Original Research Paper

Volume - 14 | Issue - 03 | March - 2024 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Ophthalomology

A RANDOMISED CLINICAL TRIAL COMPARING TOPICAL ITRACONAZOLE 1% WITH TOPICAL NATAMYCIN 5% FOR THE TREATMENT OF FILAMENTOUS FUNGAL KERATITIS

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ABSTRACT **Aim:** To compare the clinical efficacy of itraconazole 1% eyedrops with natamycin 5% eyedrops for topical monotherapy of filamentous fungal keratitis. **Methods:** Patients presenting with features suggestive of fungal keratitis over a period of 24 months from January2022 to December 2023 underwent detailed clinical examination and microbiological investigation. Eighty three eyes of eighty three patients with direct smear and/or culture-proven fungal keratitis were enrolled in the study after obtaining informed consent. Forty three patients received primary therapy with topical natamycin hourly labelled as group 1,and forty patients received topical itraconazole hourly labelled as group 2. Success of the treatment was defined as a healed or healing ulcer at final visit, and failure as an ulcer that worsened or remained same at final visit. **Results:** On the basis of direct microscopy and culture the most common fungal isolate found is Fusarium in 43 cases (51.8%) followed by Aspergillus in 17 cases (20.4%). In thirty-one (72%) of 43 patients in group 1 and 24 (60%) of 40 patients in group 2, the ulcer resolved completely. In keratitis due to Fusarium spp, 18 (79%) of 23 patients showed a favorable response to natamycin, whereas 8 (44%) of 20 patients showed a favorable response to itraconazole. However, no such difference was evident in keratitis due to Aspergillus spp or Curvularia spp. Both antifungal formulations were generally well tolerated with no obvious adverse effects. **Conclusions:** Topical 5% natamycin appears to be safe and effective therapy for the management of fungal keratitis and should be considered as the treatment of choice for filamentous fungal keratitis, especially in cases affected with Fusarium spp. Topical itraconazole therapy could be considered , particularly if the infections are due to Aspergillus or Curvularia spp.

KEYWORDS : Fungal Keratitis, Itraconazole, Natamycin.

Corneal ulcer is a major public health problem in the developing world causing prolonged ocular morbidity and loss of vision.[1] Corneal blindness is responsible for 1.5-2 million new cases of monocular blindness every year.[2] In a vast agricultural country like India particularly where primary health care and referral systems are weak, minor eye injuries sustained in agricultural farms often lead to corneal ulceration of fungal etiology and loss of vision.[3]

Corneal infection of fungal etiology is common in India (19-45%) and represents 30 to 40 % of all cases of culture positive infectious keratitis in South India.[4] Filamentous fungi, such as Aspergillus spp and Fusarium spp, and dematiaceous fungi, such as Curvularia spp, are the most important causes of such infections in tropical and subtropical regions.[5-7].History of injury with vegetable matter, dry looking ulcer, feathery edges, satellite lesions, endothelial plaque and thick hypopyon form a typical presentation.

Common predisposing factors are trauma by a vegetative matter such as crop leaf, branch of a tree, straw, hay or decaying vegetative matter or injury by animal tail, prolonged use of topical steroids, structurally altered ocular surface, contact lens wearer.[8]To establish the diagnosis of fungal keratitis the use of smears and cultures is of extreme importance. 10% KOH, Gram stain, Gomori silver methamine stain and lactophenol cotton blue stains are frequently employed wherever the facilities are available. For culture Sabouraud's dextrose agar (SDA) is most frequently used. Fungal keratitis is managed by medical or surgical means. Medical therapy consists of non specific measures and the use of specific antifungal agents. The polyene natamycin , the first antifungal compound approved by the U.S. Food and Drug Administration for topical ocular use, is available as a 5% suspension for topical administration.[9] It has been recommended and is used wherever available as the drug of choice for first-line treatment of filamentous fungal keratitis.[5,10] Itraconazole, a synthetic dioxolane triazole, is well absorbed after oral administration and has pronounced in vitro antifungal activity against a wide range of fungi, including Aspergillus spp and Curvularia spp.[4] In this study we compared the potential clinical efficacy of itraconazole 1% eyedrop with natamycin 5% eyedrops for the treatment of fungal keratitis.

MATERIALAND METHODS

Patient with features suggestive of fungal keratitis who presented to the department between January 2022 to December 2023 had a detailed demographic history and clinical examination using a slit lamp biomicroscope to measure size, depth of ulceration and infiltration. Ocular adnexa was also examined and syringing was performed to know the patency of nasolacrimal duct. Scraping of the corneal ulcer using a 15 no. blade was performed under magnification. The material obtained from the initial scraping was subjected to Gram stain evaluation to identify bacteria, and 10% potassium hydroxide mount to identify fungus. Subsequent scrapings were plated onto blood agar and Sabouraud's dextrose agar.

Patients with proved fungal keratitis (smear or culture positive for fungus) with an ulcer were included in this study. Patients with mixed infections, those in whom direct microscopy and culture did not yield significant findings, and those who had previously received antifungal therapy were excluded from this study. Patients who were not willing to be part of the study were also excluded from the study. After obtaining necessary informed consent, subjects were randomised to receive either 1% itraconazole or 5% natamycin. All participating subjects were admitted to the wards for a week, and had either 5% natamycin (Group 1) or 1% itraconazole eye drops (Group 2) instilled on an hourly basis for 1 – 2 weeks and then 2 hourly for next 3 – 4 weeks. Fungal ulcers which are large (>6mm) and deep (involving >2/3 of stroma) were categorized as severe and systemic antifungal were recommended in such cases. Adjunctive therapy consisting of 0.5% moxifloxacin eyedrop, 1% atropine sulphate and systemic analgesics were given to all the patients. All the subjects were examined on a daily basis using a slit lamp biomicroscope, and the size and depth of ulcer and infiltration were measured. When an obvious improvement is noted, the treatment is continued until there is complete healing and then the treatment is gradually tapered. If there was no clinical improvement or if there was progressive ulceration, treatment was discontinued and other treatment modalities were incorporated.

The ulcer is defined a healed corneal ulcer when epithelial defect is completely healed with no stain on fluorescein application, and non-progression of the stromal infiltration. A corneal ulcer was considered to be healing if the epithelial defect decreased in size with non-progression or decrease in the size of the stromal infiltration, and an ulcer was considered to worsened if the size and depth of the ulcer increased or if the ulcer perforated. Success of the treatment was defined as a healed or healing ulcer at final visit, and failure as an ulcer that worsened at final visit.

RESULTS

A total 83 eyes of eighty three patients were included. Males were 58

(69.9%) and females were 25 (31.1%). The mean age of the patients was 48.76 years and the most common age group affected was between 41-50 years. Seventy two (85.7%) out of 83 patients were from rural area and 78.5% of patients were farmer by occupation. Out of 83 cases, 77 (92.8%) had a history of injury with vegetative matter while working in the agriculture field. In this study 69 (83.13%) patients presented within 7 days of presenting symptoms while 14 (16.86%) cases presented within 7-14 days.

forty three (51.8%) subjects were randomised to receive natamycin labelled as group 1 and 40 (48.1%) to receive itraconazole labelled as group 2. There was no difference in age or sex between group 1 and group 2. There was no significant difference at baseline in either size of epithelial defect, size of infiltrate, or depth of infiltrate between the two groups of the study. On the basis of direct microscopy and culture the most common fungal isolate found is Fusarium in 43 cases (51.8%) followed by Aspergillus in 17 cases (20.4%), Curvularia is found in 8 cases (9.6%). In thirty-one (72%) of 43 patients in group 1 and 24 (60%) of 40 patients in group 2, the ulcer resolved completely. In group 1 eleven patients had severe ulcer, out of which seven patients (63.6%) showed signs of healing or healed ulcer at final visit while in group 2 nine patients had severe ulcer, out of which four patients (44.4%) showed a favourable response. The most commonly isolated fungal pathogen in both treatment groups was Fusarium (53.4% in group 1 and 50% in group 2). In keratitis due to Fusarium spp, 18 (78.2%) of 23 patients showed a favorable response to primary natamycin therapy, in contrast to 8 (44%) of 20 patients who responded to topical itraconazole therapy, this difference was statistically significant. In keratitis due to Aspergillus spp, 5 (55.5%) of 9 patients showed a favorable response to primary therapy with topical natamycin 5% compared with 4 (50%) of 8 patients who had received primary treatment with itraconazole; this difference was not statistically significant.

The mean duration of treatment was 21 ± 5 days in group 1 (primary natamycin therapy) and 22.1 ± 8.5 days in group 2 (primary itraconazole therapy); this difference was not statistically significant.

Table 1- Characteristics of patients in both the groups.

parameters	Group I (Natamycin therapy)	Goupr II (Itraconazole therapy)
Total Cases	43	40
Male	30	28
Female	13	12
Severity		
Non severe	32	31
Severe	11	9
Isolated fungus		
Fusarium	23	20
Aspergillus	09	8
Curvularia	3	5
Other	3	3
No growth	5	4

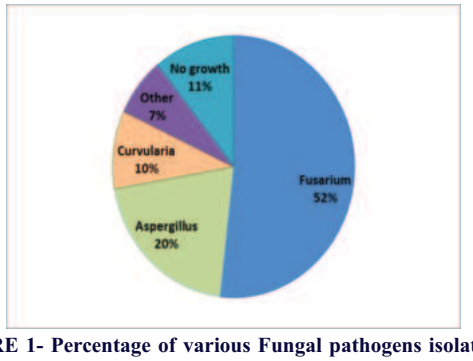

FIGURE 1- Percentage of various Fungal pathogens isolated in positive cases.

DISCUSSION

In our study there is increased prevalence of the disease among the age group of 41-50 Years (47% cases), followed by the age group of 51-60 years which accounts for 32.50%. This has a considerable social impact because people of this age group are bread earners of the family. Bharathi et al have described in their study that a larger group of patients were between the ages 21 to 50 years (66.85%)[11]. Males were more commonly affected than females. Out of 83 patients, 77 (92.8%) gave history of trauma to the eye, majority of which had history of trauma with vegetative matter. Corneal trauma has always been identified as a cause of microbial keratitis. Predisposing ocular conditions, use of corticosteroids and diabetes mellitus has been reported to be associated with development of fungal keratitis. [6,11,12]

Fusarium and Aspergillus are the most common causes of fungal keratitis in the developing world.[13] Natamycin is the most effective medication against these organisms.[14,15] It has a broad spectrum of antifungal activity, especially against Fusarium spp. it is well tolerated and causes no pain or secondary corneal damage. However, natamycin barely penetrates an intact corneal epithelium, because of which topical natamycin therapy should be given in combination with oral azole therapy in deep (severe) keratitis. In our study, thirty-one (72%) of 43 patients receiving natamycin showed favourable response to treatment. Similar results were seen in study done by C.M. Kalavathy et al. and they noticed healing in 61% of such ulcers by using topical natamycin as primary monotherapy even in severe keratitis.[16]

Itraconazole, a member of the triazole group of antifungal agents, has a broad spectrum of activity. It has greater efficacy against filamentous fungi, particularly Aspergillus fumigatus and dematiaceous fungi.. Itraconazole shows a much higher affinity in vitro for cytochrome P450 than either fluconazole or miconazole. Pankaj et al evaluated the efficacy of topical 1% and systemic itraconazole in 54 patients with fungal keratitis and a favorable response was obtained in 77% of cases.[17]In the present study ,favorable response noted in 24 (60%) out of 40 cases receiving itraconazole (44.4% of severe ulcers responded to primary topical itraconazole therapy).

In our study, Curvularia spp was isolated in eight cases (natamycin given in 3 patients and itraconazole in 5 patients) and six cases(75%) showed signs of healing. Natamycin demonstrated significant in vitro activity and a resolution of vision in most of the patients with corneal curvulariosis in a study done by Wilhelmus et al.[18] Moreover, oral and topical use of itraconazole is also useful, particularly in refractory cases. Hence,while advocating the use of natamycin as first-line therapy for keratitis due to Curvularia spp, itraconazole could be considered as an effective alternative. No adverse effects were reported from either treatment group.

In this study, it was oserved that in patients with Fusarium keratitis, a significantly higher proportion responded to topical natamycin than to topical itraconazole. Overall, a higher proportion of patients treated with natamycin exhibited favorable responses than those receiving topical itraconazole.

CONCLUSION

Fungal keratitis continues to be a cause of concern because of its vision threatening complications. Predominance of agricultural activity is the principal causative factor. KOH wet mount preparation is a sensitive and conventional method in the diagnosis. Natamycin was a preferable choice in the treatment of fungal keratitis, especially in cases with fusarium keratitis. Overall, a higher proportion of patients treated with natamycin exhibited favorable responses than those receiving topical itraconazole. The mean duration of treatment was marginally longer in the itraconazole-treated group than in the natamycin-treated group. These results suggest that topical natamycin should continue to be considered as the therapy for choice for filamentous fungal keratitis. Further RCTs with large sample size areneeded for the search of more effective and cheaper interventions for fungal keratitis.

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