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Original Research Article

Comparison of 5% Natamycin and 1% Voriconazole in Fungal Corneal Ulcer Patients

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Abstract:

Background: Globally infectious keratitis is a major cause of blindness. Fungal infections account for a significant proportion of corneal ulcers. These cases are often challenging and difficult to treat and cause significant visual impairment**.**

Objective: To compare the efficacy of 5% Natamycin and 1% Voriconazole in fungal corneal ulcer patients.

Study Design: Randomized Controlled Trial.

Methods: 40 patients were included in the study. Group A patients having corneal ulcer were treated with 5% Natamycin and Group B patients having corneal ulcer were treated with 1% Voriconazole.

Results: Baseline mean infiltrate size in Natamycin group was 4.375 mm and in Voriconazole group was 3.925 mm. There was no statistically significant difference between the two groups at baseline. Average time of resolution was 27.3 days in Natamycin group and 30.8 days in Voriconazole group. This difference was statistically significant ($p = 0.034$). Incidence of perforation was more in Voriconazole group, which was statistically significant.

Conclusion: Average time of resolution was lesser in Natamycin group compared to Voriconazole group. Incidence of perforation was more in Voriconazole group as compared to Natamycin.

Keywords: Natamycin, Voriconazole, Corneal Ulcer.

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Introduction

Corneal ulcer is defined as loss of corneal epithelium with underlying stromal infiltrate and suppuration associated with signs of inflammation, with or without hypopyon. [1]

Blindness continues to be one of the major public health problems in developing countries. Cataract and corneal diseases are major causes of blindness in countries with less-developed economies. [2] According to the World Health Organization, corneal diseases are among the major causes of vision loss and blindness in the world today, after cataract and glaucoma. In India, it is estimated that there are approximately 6.8 million people who have vision less than 6/60 in at least one eye due to corneal diseases; of these, about a million have bilateral involvement. [2] According to National Programme for Control of Blindness survey, corneal blindness accounts for 0.9% of total blindness. [2]

The 2005–2006 Fusarium keratitis outbreak associated with contact lens wear occurred in the United States, Europe, and Asia, and this outbreak heightened the concern about how to give best care to these patients.[3] Symptoms are less in fungal keratitis as compared to bacterial keratitis so the presentation is delayed, also the treatment duration is longer. Various newer antifungal drugs have been proposed, e.g. Voriconazole, Caspofungin,[4] Posaconazole. Excellent results have been reported following off-label use in keratitis caused by Candida spp., Aspergillus spp.,[5] Scedosporium apiospermum, Paecilomyces and Fusarium.

MIC of Voriconazole is lowest of all azoles and it is reported to be effective in recalcitrant cases.[6] It achieves variable but adequate aqueous humour concentrations when used topically.[7] The superior in vitro susceptibility profile and increased penetration of Voriconazole compared with

Natamycin could be an advantage, particularly for corneal ulcers deep in the stroma. [8-11]

In vitro results and case reports may hypothesise, but they are insufficient to answer the question: which drug should be used in patients with fungal keratitis

Based on the above premise, a comparative study was undertaken to evaluate the therapeutic efficacy and safety of topical 5% Natamycin versus topical 1% Voriconazole in the management of microbiologically proven fungal corneal ulcer in a tertiary care ophthalmology centre.

Methods

Study Design: Randomized Controlled Trial.

Study Area: Department of Ophthalmology, Tertiary care centre of north India.

Study Population: Patients attending cornea clinic diagnosed with fungal corneal ulcer.

Sample Size: All patients meeting inclusion criteria during data collection period.

Sampling Technique: Randomly assigned by computer-generated numbers to two groups — one receiving 5% Natamycin and other receiving 1% Voriconazole.

Inclusion Criteria

- All diagnosed cases of fungal corneal ulcer.
- Patients willing to return for follow-up visits.
- Patients providing appropriate consent per Helsinki declaration.

Exclusion Criteria

- Subjects with any corneal dystrophy.
- Subjects with total corneal ulcers.
- Subjects with impending perforation or corneal perforation.
- Subjects with history of corneal scar in affected eye.
- Subjects with evidence of herpetic keratitis.
- Subjects with no light perception in affected eye.
- Monocular patients.
- Patients unable or unwilling to follow up.

Ocular Examination

- Diffuse light examination for gross lesion of lid, conjunctiva, cornea.
- Regurgitation test to rule out lacrimal sac infection.
- Slit lamp examination: fluorescein staining to note size, shape, depth, margin, floor of ulcer.
- Presence of keratic precipitates, depth of anterior chamber, condition of lens and iris.
- Corneal sensation assessment.

Material for investigation was obtained by scraping of base and margin of corneal ulcer under topical anaesthesia by Kimura spatula or 26G½ gauge needle. Material was used for:

1. Gram and Giemsa staining for possible identification of organism.
2. 10% KOH wet preparation for identification of fungal hyphae.
3. Culture on Sabouraud's Dextrose Agar.

Efficacy Assessment — The Drugs were Compared Based on:

- Symptomatic relief, decrease in size of ulcer, decrease in hypopyon and regression of infiltrate by slit lamp examination.
- Fluorescein staining study to look for ulcer size.
- Best corrected visual acuity (BCVA) by Snellen's chart on 2nd day, 7th day, 2 weeks, 1 month and 2 months from enrolment.

Data Analysis: The data gathered was analysed using appropriate statistical methods and software.

Results

Table 1: Baseline Clinical Characteristics

Characteristic	NTM (n=20)	VCZ (n=20)	Total (n=40)	P value
Visual acuity (logMAR)	0.8–2.5	0.6–2.5	0.6–2.5	0.65
Infiltrate size (mm)	3–6.5	3–6	3–6.5	0.45
Hypopyon	09	08	17	0.60
Dacryocystitis	0	0	0	>0.99
Lid/lash abnormalities	02	03	05	0.77
Systemic diseases	06	05	11	0.83

Baseline characteristics were similar in both groups with no statistically significant difference ($P > 0.05$ for all parameters).

Table 2: Comparison of Visual Acuity at 2 Weeks

Drug	Eyes	Baseline Mean VA (logMAR)	Treatment Mean VA (logMAR)	Change VA	% Change
NTM (n=20)	20	1.41 (0.69)	1.32 (0.55)	0.09	6.38
VCZ (n=20)	20	1.46 (0.65)	1.37 (0.56)	0.09	6.16

At end of 2 weeks, improvement in Natamycin group (6.38%) was slightly more than Voriconazole group (6.16%). The difference was not statistically significant.

Table 3: Comparison of Visual Acuity at 2 Months

Drug	Eyes	Baseline Mean VA (logMAR)	Treatment Mean VA (logMAR)	Change VA	% Change
NTM (n=20)	20	1.41 (0.69)	1.23 (0.54)	0.18	12.71
VCZ (n=20)	20	1.46 (0.65)	1.29 (0.58)	0.17	11.64

At end of 2 months, improvement in Natamycin group (12.71%) was more than Voriconazole group (11.64%). This difference was statistically insignificant.

Table 4: Comparison Of Visual Acuity At 2 Months

Drug	Eyes	Baseline Mean VA (logMAR)	Treatment Mean VA (logMAR)	Change VA	% Change
NTM (n=20)	20	1.41 (0.69)	1.23 (0.54)	0.18	12.71
VCZ (n=20)	20	1.46 (0.65)	1.29 (0.58)	0.17	11.64

At end of 2 months, improvement in Natamycin group (12.71%) was more than Voriconazole group (11.64%). This difference was statistically insignificant.

Table 5: Statistical Significance — Infiltrate Size

Duration	Natamycin Change in Infiltrate	Voriconazole Change in Infiltrate	T Value	P Value
2 weeks	–0.237	–0.250	–0.751	0.652
2 months	–0.690	–0.600	–0.615	0.546

On comparison, reduction of infiltrate/scar size was statistically insignificant in both groups at all durations.

Table 6: Type Of Fungal Isolate

Organism	No. of Patients	Percentage
Aspergillus fumigatus	7	17.5%
Aspergillus flavus	5	12.5%
Aspergillus niger	2	5%
Candida	1	2.5%
Fusarium	9	22.5%
No organism isolated	16	40%

Out of 40 patients: 7 (17.5%) had Aspergillus fumigatus, 5 (12.5%) had A. flavus, 2 (5%) A. niger, 1 (2.5%) Candida, 9 (22.5%) Fusarium. In 16 (40%) cases no organism was isolated. Overall Aspergillus 14 (35%) was the most common organism isolated.

Table 7: Time of Resolution

Group	No. of Days
Natamycin	27.3
Voriconazole	30.8

Average time of resolution was 27.3 days in Natamycin group and 30.8 days in Voriconazole group. This difference was statistically significant ($p = 0.034$).

Table 8: Comparison of Perforation

Group	No. of Patients with Perforation
Natamycin	2
Voriconazole	4

Number of cases of perforation in Voriconazole group (4) was more than in Natamycin group (2). This difference was statistically significant ($p = 0.023$).

Discussion

Age Distribution: The patients were divided into 4 groups: <20 years, 21–40 years, 41–60 years, >60

years. 23 (57.5%) cases belonged to 41–60 years of age group. 2 (5%) cases were in age group less than 20 years.

Sex Distribution: Out of 40 patients, 25 (62.5%) were males and 15 (37.5%) were females. Males had predominance, with M:F ratio of 1.6:1. This is because males are more commonly involved in outdoor agricultural activities, exposing them to vegetative trauma to the eye.

Type of Fungal Isolate: In our study: 9 (22.5%) had Fusarium spp., 7 (17.5%) had A. fumigatus, 5 (12.5%) had A. flavus, 2 (5%) had A. niger and 1 (2.5%) had Candida. In 16 (40%) cases no organism was isolated. Overall Aspergillus 14 (35%) was the most common organism isolated.

Visual Acuity and Infiltrate / Scar Size: In our study, baseline mean VA in Natamycin group was 1.41 (0.69) and in Voriconazole group was 1.46 (0.65). Baseline mean infiltrate size in NTM group was 4.375 mm and in VCZ group was 3.925 mm. There was no statistically significant difference between the two groups at baseline.

Time of Resolution: Average time of resolution was 27.3 days in Natamycin group and 30.8 days in Voriconazole group. This difference was statistically significant ($p = 0.034$), favouring Natamycin.

Non-Responding Cases: Total 9 ulcers did not improve — 4 in Natamycin group and 5 in Voriconazole group. Intrastromal voriconazole and topical amphotericin B were tried in these cases. 3 cases resolved and in 6 cases perforation occurred, requiring therapeutic keratoplasty. 2 perforations were in Natamycin group and 4 in Voriconazole group. Incidence of perforation was more in Voriconazole group, which was statistically significant.

After the intervention, a faster reduction in the size of corneal infiltration was documented and complete resolution of the ulcers was seen within three weeks in all cases. Targeted delivery of voriconazole by intracorneal injection may be a safe and effective way to treat cases of deep-seated recalcitrant fungal keratitis responding poorly to conventional therapy.

In summary, our study demonstrates that both 5% Natamycin and 1% Voriconazole show comparable efficacy in terms of visual acuity improvement and infiltrate reduction. However, Natamycin showed a statistically significant advantage in terms of time of resolution (27.3 vs 30.8 days, $p = 0.034$) and lower incidence of perforation (2 vs 4 cases, $p = 0.023$).

The higher perforation rate in the Voriconazole group may be attributable to its relatively lower efficacy against Fusarium species, which was the second most common organism isolated in our study. Aspergillus species, for which both drugs show comparable MICs, were the most common isolates overall.

The lack of organism isolation in 40% of cases is a limitation of culture-based diagnosis and may reflect prior antibiotic treatment, suboptimal specimen collection, or fastidious growth requirements of certain fungi. Despite this, all patients were managed as presumed fungal keratitis based on clinical criteria.

Both study groups were well-matched at baseline for age, sex, visual acuity, infiltrate size, presence of hypopyon, and associated systemic conditions. This ensures that the observed differences in outcomes are attributable to the study drugs rather than confounding factors.

The double-masked randomization of patients to treatment groups minimises selection bias and observer bias in outcome assessment. However, the relatively small sample size of 20 patients per group limits the statistical power to detect small differences between treatment groups.

Further prospective randomized controlled trials with larger sample sizes, including organism-specific subgroup analyses, would be valuable to definitively establish the comparative efficacy of Natamycin and Voriconazole in different types of fungal keratitis.

Conclusion

In our study the most common age group affected was 41–60 yrs. Males were more commonly involved with sex distribution (M:F) 1.5:1. Aspergillus fumigatus was the most commonly isolated fungus. On comparison of visual acuity at end of 2 months, no statistically significant difference was observed between Natamycin and Voriconazole group. No significant difference was seen in infiltrate/scar size between the two groups. Average time of resolution was lesser in Natamycin group compared to Voriconazole group and this difference was statistically significant ($p = 0.034$). Incidence of perforation was more in Voriconazole group as compared to Natamycin which was statistically significant ($p = 0.023$).

Limitations

Since the number of participants in our study is relatively small, it is required to perform further studies to confirm our results with a much larger sample size. Long-term follow-up studies comparing the two drugs in various subtypes of fungal keratitis are also recommended.

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