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Gender differences in re-epithelialisation time in fungal corneal ulcers

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Introduction

Animal studies have demonstrated that female mice may have a slower re-epithelialisation following corneal injury compared with males.[1] However, it is unknown if this translates to humans. In this report, we compare re-epithelialisation time in men and women using data collected as part of a prospective, randomised clinical trial on fungal corneal ulcers.

Methods

Clinical outcome measures were obtained in a standardised manner from a clinical trial on fungal corneal ulcers, which has been previously described.[2] Patients were randomised to voriconazole or natamycin and to rescraping or no rescraping of the corneal epithelium at 1 and 2 weeks after a positive fungal smear. Epithelial defect size and infiltrate/scar size were measured by slit-lamp examination every 3 days (±1 day) until re-epithelialisation. Re-epithelialisation time was defined as the midpoint between the last observed date with an epithelial defect and the date of the first visit with no epithelial defect. The best spectacle-corrected visual acuity (BSCVA) was assessed at enrolment, 3 weeks and 3 months. Ethical approval was obtained from the University of California, San Francisco and the Aravind Eye Care System.

Epithelial defect and infiltrate/scar size were analysed as the geometric mean of the longest dimension and the longest perpendicular to that dimension. The median time to re-epithelialisation was analysed using Kaplane–Meier survival analysis, censoring at 21 days from enrolment. A Cox proportional hazards model was used to analyse gender and re-

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Competing interests None.

Ethics approval Ethical approval was obtained from the University of California, San Francisco and the Aravind Eye Care System.

Contributors TK: PI of Pondicherry centre, involved in design of study, reviewed and interpreted results, drafting and critical review of manuscript; NVP: PI of Madurai site, design of study, interpretation of result, critically reviewed manuscript; KG: study concept and design, analysis of data, drafting manuscript; CEO: data collection, analysis, drafted and revised manuscript; KJR: data collection, analysis, critical review of manuscript; JDK: investigator, analysis and interpretation of data, critical revision of manuscript; TML: co-PI of study, study design, implementation of study, obtaining funding, interpretation of results, critical review of manuscript; NRA: co-PI of study, design of study, review and interpretation results, drafting and revision of manuscript, and responsibility for integrity of study and results.

epithelialisation time, controlling for treatment arm, rescraping or no rescraping, age, and epithelial defect and infiltrate/scar size at baseline. The size of the infiltrate at baseline and size of the epithelial defect are both potentially important factors affecting the time to re-epithelialisation, so both were included in our regression model. A Fisher exact test or Wilcoxon rank-sum test was used to compare ulcer characteristics between men and women. All analyses were conducted in STATA V.10.0.

Results

Of 120 patients enrolled in the trial, 79 (66%) were male, and 41 (34%) were female. The median age in men and women was 48 and 50 years, respectively (p=0.66). Sixty patients (42 male, 18 female) were randomised to receive natamycin and 60 (37 male, 23 female) to receive voriconazole, (p=0.44). Sixty patients (39 male, 21 female) were randomised to receive repeat epithelial debridement and 60 (40 male, 20 female) to receive no rescraping, (p=1.0). There were no significant differences in baseline characteristics in men and women (table 1).

The median duration of treatment with the study antifungal was 23 days (IQR 16 to 40 days). The overall median time to re-epithelialisation was 18.5 days (IQR 6.5 days to not estimable). The median time to re-epithelialisation in men was 15.5 days (IQR 7 days to NE), compared with 19.5 days in women (IQR 5 days to not estimable). The 3-month BSCVA was 0.21 logMAR overall (IQR 0 to 0.84); 0.18 (IQR 0 to 0.84) in men and 0.28 (IQR 0.02 to 1.3) in women (p=0.46). The infiltrate/scar size at 3 months overall was 3.5 mm (IQR 2.7 to 5.3 mm); 3.9 mm (IQR 2.7 to 5.3 mm) in men and 3.1 mm (2.5 to 5.6 mm) in women (p=0.26). In a model controlling for treatment arm, rescraping, age, baseline epithelial defect and infiltrate size, women re-epithe-lialised twice as slowly as men (HR=0.49, 95% CI 0.28 to 0.87, p=0.013, table 2). Every 10-year increase in age was associated with a 25% slower re-epithelialisation time (HR=0.75, 95% CI 0.62 to 0.90, p=0.002). There was no significant difference in time to re-epithelialisation between patients randomised to receive corneal rescraping or not (HR 1.16, 95% CI 0.70 to 1.92, p=0.56).

Comment

To our knowledge, differences in clinical outcome in corneal ulcers between men and women have never been reported. A case series in acanthamoeba keratitis suggested that women may have a worse prognoses but did not reach statistical significance.[3] Women may have reduced ocular surface healing because of the way androgens mediate the lacrimal and meibomian glands.[4] In animals, delayed wound healing in females may be due to oestrogen affecting lipid circuits which modulate inflammation and angiogenesis.[15] These mechanisms could explain our findings.

Allocation of health resources is not always equal between men and women.[6] Women may have a harder time accessing the hospital, and once they have received care, barriers may exist in receiving follow-up care or in compliance with treatment. In our study, patients were requested to stay in the hospital until they re-epithelialised, where they received a standardised treatment regimen. Therefore, it is unlikely that they received differential care. In summary, our study suggests that re-epithelialisation time is increased in women compared with men. Further study of sex-specific differences in corneal wound healing is warranted.

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Table 1
Baseline characteristics between men and women

Characteristic	Men (N=79)	Women (N=41)	Total (N=120)	p Value
Age in years, median (IQR)	48 (35 to 59)	50 (38 to 55)	49 (35 to 57.5)	0.66 *
Duration of symptoms in days, median (IQR)	6 (4 to 10)	5 (4 to 7)	5 (4 to 8)	0.07 *
Causative organism				
Fusarium spp, N (%)	29 (37)	15 (37)	44 (37)	0.87 †
Aspergillus spp, N (%)	11 (14)	6 (14)	17 (14)	
Other, * N (%)	39 (49)	20 (49)	59 (49)	
History of trauma, N (%)	44 (56)	21 (51)	65 (54)	0.70 †
History of vegetative matter injury, N (%)	20 (25)	10 (24)	30 (25)	1.0 †
Agricultural occupation, N (%)	42 (53)	21 (51)	63 (52)	0.85 †
Epithelial defect size, in mm, at baseline, median (IQR)	3.1 (2.0 to 3.9)	2.4 (1.7 to 3.7)	2.8 (2.0 to 3.9)	0.16 *
Infiltrate/scar size, in mm, at baseline, median (IQR)	3.8 (2.7 to 5.2)	3.1 (2.3 to 4.3)	3.6 (2.3 to 5.1)	0.09 *
Baseline visual acuity, logMAR, median (IQR)	0.68 (0.40 to 1.7)	0.72 (0.44 to 1.7)	0.71 (0.42 to 1.7)	0.96 *

* Wilcoxon rank-sum test.

† Fisher exact test.

Includes Curvularia spp, Bipolaris spp, Exserohilum spp, Lasiodiplodia spp, Alternaria spp, Scedosporium spp and unidentified fungi.

Table 2
Cox proportional-hazards model predicting time to re-epithelialisation

Covariate	HR (95% CI)	p Value
Female	0.49 (0.28 to 0.87)	0.013
Age (by decade)	0.75 (0.62 to 0.90)	0.002
Voriconazole (vs natamycin)	1.16 (0.71 to 1.93)	0.55
Rescraping (vs no rescraping)	1.16 (0.70 to 1.92)	0.56
Epithelial defect size at baseline (geometric mean in mm)	0.75 (0.47 to 1.19)	0.22
Infiltrate size at baseline (geometric mean in mm)	0.49 (0.33 to 0.72)	<0.001