

EXTENDED REPORT

A randomised clinical trial comparing 2% econazole and 5% natamycin for the treatment of fungal keratitis

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Aim: To compare 2% econazole and 5% natamycin in the management of fungal keratitis.

Methods: A randomised clinical trial was performed using 2% econazole or 5% natamycin as the two treatment arms on patients presenting with culture positive fungal keratitis to the cornea service at Aravind Eye Care System, Madurai, India.

Results: 116 patients were recruited, and 112 continued in the study. There were no significant differences between the two arms at baseline or for success (defined as a healed or healing ulcer) at final visit ($p=0.79$).

Conclusions: 2% Econazole appears to be as effective as 5% natamycin for the management of fungal keratitis.

Corneal scarring, either as a result of trauma or corneal infections, is recognised as a major cause for vision impairment and blindness.^{1–5} There is wide geographical variation in the epidemiological pattern of corneal ulcers across and even within countries.⁶ Recent reports suggest an increasing prevalence for fungal ulcers in developing countries.^{6–8} A previous study reported the incidence of corneal ulcers in Madurai district of southern Tamil Nadu in India to be 113 per 100 000 population (approximately 10 times the incidence reported from the United States).⁹ A study conducted by Srinivasan *et al* reported fungal keratitis as an enormous public health problem in south India.⁶ Fungi, especially *Fusarium* (47%) and *Aspergillus* (16%), were identified as the aetiological agents responsible for 44% of all corneal ulcers in that study.⁶ Previous reports from Ghana⁷ and northern Tanzania⁸ have reported fungi as the aetiological agent in over 50% of culture positive cases of keratitis. The aetiological agent for fungal keratitis may vary within countries—*Fusarium* species is more commonly associated with fungal keratitis in southern India,⁷ while *Aspergillus* species is more often implicated in northern India and adjoining Nepal.¹⁰ Besides *Fusarium* and *Aspergillus*, a large number of demataceous fungi, filamentous fungi, yeasts, and other dimorphic organisms have been implicated as aetiological agents for fungal keratitis. Until recently, only a single drug was available for the management of fungal keratitis in developing countries despite the known potential for vision impairment and blindness associated with fungal keratitis,⁸ and the large number of fungal species identified with keratitis. We designed a randomised clinical trial to compare the efficacy and safety of 2% topical econazole with 5% topical natamycin for the management of fungal keratitis.

METHODS

The patients for this study were recruited from the cornea service of Aravind Eye Care System, Madurai. Each patient with keratitis who presented to the department had a clinical examination using a slit lamp biomicroscope to measure size and depth of ulceration following a detailed clinical and demographic history. Scraping of the corneal ulcer using a Kimura spatula 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 potato dextrose agar. Patients with proved fungal keratitis (smear and culture positive for fungus) with an ulcer area of at least 2 mm² and not more than 60 mm² were identified as potential participants for the study. Patients who were not willing to be part of the study, and who did not meet entry criteria were excluded from the study.

After obtaining necessary informed consent subjects were randomised to receive either 2% econazole or 5% natamycin. Since natamycin is available as a suspension, and precipitates in the corneal tissue, it was not possible to mask the investigator to the drugs used on subsequent visits. All participating subjects were admitted to the wards for a week, and had either 2% econazole or 5% natamycin eye drops instilled on an hourly basis between 7 am and 9 pm. Additionally, 1% atropine sulphate ointment was applied three times per day in the affected eye at least 15 minutes after application of the antifungal eye drops. The clinical investigator examined each subject on a daily basis using a slit lamp biomicroscope, and measured the size and depth of the infiltration.

Subjects were discharged from the hospital at the end of the first week with instructions to instil the eye drops in the affected eye at intervals of 2 hours between 7 am and 9 pm. Each subject was examined at the slit lamp for size and depth of the infiltrate at weekly intervals for up to 4 weeks after entry into the study. Exit criteria from the study were determined as a clinical worsening of the ulcer—if the size and depth of the infiltrate had increased by at least 20% with respect to the previous visit or perforation—or adverse reactions to the drops. Additionally, details of signs including lid oedema, congestion of the conjunctiva, and hypopyon were recorded for each subject. The presence or absence of hypopyon in the anterior chamber was noted, and quantified in millimetres.

We defined a healed corneal ulcer as a completely healed epithelial defect 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 by at least 20%, with non-progression or decrease in the size of the stromal infiltration by at least 20%. A corneal ulcer was considered to remain the same if the size and depth of the infiltrate remained same after initiating treatment. An

ulcer was considered to worsened if the size and depth of the ulcer increased by at least 20%, 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 or remained same at final visit. We analysed the time to event (success) for comparing the efficacy of the two medications, and the influence of the medications on signs including lid oedema, congestion, and hypopyon was taken as the measure to compare safety of the medications. Tests for significance included *t* test to compare the means of continuous variables, Pearson χ^2 and Fisher's exact test for categorical variables, log rank test for the mean of survival rates, and Kaplan-Meier procedure to estimate survival rate at each point of time with a healed or healing ulcer considered as an event.

RESULTS

We recruited and randomised 116 culture positive eyes of 116 patients of fungal keratitis who presented to the cornea clinic from March to October 2002, to either 2% econazole or 5% natamycin. Four of the 116 patients randomised at baseline did not return for further follow up (Fig 1) and were dropped from the study. All these cases were males, and were equally distributed between econazole and natamycin.

The mean age of subjects was 37.0 years (SD 13.8, median 36.0 years, range 7.0–84 years), and 72 (64.3%) were males. Fifty nine (52.7%) subjects were randomised to econazole and 53 (47.3%) to natamycin. There was no difference in age ($p = 0.43$) or sex ($p = 0.70$) between those randomised to receive either econazole or natamycin. There was no significant difference at baseline in either size of epithelial defect ($p = 0.89$), size of infiltrate ($p = 0.95$), or depth of infiltrate ($p = 0.24$) between the two arms of the study. There was no significant difference in lid oedema ($p = 0.22$), congestion ($p = 0.78$), or hypopyon ($p = 1.0$) between the two arms at baseline. Organisms responsible for fungal

keratitis were also not significantly different between the two groups (see Table 1).

There was no significant difference (log rank 0.52, $p = 0.47$) between the two arms for success. There was no significant difference in the time to heal based on baseline size of epithelial defects (log rank 0.82, $p = 0.37$), size of infiltrate (log rank 0.86, $p = 0.35$) or depth of infiltrate (log rank 0.74, $p = 0.39$) between the two arms of the study. There was no difference in the time to subside for signs including lid oedema (log rank 1.05, $p = 0.31$), congestion of the conjunctiva (log rank 0.51, $p = 0.47$) or hypopyon (log rank 0.23, $p = 0.63$) between the two arms. Figure 2 shows the Kaplan-Meier survival curves for the two arms based on time taken to heal in days.

DISCUSSION

Although multiple randomised clinical trials are performed on a regular basis to address bacterial keratitis, there are few randomised clinical trials addressing fungal keratitis.^{11–12} Data from our study suggest that 2% econazole can be used as an alternative to 5% natamycin in the management of fungal keratitis.

The use of imidazoles as antifungal agents has been reported previously.^{13–15} Two small case series have also reported use of econazole as a useful agent in the management of fungal keratitis.^{16–17} Natamycin is currently considered the most effective medication against *Fusarium* and *Aspergillus*,¹⁸ which are responsible for most fungal keratitis, and until recently was the only topical antifungal agent available in India. Previous studies have reported poor outcomes for patients with fungal keratitis with one study reporting evisceration in 25% of patients suggesting that current treatments may not be very effective.⁸

Natamycin binds preferentially to ergosterol on the fungal plasma membrane and causes localised membrane disrupt-

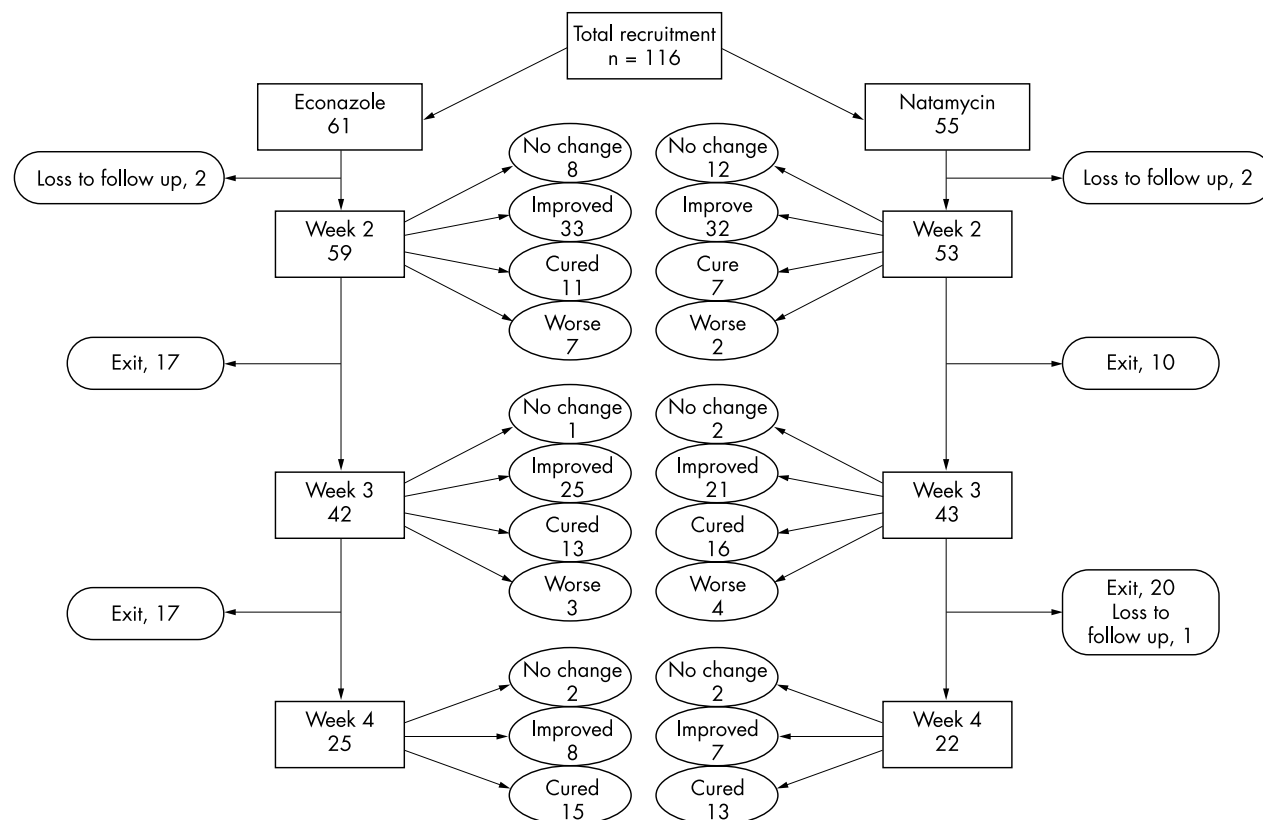
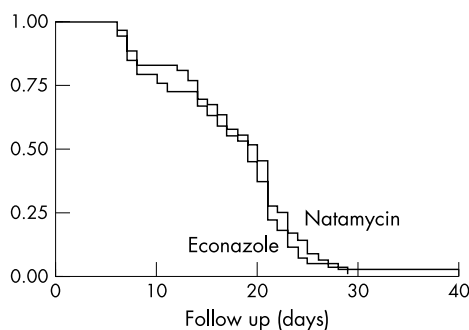


Figure 1 Flow chart of the participation in the study.

Table 1 Aetiological organisms of fungal keratitis by treatment arm

Organism	Econazole	Natamycin	Total
<i>Aspergillus flavus</i>	10 (16.9)	11 (20.7)	21 (18.7)
<i>Aspergillus fumigatus</i>	3 (5.1)	2 (3.8)	5 (4.5)
<i>Aspergillus niger</i>	3 (5.1)	1 (1.9)	4 (3.6)
<i>Cladosporium</i>	1 (1.7)	1 (1.9)	2 (1.8)
<i>Curvularia</i>	3 (5.1)	3 (5.7)	6 (5.4)
<i>Fusarium</i> species	32 (54.2)	32 (60.4)	64 (57.1)
Unidentified hyaline	7 (11.9)	3 (5.7)	10 (8.9)
Total	59 (100.0)	53 (100.0)	112 (100.0)

**Figure 2** Survival curves comparing 2% econazole and 5% natamycin for fungal keratitis.

tions by altering membrane permeability.¹⁹ The imidazoles exhibit antifungal activity through two mechanisms of action depending on the concentration. At lower concentrations, they are fungistatic and inhibit sterol-4-alpha demethylase, a microsomal P450 related enzyme,²⁰ while they are fungicidal at higher concentrations causing direct membrane damage to the phospholipids present in the fungal cell wall.²¹ It is possible that use of both natamycin and econazole in the management of fungal keratitis may improve chances for more rapid resolution of corneal ulcers, especially since the mechanisms of action are different. However, further studies are required to validate this hypothesis.

While means to identify aetiological agents are available, the lack of effective antifungal agents often translates to an inability to treat the keratitis despite diagnosis. However, currently, fungal keratitis does not appear to be a priority or focus for pharmaceutical companies that apparently prefer to develop new lines of antibiotics against bacterial keratitis, which is more prevalent in the developed world.

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