed treatment efficacy (28%), and 33 of 50 patients had inefficacious results (66%). Overall, efficacy rate when compared of both the groups had $P < 0.0001$, indicating significant results of Group 1, that is, patients receiving combined therapy.

Conclusion: After the comparison of the data in both the groups, the patients started on combined therapy of topical natamycin 5% and fluconazole 0.3% showed better response to therapy ($P < 0.0001$) as compared to the patients started on natamycin 5% alone therapy, indicating that combined therapy is better as compared to monotherapy with just natamycin 5% drops.

Key words: Fluconazole, Fungal keratitis, Healing ulcer, Natamycin

INTRODUCTION

The first case of fungal corneal ulcer was reported by Leber, in 1879. This keratomycosis was caused by *Aspergillus glaucus*.[1] Since then, the ophthalmologists and microbiologists have realized the importance of fungal infections in relation to cornea. In fact, keratomycosis constitutes up to one-third to half of the suppurative keratitis in tropical parts of the world.[2] In spite of increasing awareness and recognition during the past 20 years, keratomycosis still remains a diagnostic and therapeutic challenge to the ophthalmologists.

It is due to awareness, better recognition, and improved laboratory diagnostic technique, the correct diagnosis of keratomycosis has increased. Srinivasan *et al*.[3] reported the

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highest incidence (up to 51.9%) fungal infections among all culture-positive corneal ulcer patients. This high prevalence of keratomycosis in South India is significantly higher than found in similar studies in Nepal (17%), Bangladesh (36%), and South Florida (35%).[2,3]

The epidemiological pattern of keratomycosis varies significantly from country to country, and even from region to region within the same country. It is also climate specific. At least 70 different types of fungi have been identified as causative agent of keratomycosis.[4]

In tropical and subtropical countries, filamentary fungi predominate. *Candida* species, however, is a part of indigenous human flora and is present worldwide. Its relative frequency as a cause of keratomycosis is increasing in the temperate zone.[5]

During the past 15 years, there has been a major change in the outlook for fungal infections of the cornea. In any suppurative keratitis, corneal scraping followed by simple potassium hydroxide (KOH) mount preparation is a simple way to diagnose keratomycosis early. Newer antifungal agents with relatively low toxicity are now available to treat keratomycosis more effectively. Emphasis should be given on preventive aspect and early diagnosis. Better understanding of pathogenic mechanisms in corneal inflammation will help further advancement in treating these difficult cases in future.

In recent decade, the incidence of fungal keratitis in Uttarakhand has shown an increase with *Fusarium* sp. and *Aspergillus* sp. as major pathogens.[6] This is probably a result of the hilly terrain and vegetation of this area, leading to high rate of vegetative trauma. Medicine administration seldom yields to a desirable efficacy against fungal keratitis. Moreover, delayed diagnosis and treatment worsens the severity of this disease and increase difficulty of treatment, leading to a poor efficacy, a high rate of blindness, and even loss of eyeball.

Combined use of medicines has been frequently adopted to elevate their antifungal activity.

Hence, the present study compares the efficacy of the combined therapy of natamycin and fluconazole eye drops versus natamycin alone in the treatment of deep fungal keratitis.

MATERIALS AND METHODS

This prospective, randomized, and clinical study was conducted on patients attending the eye OPD of VCSG Government Medical College, Srinagar, Uttarakhand, India, during October 2017–September 2018.

A total of 100 patients with severe form of deep fungal keratitis were studied and patients were divided into two groups.

- Group-1: Comprised 50 patients receiving combined therapy of natamycin 5% and fluconazole 0.3% eye drops 1 hourly 12 times a day for 10–14 days.
- Group-2: Comprised 50 patients receiving monotherapy of natamycin 5% eye drops 1 hourly 12 times a day for 10–14 days.

Informed consent was obtained from all participants. Sampling was performed at the ulcer base, observed with a microscope (KOH examination), and samples were subjected to fungal culture.

Grading of Keratitis

Based on the depth of corneal inflammation infiltration, size of the ulcer, and hypopyon, the keratitis was graded into severe and non-severe types.

In non-severe type, the ulcer inflammation infiltrated into shallow and medium layers, <2/3 of stroma thickness, and ulcer diameter <6 mm.

In severe type, corneal ulcer inflammation infiltrated into deep layer, >2/3 of corneal thickness or full-thickness cornea, ulcer diameter >6 mm, and complicated hypopyon.

Treatment Method

All patients in Group 1 received combined use of 5% natamycin and 0.3% fluconazole eye drops, once per hour, and patients in Group 2 received 5% natamycin also once per hour. During the first administration, fluconazole was initially given and 15 min later, natamycin was delivered, allowing for sufficient time for the natamycin to adhere to the ulcer surface. The drops were administered once an hour, 12–13 times daily. Atropine was also given for mydriasis as necessary in both the groups. The patients also took oral itraconazole 100 mg twice a day. All the patients followed a treatment course for 10–14 days and surgical methods if necessary were considered and timely performed.

Efficacy Evaluation

Healing

Corneal ulcer was healed, negative for fluorescein dye, stromal inflammation infiltration was basically recovered, scar formation was evident, and hypopyon was absorbed.

Efficacious

Corneal ulcer or inflammation was alleviated and hypopyon was decreased or completely absorbed.

Inefficacious

Corneal inflammation remained the same or was aggravated, no changes in hypopyon, deteriorated corneal

ulcer, and corneal perforation were evident.

RESULTS

Laboratory Examination

Direct smears were obtained from all 100 patients in the study and were observed under microscope (KOH examination). Of these, 90 cases were positive for fungal hyphae (positive rate 90%) and 10 were negative. However, these 10 cases were positive for fungal culture and fungal growth was noted. The fungal species identified were as follows: 56 cases of *Aspergillus* spp. (56 %), 24 cases were of *Fusarium* spp. (24%), 10 cases were of *Curvularia* spp. (10%), 5 cases were of *Helminthosporium gramineum* (5%), 3 cases were of *Penicillium* (3%), and rest were not identified.

Treatment Results

The treatment results are demonstrated by the given self-explanatory tables and graphs. $P < 0.05$ was considered statistically significant.

Age

As shown in the Table 1 – The mean age of patients put on combined therapy(Group 1) was 57.87+_14.84 and mean age of patients receiving monotherapy was 53.28+_14.19 (p=0.121)

Sex

Regarding laterality of gender as in Table 2. Group 1 had 34 male and 16 female patients whereas group 2 had 32 males and 18 female patients.

Healing

As shown in Table 3 -21 patients in group 1 were healed whereas only 3 patients in group 2 were actually healed (p<0.0001)

Efficacy

Regarding Efficacy 20 patients in group 1 showed signs of treatment efficacy according to Table 4 whereas 14 patients in group 2 showed signs of efficacy.(p=0.071)

Inefficacy

Regarding Inefficacy only 9 patients in group 1 showed inefficacious results (Table 5) whereas its number was 33 in the group 2 showing significant results.(p<0.0001)

Overall Efficacy

Overall per cent efficacy was way better in group 1 (82%) as compared to group 2 (17%) as shown in Table 6.(p<0.0001)

DISCUSSION

Recent studies conducted in Uttarakhand region of India indicated that the incidence of fungal keratitis by *Aspergillus* spp. and *Fusarium* spp. has constantly increased in the past decade.[6] The hilly mountain terrain of this region and occupation of local people are a chief factor contributing to this high incidence in this region. The incidence of fungal infection will be significantly higher compared to other regions if scanty attention was paid to public and individual

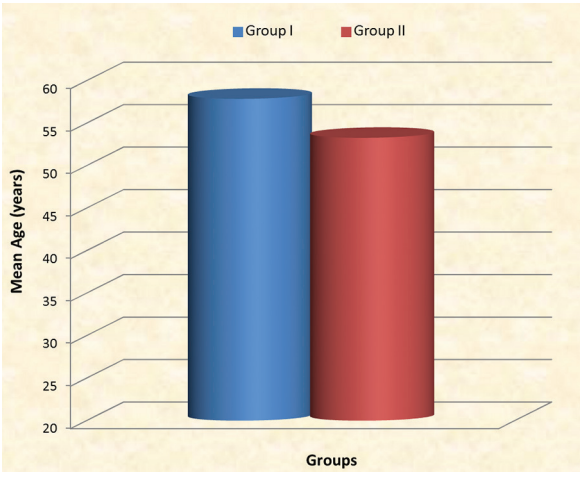
Table 1: Group comparison for the age of patients

Groups	Age of patients (mean±SD)
Group 1	57.87±14.84
Group 2	53.28±14.19
P	0.121

Group 1: Patients receiving combined therapy of 5% natamycin and 0.3% fluconazole eye drops. Group 2: Patients receiving 5% natamycin alone.
SD: Standard deviation

Table 2: Group comparison of patients according to sex

Sex distribution	Number of patients (%)	
	Group 1	Group 2
Male	34 (68.0)	32 (64.0)
Female	16 (32.0)	18 (36.0)
P	0.554	



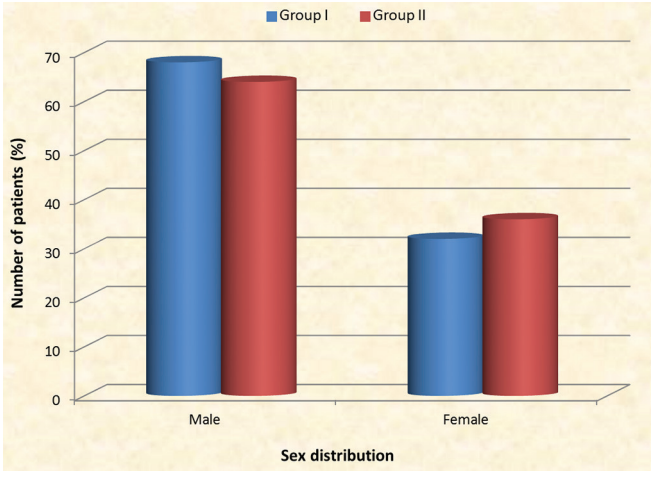


Table 3: Group comparison of patients according to healing

Healing	Number of patients (%)	
	Group 1	Group 2
Yes	21 (42.0)	3 (6.0)
No	29 (58.0)	47 (94.0)
P	<0.0001	

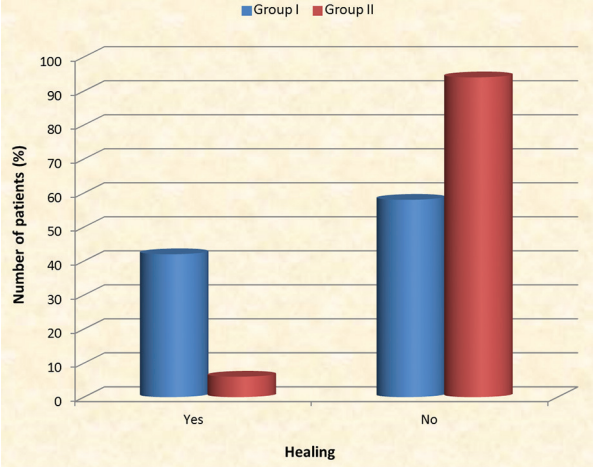


Table 4: Group comparison of patients according to efficacious

Efficacious	Number of patients (%)	
	Group 1	Group 2
Yes	20 (40.0)	14 (28.0)
No	30 (60.0)	36 (72.0)
P	0.071	

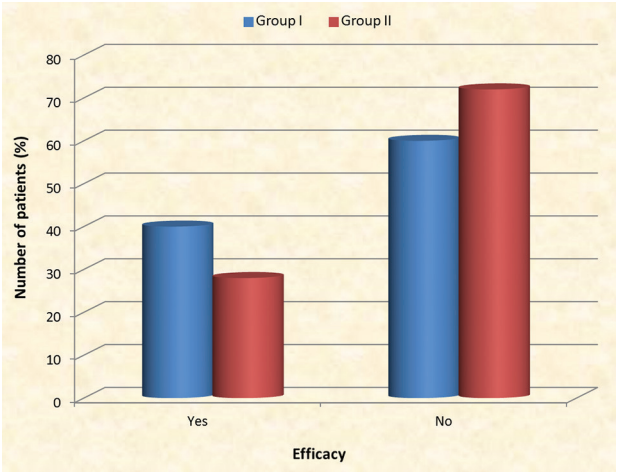


Table 5: Group comparison of patients according to inefficacious

Inefficacious	Number of patients (%)	
	Group 1	Group 2
Yes	9 (18.0)	33 (66.0)
No	41 (82.0)	17 (34.0)
P	<0.0001	

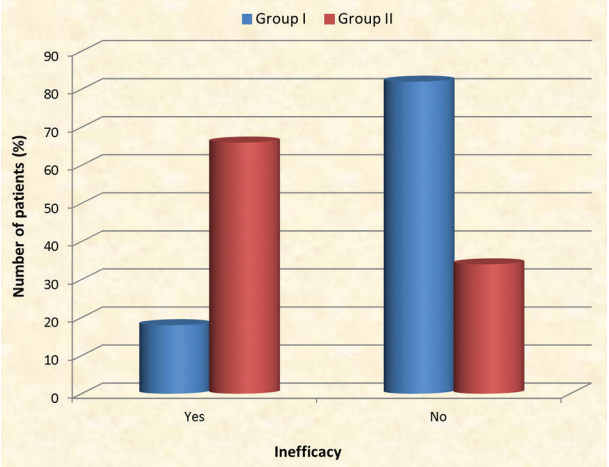
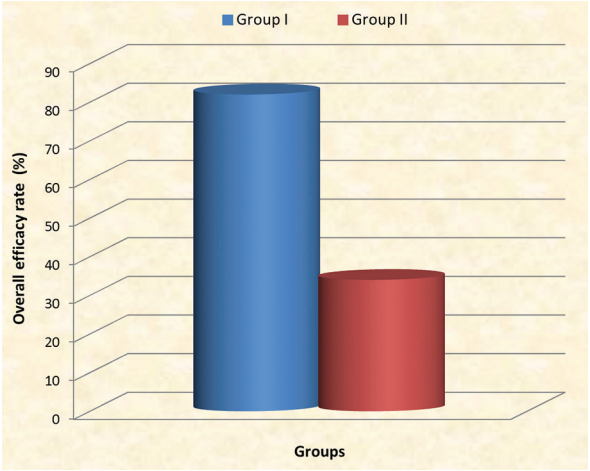


Table 6: Group comparison of patients according to overall efficacy

Overall efficacy	Number of patients (%)	
	Group 1	Group 2
Healing	21 (42.0)	3 (6.0)
Efficacious	20 (40.0)	14 (28.0)
Overall	41 (82.0)	17 (34.0)
P	<0.0001	



hygiene. The number of cases in this study was 56 of 100 of *Aspergillus* spp. and 24 cases of 100 of *Fusarium* spp. Rest were of *Curvularia*, *Penicillium,* and *Helminthosporium* spp. However, the ranking of alternative pathogenic fungi changes and species of infectious fungi become intricate.

At present, administration of topical ocular drops serves as the primary treatment for fungal keratitis and the medicine used must be highly efficacious and yield low toxicity. Previously, amphotericin B was frequently applied for the treatment of fungal keratitis, but it is gradually substituted

by natamycin due to high toxicity and other limiting factors.[7] Natamycin acts as a broad-spectrum antifungal agent against *Candida*, *Fusarium*, *Curvularia, Penicillium,* etc.

The sensitivity of *Fusarium* toward natamycin was as high as 93.4%.[8] Natamycin eye drops are stable and cause no irritation or toxicity. Similar to amphotericin B, natamycin has poor penetration into corneal epithelia. However, the injured epithelial layer in patients with fungal keratitis provides access to the medicine molecular penetration. In addition, the binding between natamycin and corneal tissues prolongs the contact time, reduces the dilution effect of conjunctival sac tears,[7] and increases the antifungal concentration of natamycin within the cornea. Since the majority of cases have severe fungal keratitis, the use of 5% natamycin and 0.3% fluconazole is combined with the aim of improving antifungal efficacy and minimizing the incidence of drug resistance.

Komdima *et al*. reported that the application of natamycin in combination with ketoconazole is efficacious for Aspergillus keratitis in an animal experiment. It has been suggested that the combined use of natamycin and econazole eye drops yields neither additive nor toxic effects.[9] The cure rate of amphotericin B combined with fluconazole is reported to range from 81% to 88.9%.[10]

In the present study, natamycin and fluconazole eye drops were selected due to lower toxicity compared with amphotericin B. In addition, natamycin is highly sensitive toward mycelia fungi, especially *Fusarium* and *Aspergillus*.[11] Furthermore, fluconazole is effective against a variety of *Candida* and infiltrates into the deep corneal layer and anterior chamber. These advantages collectively enhance the treatment efficacy of deep fungal keratitis. Clinical observation in this study revealed efficacy rate of 82% for combined therapy and no toxic responses were noted. Sun *et al.* utilized 5% natamycin eye drops alone to treat deep keratitis after debridement. The achieved cure rates were 71% and 43%,[12] smaller than achieved in previous studies. The combined use of two medicines is likely to have additive effect rather than antagonistic effects. In addition, the combined therapy of natamycin and fluconazole is an efficacious treatment against *Fusarium*, *Aspergillus,* and *Penicillium*-induced keratitis.

In Uttarakhand, the incidence of fungal keratitis is constantly increasing, mainly attacking peasants. Most cases are correlated with ocular trauma of various degrees. In the study, most of the cases of deep keratitis were associated with delayed treatment. The combined therapy of 5% natamycin and 0.3% fluconazole was significantly efficacious for the patients of deep keratitis, and this therapy is highly recommended for rapid control of corneal fungal infections (including filamentous fungi and yeast-like fungi) and increasing cure rate of fungal keratitis.

CONCLUSION

The present study concludes that the treatment efficacy of the combined therapy of natamycin 5% eye drops and fluconazole 0.3% (overall efficacy rate of 82%) and ($P < 0.0001$) is better than the monotherapy with natamycin 5% alone (overall efficacy rate of 33%). This is due to the ability of fluconazole to penetrate into the deeper corneal layers as compared to natamycin which acts at a more superficial layer of cornea. Combined therapy, hence, provides an additive effect or rather a synergistic effect rather than a monotherapy with natamycin alone.

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