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

N V Prajna, R K John, P K Nirmalan, P Lalitha, M Srinivasan

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.
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 χ² 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 disrup-
Econazole and natamycin for the treatment of fungal keratitis

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

Table 1  Aetiological organisms of fungal keratitis by treatment arm

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

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Authors’ affiliations
N V Prinja, R K John, P K Nirmalan, P Lalitha, M Srinivasan, Aravind Eye Care System, Madurai, India
R K John, P K Nirmalan, Lions Aravind Institute of Community Ophthalmology, Madurai, India

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