ORIGINAL ARTICLE

Selection of Best Topical Medication for Treating Fungal Corneal Ulcers in Our Community

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ABSTRACT

Object: To determine the best available topical antifungal drug for treating fungal corneal ulcers in our community.

Study Design: Prospective randomized control study.

Place & Duration: Department of Ophthalmology Peoples university Hospital Nawabshah and Ghulam Muhammad Mehar Medical College Sukkhur during October 2013 to October 2014.

Material & Methods: Patients with clinical signs mimicking fungal keratitis were admitted in Eye department. Corneal scraping under topical anesthesia was taken from the base and edges of ulcer and was subjected to KOH preparation for direct microscopy. Only patients with positive stain were included in the study. Patients were subdivided into three groups A, B, and C (50 patients each) according to drug used. Group A were given Topical Natamycin 5%, Group B were given Topical reconstituted Fluconazole 1%, Group C were given Topical reconstituted Amphotericin B 0.15%.Clinical improvement was measured on the basis of reduction of the density of the suppuration, reduction in cellular infiltrate and edema in the surrounding stroma, reduction in anterior chamber inflammation, progressive re-epithelization, and Loss of the feathery perimeter of the stromal inflammation.

Results: Out of 50 patients with clinical and laboratory proven fungal keratitis in group A, 44 healed without any consequence by 12 weeks, 6 patients did not responded well and ended up with corneal perforation, endophthalmitis or surgical intervention. In group B out of 50 patients 38 healed without any consequence, while 12 ended up with corneal perforation, endophthalmitis or surgical intervention. In group C out of 50 only 18 patients had a good healing by 12 weeks while remainder did not responded.

Conclusion: Natamycin 5% is still the drug of choice for fungal keratitis in our community as most of them are of filamentous origin.

Key words: Fungal Keratitis, Natamycin 5%, Fluconazole 1%, Amphotericin B 0.15%.

INTRODUCTION:

Corneal ulcers caused by fungi have always been a challenging module for Ophthalmologists. The reason for which is not only the extent of the fungal penetration into the cornea but also the resemblance of the stromal inflammation to other conditions and the efficacy of available antifungal agents. Fungal corneal ulcer is prevalent Globaly[1,2], but the penetration is more in tropical areas. More than 50% of the eyes affected by fungi are due to Mycotic keratitis[3,4]. Fungi has been subclassified into two variants.Filamentous Fungi like Fusarium and Aspergillus which is more prevalent in tropical and subtropical zones while nonfilamentous Fungi are yeast like candida[5].

Fungal keratitis can either affect healthy individuals where the predisposing factor is

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Trauma or it can infect immunocompromised individuals. Like any other microbial agent, fungi enter an abraded cornea. Other than trauma the common precipitating factors are environmental agents like humidity & wind[6,7,8,9], corticosteroids(topical) and the use of contact lenses[10,11,12]

Among the antifungals Natamycin , a polyene available in 5% suspension has been the choice of therapy against filamentous fungi causing corneal infections. The mode of action of Natamycin is that it binds fungal cell membrane and brings about a change in the cell membrane permeability which leads to release of essential cellular components.This cause fungal destruction and so forth are Fungicidal[13].

Another antifungal is Fluconazole a bistriazole Oral (200 mg/day) used in reconstituted form topically 12% solution has disadvantage of less efficacy against filamentous fungi. In this Fungistatic group Fluconazole is an alternative to ketoconazole which destroys the cell membrane of fungus by preventing conversion of Lanosterol to Ergosterol[14].

Finally another available option to treat Fungal Keratitis is Amphotericin B. For ocular use it is reconstituted in 0.1 -0.25%. It has the characteristics of both Fungistatic and Fungicidal. The mode of action of this drug is that it binds sterols of fungal cell membrane causing leakage of cellular components and therefore cell death. Amphotericin B has been found to be active against yeast like candida. The main disadvantage is irritation to eye as used in topical reconstituted form as well as has to be protected from light and heat[15].

The prognosis of corneal infection secondary to Fungi varies according to the characteristic of antifungal agent, infectious and inflammatory reactions of the host and the most important predisposing factors that can alter the fate of the ulcer.

MATERIAL & METHODS:

It was a prospective randomized control study that was carried out simultaneously at Peoples University of medical and health sciences Hospital Nawabshah and Ghulam Muhammad Mehar Medical college Sukkhur. A total of 150 patients were registered in the study. Out of 150 patients 97 were males and 53 were females. The range of age of patients included in the study were from 5 years to 80 years. The time period of the study was one year i-e from October 2013 to October 2014. The diagnosis was based on clinical presentation of fungal corneal ulcer as well as laboratory proof of positive KOH preparation done for the scrapings of the ulcer. The scrapings were taken in sterilized OT existing in the department and slides were examined by one of the researcher for KOH stain. Only positive cases were included in the study.

Patients were subdivided into three groups randomly by lottery method. Group A (50 patients) were given Topical Natamycin 5%, Group B (50 patients) were given Topical reconstituted Fluconazole 1%, and Group C(50 patients) were given Topical reconstituted Amphotericin B 0.15%. Written informed consent was taken from all the patients.

The patients were followed for 12 weeks i-e weekly in first month and than twice a month. Mean of determination of main outcome was measurement of the efficacy for each medication. Biomicroscopic signs that that were standardized to evaluate efficacy were:

* Blunting of the perimeters of the infiltrate
* Reduction of the density of the suppuration
* Reduction in cellular infiltrate and edema in the surrounding stroma
* Reduction in anterior chamber inflammation
* Progressive re-epithelization
* Loss of the feathery perimeter of the stromal inflammation.

The main confounding variable was superadded bacterial keratitis which was excluded from the study by laboratory investigations like gram staining. Patients with other ocular comorbidities, ulcerative corneal perforation & endophthalmitis were excluded from the study. No side effect was observed of such severity to withdraw the medication during study. The results were measured on SPSS version 22 for statistical analysis while for data analysis the significant p value was set less than or equal to 0.05.

Results:

Among the 150 cases selected for the study The following causative or predisposing factor were found for the fungal ulcers:

a) Injuries or foreign bodies of organic nature ----------70
b) Metallic foreign bodies ----------10
c) Prolonged (one and a half months) use of topical antibiotics ----------15
d) Prolonged (Four weeks) use of steroids----20
e) Predisposed due to diabetes ----------35

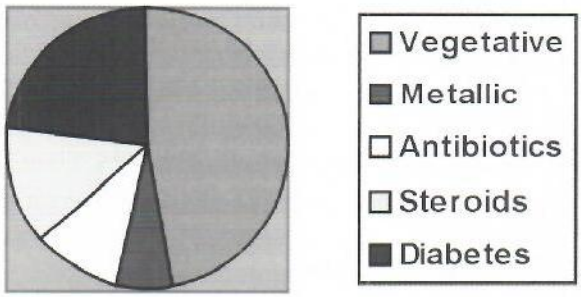

Fig. 1: Predisposing factors for fungal ulcer

Clinical course of Group A (Natamycin 5%) at 12 weeks:

a) 44(88%) healed without any consequence
b) 6 (12%)did not respond and went into complications

Clinical course of Group B (Fluconazole 1% topical) at 12 weeks

a) 38(76%) healed without any consequence
b) 12(24%) did not respond and went into complications

Clinical course of Group C (Amphotericin B 0.15%) at 12 weeks

a) 18 (36%) healed without any consequence
b) 32 (64%) did not respond and went into complications

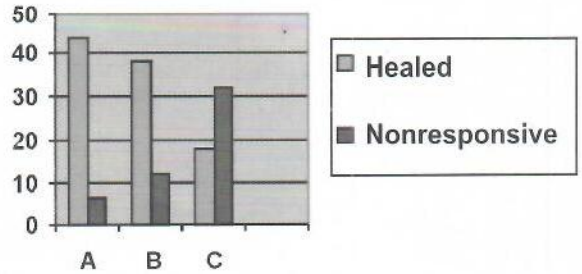

Fig.2: Clinical course of 3 groups

DISCUSSION:

The prevalence of Fungal keratitis among all other causes accounts for 10-15% in developing countries while 5 % in developed countries[16]. The reason for more prevalence in former is vegetative trauma being more common over there.The main drawback in the management of fungal corneal ulcer is it's nonspecific and indulant presentation. One also has to consider other comorbids to treat in order to have a good response from antifungal therapy.

The clinical presentations of filamentous fungi include:

* Irregular grayish white ulcer that has delicate filamentous or feathery edges.
* Superficial lesion may appear as grayish white ulcer elevating the surface of the cornea.
* Deeper lesion often associated with endothelial plaque and hypopyon.[9]
* Multifocal grayish white satellite lesions may be present[10].

Species of filamentous fungi react differently[17], Fusarium being lethal usually lead to deeper extension and therefore perforation within weeks[18].Aspergillus on the other hand causes less severe and slowly progressive keratitis.

Fungal keratitis caused by yeasts like candida is characterized by yellow white infiltration associated with dense suppuration[19].

An important factor in the progression of fungal keratitis is the self destruction of the corneal tissue because of the proteinases released by the inflammatory cells[20]. Deeper fungal infiltrations as well as prior use of corticosteroids are the reasons to explain less responsive mycotic keratitis to antifungal therapy[21].

Unfortunately no recent advancement or revolutionary change has been made in the treatment of Fungal keratitis. The existing antifungals are still unable to eliminate the fungal keratitis completely which have led to end up in surgical intervention in 15-27% of cases[18].

In these circumstances associated with high prevalence of fungal keratitis in our area of rural sindh, it deemed necessary to conduct a study which would help in establishing guidelines for

Table-1: Comparison of Studies for Different Antifungal Efficacy

RCT	Antifungal Treatment	Total Cases	Efficacy Evaluation	Final Outcome
Prajna 2003[27]	Topical econazole 2% vs Topical Natamycin 5%	112	Clinical response by healing of ulcer	No difference
Kalavathy 2005[24]	Topical Itraconazole 1% Natamycin 5%	100	Clinical response by healing of ulcer	No difference overall but Natamycin superior in Fusarium
Mahdy 2010[28]	Topical Amphotericin B 0.05% + subconjunctival injection Fluconazole 0.2% vs Topical Amphotericin 0.05%	48	Clinical response by healing of ulcer	Combination therapy superior to monotherapy
Prajna 2010[29]	Topical Voriconazole 1% vs Topical Natamycin 5%	120	Time to re-epithelialization	No difference
Arora 2010[30]	Topical Vorconazole 1% vs Topical Natamycin 5%	30	Clinical response by healing of ulcer	No significant difference

ophthalmologists to treat the disorder. Our study was unique in the sense that the therapeutic topical agents which we have used for comparison in grouping have not been studied with the same combination earlier.As a result our study proved that Natamycin 5% is still the choice of antifungal followed by reconstituted Fluconazole 1% and Amphotericin B 0.15%.This also proves that filamentous fungi are causing more cases of Fungal keratitis as compared to nonfilamentous fungi in this part of the world.Our study was comparable to another which was carried out in Asian countries and also proved that Natamycin is superior to Fluconazole, Voriconazole and Amphotericin B regarding treatment of Fusarium Keratitis[22]. Another study in 1992 by the Corneal association of United states, Asia, South America, Europe and Australia reported Natamycin being most commonly used antifungal agent followed by Amphotericin B and voriconazole[23].The healing rate of Topical Natamycin 5%, Fluconazole 1% and Amphotericin B 0.15% had been evaluated separately in the past with the results of 79%[24], 75%[25] and 46.7%[26] repectively which are comparable to our study results.

CONCLUSION:

Despite the fact that overuse of antibiotics is making the corneal ulcers further difficult to treat, emphasis should be to start treatment regimen according to micro organisim identified. Fungal ulcers themself being difficult to treat need a selection of most effective antifungal drug available for management. Our study have proven that Topical Natamycin 5% is still the most efficacious antifungal available for our community related fungal corneal ulcers.

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