Original Research Article

A comparative assessment of voriconazole vs natamycin in treatment of mycotic corneal ulcer

Namita Bariha[1*], B N R Subudhi[2]

[1]IIIrd Year Post Graduate Student, [2]HOD and Professor, Department of Ophthalmology, MKCG Medical College, Berhampur, Odisha, INDIA.
Email: namita433@gmail.com

Abstract

Background: Mycotic corneal ulcer is endemic in tropical regions accounting for as many as half of corneal ulcers. Management of fungal keratitis requires timely diagnosis of the infection and administration of appropriate antifungal therapy. Antifungal agents are still the major therapeutic options in fungal keratitis, whereby success depends on the agent's ability to penetrate into the aqueous and achieve therapeutic levels. **Aims and Objectives:** To evaluate the efficacy and safety of topical ophthalmic solution Voriconazole (1%) and Natamycin (5%) ophthalmic suspension in treatment of mycotic corneal ulcer and its comparison. **Materials and Method:** Study was carried out in the Department of Ophthalmology, M.K.C.G. Medical College and Hospital, Berhampur, Odisha from October 2014 to september 2016. Study included 40 patients with fungal kertitis at M.K.C.G. Hospital in India who were randomized to receive either topical natamycin or topical voriconazole. The mean size of corneal ulcer,depth of infiltrate and visual acuity were comparable in both groups. **Results:** The improvement in signs like size of corneal ulcer, depth of infiltrate and visual acuity was 60%, 80%, 75% in natamycin group and 50%, 60%, 55% in voriconazole group at 1week follow-up. **Conclusion:** Topical 1% voriconazole was found to be safe and effective drug in primary management of fungal keratitis, its efficacy matching conventional topical 5% natamycin. There was no extra advantage of using topical 1% voriconazole over topical natamycin 5% as primary treatment in fungal keratitis and can be used as a reserve drug in case of failure of conventional therapy. Hence, the results of our study showed efficacy of both natamycin and voriconazole in treatment of fungal keratitis with no added advantage over natamycin.

Key Words: Mycotic corneal ulcer, Voriconazole, Natamycin.

[*]**Address for Correspondence:**
Dr. Namita Bariha, Kuluthkani, Dhanupali Sambalpur Odisha -768005, INDIA.
Email: namita433@gmail.com
Received Date: 06/05/2017 Revised Date: 12/06/2017 Accepted Date: 08/07/2017
DOI: https://doi.org/10.26611/1009315

Access this article online	
Quick Response Code:	Website: www.medpulse.in
	Accessed Date: 12 July 2017

INTRODUCTION

Corneal ulcer is a leading cause of monocular vision loss worldwide. As much as 50% of corneal ulcers are proven to be of fungal etiology in developing countries.[1]Mycotic corneal ulcers are typically seen after injury with vegetable matter such as a thorn or wooden stick and are characterized by a relatively indolent course. Symptoms are much milder than the clinical signs. Mycotic corneal ulcers can be more difficult to treat than bacterial corneal ulcers with worse outcomes.[2] The management consists of medical in the form of topical or systemic antifungal agents or surgical in the form of therapeutic penetrating keratoplasty.[3]Natamycin, the only FDA-approved agent for the treatment of fungal keratitis, is a fungicidal tetraene polyene antibiotic, derived from Streptomyces natalensis that possesses in vitro activity against a variety of yeast and filamentous fungi, including Candida, Aspergillus, Cephalosporium, Fusarium and Penicillium species.[4]Voriconazole is a new broad spectrum antifungal agent that is effective against yeasts and molds.[5] The current study is intended to compare the efficacy of topical 1% voriconazole ophthalmic solutions with 5% natamycin ophthalmic suspension in treatment of mycotic corneal ulcer patients.

MATERIALS AND METHOD

The present study was carried out in the department of Ophthalmology MKCG Medical College Hospital,

Berhampur from October 2014 to September 2016. During the study, cases were selected from the patients attending the Outpatient Department, Department of Ophthalmology, M.K.C.G. Medical College, Berhampur, Odisha. Total 40 patients who fulfilled the inclusion criteria were studied.

Inclusion Criteria

1. All patients attending the Outpatient Department of Department of Ophthalmology, M.K.C.G. Medical College and Hospital, Berhampur, Odisha who were diagnosed as case of mycotic corneal ulcer.
2. Patients of both sexes above the age of 16 years.
3. Patients giving consent for ocular examination.

Exclusion Criteria

1. Patients with impending perforation.
2. Patients with history of corneal scar in affected eye.
3. Patients with previous keratoplasty in affected eye.
4. Patients with known allergy to study medications.
5. Patients with history of pregnancy or breast feeding.
6. Patients with total corneal ulcers.
7. Patients with no light perception in affected eye.

A detailed history of any systemic disease or local predisposing factors like trauma, contact lens use and usage of topical steroids was taken. A detailed clinical examination was carried out including visual acuity, measurements of the size of corneal ulcer, stromal infiltrate, hypopyon and examination of ocular adnexa. Intraocular pressure was assessed digitally. Corneal scraping was performed for every patient after instillation of local anaesthetic (Xylocaine 4%) agent. Either a blunt Kimura's spatula or a sterile no. 11 surgical blade was used to perform scraping and the material taken both from the base as well as the edges of the ulcer. The material thus obtained from scraping was used for direct microscopic examination using Gram's stain and 10% KOH mount and also inoculated into Sabouraud dextrose agar and brain heart infusion broth for transportation to our referral laboratory for culture and identification of species by standard microbiological procedures. Among the study medications, 5% natamycin topical formulation available commercially was used, and topical 1% VRC eye drops were prepared by reconstituting sterile lyophilized powder available as 30 mg vials with 3ml of sterile water for injection to make 1% solution of voriconazole. The treatment comprising of either 5% natamycin or 1% Voriconazole eye drop was instituted. One drop of randomized medication was applied 1 hourly to the affected eye at least till 2 weeks. The treatment regimen was strictly monitored, and the patients were admitted in the hospital. Further dosage titrated according to the patient's response. All the parameters including visual acuity, corneal infiltrate, corneal ulcer size were recorded during the follow up. Standard follow-up visits were taken as after 1, 2, 4 and 8 weeks for statistical analysis. The efficacy of two drugs were compared based on Visual acuity by Snellen's chart, regression of size of corneal ulcer and infiltrate by using slit lamp examination. Ocular examination included visual acuity testing on Snellen's chart, corneal ulcer size, corneal infilterates were all graded according to scoring system. Grades of corneal ulcer size :Grade 0:less than 0.5mm, Grade 1:0.5-1mm, Grade 2:>1-2mm,Grade 3:2-5mm,Grade 4:>5mm. Grades of corneal infilterates : Grade 0; no infilterates, Grade 1; only up to epithelial surface, Grade 2; infilterates may be dense but superficial and limited to ulcer base, Grade 3; dense infilterates extending to mid stroma, Grade 4; dense infilterates extending deeper than mid stroma or up to sclera. Grades of visual acuity : Grade 0 ; Normal, Grade1; 6/6-6/18, Grade 2; 6/24-6/60 Grade 3; < 6/60-3/60,Grade 4;< 3/60.

Statistical Analysis

The collected data were entered and analyzed by using the SPSS(Statistical Presentation System Software) version 21.The level of statistical significance was $p< 0.05$. Pearson Chi square test was used as the test of significance. Standard follow up visits were taken as after 1 week, 2 weeks, 4 weeks and 8 weeks for statistical analysis.

OBSERVATIONS AND RESULTS

Signs of 40 patients were assessed on day 0(presentation) and at 1 week, 2 weeks, 4weeks, 8 weeks. Symptoms were excluded from analysis because of symptoms are much milder than the clinical signs.

Table 1: Corneal ulcer size score at day 0 (Presentation)

Drug	Corneal ulcer size Score				
	0	1	2	3	4
Group -A Natamycin (n=20)	---	---	02(10%)	15(75%)	3(15%)
Group-B Voriconazole(n=20)	---	---	03(15%)	13(65%)	4(20%)

In present study table-1 shows that at presentation,75% patients in group A and 65% patients in group B had grade 3 size of corneal ulcer, while grade 2 size of corneal ulcers were present in 10% patients of group A and 15% patients of group B. 15% patients in group A and 20% patients in group B had grade 4 size of corneal ulcer and it was comparable in both the groups p-value being >0.05.

Table 2: Corneal ulcer size score at 1 weeks

Drug	Corneal ulcer size Score				
	0	1	2	3	4
Group -A Natamycin(n=20)	---	04(20%)	04 (20%)	12(60%)	---
Group-B Voriconazole(n=20)	---	03(15%)	07(35%)	10(50%)	---

In present study table-2 shows that after 1 week, 60% patient in group A and 50% in group B had grade 3 size of corneal ulcer, while grade 2 size of corneal ulcers were present in 20% patients of group A and 35% patients of group B. 20% patient in group A and 15% in group B had grade 1 size of corneal ulcer and no patient had grade 4 size of corneal ulcer

The difference was statistically not significant (p=0.565).

Table 3: Corneal ulcer size score at 2 weeks

Drug	Corneal ulcer size Score				
	0	1	2	3	4
Group -A Natamycin(n=20)	---	04(20%)	16 (80%)	---	---
Group-B Voriconazole(n=20)	---	03(15%)	17(85%)	---	---

In present study table-3 shows that at 2weeks, 80% patient in group A and 85% in group B had grade 2 size of corneal ulcer, while grade 1 size of corneal ulcers were present in 20% patients of group A and 15% patients of group B and no patient had grade 3 and 4 size of corneal ulcer. The difference was statistically not significant (p=0.677).

Table 4: Corneal ulcer size score at 4 weeks

Drug	Corneal ulcer size Score				
	0	1	2	3	4
Group -A Natamycin(n=20)	11(55%)	09(45%)	---	---	---
Group-B (n=20)	08(40%)	12(60%)	---	---	---

In present study above table-4 shows that at 4 weeks, 45 % patient in group A and 60% in group B had grade 1 size of corneal ulcer, while grade 0 size of corneal ulcers were present in 55 % patients of group A and 40% patients of group B and no patient had grade 2, 3 and 4 size of corneal ulcer. The difference was statistically not significant (p=0.342).

Table 5: Corneal ulcer size score at 8 weeks

Drug	Corneal ulcer size Score				
	0	1	2	3	4
Group -A Natamycin(n=20)	16(80%)	04(20%)	---	---	---
Group-B Voriconazole(n=20)	15(75%)	05(25%)	---	---	---

In present study above table-5 shows that at 8 weeks, 20 % patient in group A and 25% in group B had grade 1 size of corneal ulcer, while grade 0 size of corneal ulcers were present in 80% patients of group A and 75% patients of group B and no patient had grade 2, 3 and 4 size of corneal ulcer. The difference was statistically not significant (p=0.705).

Table 6: Corneal infiltrate score at day 0 (Presentation)

Drug	Corneal infiltrate Score				
	0	1	2	3	4
Group -A Natamycin(n=20)	---	---	01(5%)	04(20%)	15(75%)
Group-B Voriconazole(n=20)	---	---	01(5%)	06(30%)	13(65%)

In present study above Table-6 shows that at presentation, 75% patients in group A and 65% patients in group B had grade 4 size of corneal infiltrate, while grade 3 size of corneal infiltrate were present in 20% patients of group A and 30% patients of group B. 15% patients in group A and 15% patients in group B had grade 2 size of cornel infiltrate and it was comparable in both the groups p-value being >0.05.

Table 7: Corneal infiltrate score at 1 weeks

Drug	Corneal infiltrate Score				
	0	1	2	3	4
Group -A Natamycin(n=20)	---	---	01(5 %)	16(80%)	03(15%)
Group-B Voriconazole(n=20)	---	---	01(5 %)	12(60%)	07(35%)

In present study above Table-7 shows that at 1 week, 15% patients in group A and 35% patients in group B had grade 4 size of corneal infiltrate, while grade 3 size of corneal infiltrate were present in 80% patients of group A and 60% patients of group B. 15% patients in group A and 15% patients in group B had grade 2 size of cornel infiltrate. The difference was statistically not significant (p=0.338).

Table 8: Corneal infiltrate score at 2 weeks

Drug	Corneal infiltrate Score				
	0	1	2	3	4
Group -A Natamycin(n=20)	---	04(20%)	13(65%)	03(15 %)	---
Group-B Voriconazole(n=20)	---	02(10%)	11(55%)	07(35 %)	---

In present study above table-8 shows that at 2 weeks, 15% patients in group A and 35% patients in group B had grade 3 size of corneal infiltrate, while grade 2 size of corneal infiltrate were present in 65% patients of group A and 55% patients of group B. 20% patients in group A and 10% patients in group B had grade 1 size of cornel infiltrate. The difference was statistically not significant (p=0.296).

Table 9: Corneal infiltrate score at 4 weeks

Drug	Corneal infiltrate Score				
	0	1	2	3	4
Group -A Natamycin (n=20)	06(30%)	11(55%)	03(15%)	---	---
Group-B Voriconazole(n=20)	08(40%)	08(40%)	04(20%)	---	---

In present study above Table-9 shows that at 4 weeks, 15% patients in group A and 20% patients in group B had grade 2 size of corneal infiltrate, while grade 1 size of corneal infiltrate were present in 55% patients of group A and 40% patients of group B. 30% patients in group A and 40% patients in group B had grade 0 size of cornel infiltrate. The difference was statistically not significant (p=0.637).

Table 10: Corneal infiltrate score at 8 weeks

Drug	Corneal infiltrate Score				
	0	1	2	3	4
Natamycin (n=20)	11(55%)	09(45%)	0(0%)	---	---
Voriconazole (n=20)	09(45%)	10(50%)	01(5%)	---	---

In present study above table-10 shows that at 8 weeks, grade 1 size of corneal infiltrate were present in 45% patients of group A and 50% patients of group B. 55% patients in group A and 45% patients in group B had grade 0 size of cornel infiltrate. The difference was statistically not significant (p=0.535).

DISCUSSION

Mycotic corneal ulcer is a leading cause of avoidable blindness in developing nations. It is second to cataract as the commonest cause of visual debility in the world today. Corneal infection of fungal etiology are common and represent 30-40% of all cases of culture-positive infectious keratitis in india. The major predisposing facto for mycotic corneal ulcer has been trauma and contact lens use. Trauma has been reported to be associated with 55-65% of mycotic corneal ulcers.[6] In the present study 30 cases (75%) out of 40 had history of trauma with vegetative matter to the eye, after that followed by 6 cases(15%) had history of trauma with animal tail. Mycotic corneal ulcer is difficult to treat and carries a significant risk of intraocular involvement. Natamycin has been reported as the most effective medication against Fusarium and Aspergillus.[7] Of the newer antifungal agents Voriconazole has been reported as a highly potent triazole with 100% in vitro susceptibility against common ocular fungal pathogens compared with only 60–84% for fluconazole, itraconazole, amphotericin B and ketoconazole.[8] The current study is intended to compare the efficacy of topical 1% voriconazole ophthalmic solutions with 5% natamycin ophthalmic suspension in treatment of mycotic corneal ulcer patients. In the present study on comparing the efficacy of topical 1% voriconazole with that of topical 5% natamycin with comparable drug frequencing improvement in signs like size of corneal ulcer, depth of infiltrate and visual acuity was 60%,80%,75% in natamycin group and 50%,60%,55% in voriconazole group at 1week follow-up but the difference was statistically not significant. Efficacy of both the drugs as a primary treatment in fungal keratitis is being thereby comparable. Similarly in 2011, Ritu Arora *et al* reported that improvement in signs like size of corneal ulcer, depth of infiltrate and visual acuity corneal infiltrate size was statistically not significant (p>0.05).[9] Same was also reported in 2016, Ishank Gupta,V.K. Malik randomised two groups of 25 patients received 1% voriconazole and other 5% natamycin and observed that improvement in signs like size of corneal ulcer, depth of infiltrate and visual acuity corneal infiltrate size was statistically not significant (p=0.94).[10]

CONCLUSION

The diagnosis and treatment of fungal keratitis can be quite challenging. Information derived from the microbiology laboratory is required to make a correct diagnosis. Prolonged medical treatment and prompt timing of surgical intervention are required to increase the chances of a cure. Topical 1% voriconazole was found to be safe and effective drug in primary management of fungal keratitis, its efficacy matching conventional topical 5% natamycin. There was no extra advantage of using topical 1% voriconazole over topical natamycin 5% as primary treatment in fungal keratitis and can be used as a reserve drug in case of failure of conventional therapy. Hence, the results of our study showed efficacy of both natamycin and voriconazole in treatment of fungal keratitis with no added advantage over natamycin.

REFERENCES

1. Chander J, Sharma A. Prevalence of fungal corneal ulcers in northern India. Infection. 1994;22:207-9
2. Wong TY, Ng TP, Fong KS, Tan DT. Risk factors and clinical outcomes between fungal and bacterial keratitis: a comparative study. CLAO J. 1997;23(4):275–281
3. Eudardo C, Alphonso, Robert H, Rosa, Darlene miller. Fungal keratitis. Krachmer; 86:1101 – 13
4. O'Day DM. Selection of appropriate antifungal therapy. Cornea 1987; 6: 238-45
5. Lalitha P. Shapiro BL, Srinivasan M, Prajna NV, Acharya NR et al. Antimicrobial susceptibility of Fusarium, Aspergillus, and other filamentous fungi isolated from keratitis. Arch Ophthalmol. Jun 2007; 125(6):789-93.
6. Bharathi MJ, Ramakrishnan R, Vasu S et al. Epidemiological characteristics and laboratory diagnosis

of fungal keratitis: a three-year study. Indian J Ophthalmol 2003; 51: 315–21.
7. Srinivasan M. Fungal keratitis. Curr Opin Ophthalmol. 2004;15(4):321–327
8. Bunya VY, Hammersmith KM, Rapuano CJ, Ayres BD, Cohen EJ. Topical and oral voriconazole in treatment of fungal keratitis. Am J Ophthalmol 2007; 143: 151– 3
9. Arora, Ritu, et al. "Voriconazole versus natamycin as primary treatment in fungal corneal ulcers." Clinical and experimental ophthalmology 39.5 (2011): 434-440.
10. Dr. Ishank gupta, dr. V.k. malik, dr. K.p.s.malik natamycin vs voriconazole in the treatment of mycotic corneal ulcers indian journal of applied research, vol.6, issue : 6 june 2016.

Source of Support: None Declared
Conflict of Interest: None Declared