SCIENTIFIC REPORT

Risk factors for perforation in microbial corneal ulcers in north India

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Aim: To identify predisposing factors leading to corneal perforation in patients with microbial keratitis.

Method: Two groups of 60 patients each, with perforated corneal ulcers and healed/healing corneal ulcers, respectively, were recruited in a case-control study conducted in northern India. The cases and controls were matched by age and time of presentation. A standardised proforma was used to identify potential predisposing factors for demographic, social, medical, ocular, and treatment history. All participants underwent a detailed ocular examination. Corneal scrapings were performed where relevant.

Results: The characteristics associated with corneal perforation in microbial keratitis were outdoor occupation ($p = 0.005$), illiteracy ($p = 0.02$), excessive alcohol use ($p = 0.03$), history of ''something falling into eye'' ($p = 0.003$), trauma with vegetable matter ($p = 0.008$), vision less than counting fingers at referral ($p < 0.001$), central location of ulcer ($p < 0.001$), lack of corneal vascularisation ($p < 0.001$), delay in starting initial treatment ($p < 0.001$), failure to start fortified antibiotics ($p < 0.001$), and monotherapy with fluoroquinolones ($p = 0.002$). The lack of corneal vascularisation (OR 6.4, 95% CI 4.2 to 13.5), delay in starting initial treatment (OR 35.6, 95% CI 6.9 to 68.2), and failure to start fortified antibiotics (OR 19.9, 95% CI 2.7 to 64.7) retained significance on a logistic regression model.

Conclusions: This study characterises microbial keratitis cases at increased risk of corneal perforation and reinforces the need for standardised referral and treatment protocols for patients with corneal ulcer on their first contact at primary care level in the developing world.

Microbial keratitis is an important preventable cause monocular blindness worldwide.[1–3] Several studies have evaluated the aetiology, management, and outcome of microbial keratitis.[4–11] However, there are regional variations in the prevalence, risk factors, and outcome in corneal ulcers.[6 12] In the developing world, corneal ulcers appear to be occurring in epidemic proportions, being 10 times more common than in the developed countries.[1] As trachoma and vitamin A deficiency become less common, suppurative keratitis is becoming the major cause of corneal blindness in the developing world.[13] While contact lens use is a major risk factor for corneal ulceration in the developed world, a high prevalence of fungal infections, agriculture related trauma, and use of traditional eye medicines is unique to the developing world.[14 15]

A significant percentage of patients with microbial keratitis referred to our tertiary hospital are at a stage of impending or established corneal perforation.[10] This study was conducted in an attempt to identify the predisposing factors for corneal perforation in microbial keratitis.

METHODS

A case-control study was conducted in a tertiary ophthalmic centre in north India.

Sixty cases with perforated infective corneal ulcers were matched with 60 control patients with healed or healing infective corneal ulcers by age and time of presentation.

A standardised proforma was used in assessing risk factors for perforation in corneal ulcers with respect to demographic, social, medical, ocular, and treatment history. Corneal scrapings with microbiological studies[16] were performed in all patients except the cases in whom the procedure was judged to be unsafe and the controls showing signs of complete healing.

Statistical analysis

The observed differences were evaluated by two by two tables and χ^2 test. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for statistically significant characteristics. A multivariate logistic regression model was used to determine independent significance of factors when adjusted for other significant factors in the study.

RESULTS

Demographic risk factors

The mean age of the cases and controls was 44.8 (SD 18.2) and 40.0 (SD 16.2) years, respectively ($p = 0.19$). The demographic risk factors evaluated were male sex (75% cases *v* 68% controls, $p = 0.54$), rural residence (53% cases *v* 42% controls, $p = 0.27$), outdoor manual occupation (53% cases *v* 27% controls, $p = 0.005$) and inability to read/write in any language (42% cases *v* 20% controls, $p = 0.02$).

Systemic risk factors

There was no association of recorded systemic risk factors with perforation in corneal ulcers. In all, 33% of cases and 15% of controls met the study criteria (more than 20 units a week or more than five units a day on three or more occasions per week) for excessive alcohol use ($p = 0.03$).

Ocular risk factors

There was no association of preceding ocular pathologies; such as previous keratitis in same eye (8% cases *v* 12% controls), previous keratitis in other eye (5% cases *v* 3% controls), ocular surface disorder (7% cases *v* 11% controls), trachoma (12% cases *v* 17% controls), vernal/atopic keratoconjunctivitis (2% cases *v* 7% controls), entropion/trichiasis (7% cases *v* 10% controls), with perforation in corneal ulcers. None of the cases and 3% controls were contact lens users.

Keratits episode

In all, 63% cases and 35% controls gave a recent history of ''something falling into eye'' ($p = 0.003$). Organic matter was involved in 48% cases and 23% controls ($p = 0.008$).

The first medical contact was reported as a community paramedical worker, general practitioner, ophthalmologist in

Table 1 Spectrum of organisms cultured

Organisms	Perforated ulcers (cases)		Healed ulcers (controls)	
	No	%	No	%
Positive corneal scraping	21	58	11	33
Mixed*	3	8	1	3
Bacteria	18	50	10	29
Staphylococcus epidermis	9	25	6	18
Staphylococcus aureus	2	6	1	3
Streptococcus pneumoniae	0	0	1	3
Alpha haemolytic streptococcus	1	3	0	0
Pseudomonas spp	4	11	0	0
Acinetobacter spp	1	3	0	0
Alkaligenes species	0	0	1	3
Polybacterial	1	3	1	3
Fungal	7	19	2	6
Aspergillus spp	3	8	2	6
Fusarium spp	2	6	0	0
Alternaria spp	1	3	0	0
Curvularia spp	1	3	0	0
Acanthamoeba†	0	0	0	0

Denominators used in percentage calculation were 36 cases and 34 controls with corneal scraping.
*Most mixed infections involved *Staphylococcus epidermis* associated with a single fungal species
†Performed on three patients with clinical suspicion.

private practice, or ophthalmologist in state run hospitals. The primary ophthalmic contact, as first medical contact or subsequent referral, was an ophthalmologist in private practice in 75% cases and 83% controls ($p = 0.37$). Only two patients had a corneal scraping performed on primary ophthalmic contact. A delay in commencing definite treatment by more than 5 days from onset of symptoms was seen in 77% cases and 13% controls ($p<0.001$). All patients were treated as outpatients before their referral. The initial treatment was evaluated in 68% cases and 48% controls with available treatment records: 17% of cases and 72% of controls had received fortified combination antibiotics (commonly a combination of cephazolin sodium 5% and tobramycin sulphate 1.3%) as initial treatment ($p<0.001$). A monotherapy with fluoroquinolones, in a frequency varying from 2 hourly to four times daily, was found in 68% of cases and 28% of controls ($p = 0.002$). The remaining 15% cases with available records had been given other topical antibiotics in inadequate doses. Three cases and two controls had been given 5% natamycin on clinical suspicion of fungal keratitis. Seven cases and three controls were prescribed topical steroids at some point during their treatment.

The significant ulcer characteristics were central location (68% cases *v* 23% controls), lack of corneal vascularisation (68% cases *v* 28% controls), and a referral visual acuity of less than counting fingers (98% cases *v* 17% controls) ($p<0.001$). The non-significant ulcer characteristics were presence of hypopyon, satellite lesions, and limbal involvement. The microbiological spectrum cultured from corneal scrapings, performed in 60% cases and 57% controls, is shown in table 1.

Table 2 summarises characteristics significantly associated with perforated corneal ulcers. A delay in starting definite treatment (OR 35.6, 95% CI 6.9 to 68.2), failure to start fortified antibiotics at first contact (OR 19.9, 95% CI 2.7 to 64.7) and lack of corneal vascularisation (OR 6.4, 95% CI 4.2 to 13.5) retained significance on a logistic regression model.

DISCUSSION

We conducted a case-control study[17] to identify wide demographic, social, and medical risk factors for perforation in microbial keratitis in the developing world.

Outdoor manual work[18] and illiteracy were associated with higher likelihood of perforated corneal ulcers. Similar to earlier reports,[5 19] there was no association of systemic diseases with perforation in microbial keratitis. Previously unreported, excessive alcohol use was a risk factor for perforation in corneal ulcers. Alcohol abuse may increase the risk of ocular trauma and lead to poor outcomes because of self neglect and socioeconomic fallout.

Ocular trauma is a major risk factor for corneal ulcers in the developing countries.[14 20] A history of ocular trauma, especially with organic matter, was associated with perforation in

Table 2 Summary of significant characteristics associated with perforated corneal ulcers

Factors	Proportion (%)		OR (95% CI)	p Value
	Cases	Controls		
Outdoor occupation	32/60 (53)	16/60 (27)	3.1 (1.5 to 6.7)	0.005
Illiteracy	25/60 (42)	12/60 (20)	2.9 (1.3 to 6.4)	0.02
Excessive alcohol use	20/60 (33)	9/60 (15)	2.8 (1.2 to 6.7)	0.03
History of ''something falling into eye''	38/60 (63)	21/60 (35)	3.2 (1.5 to 6.7)	0.003
Trauma with vegetable matter	29/60 (48)	14/60 (23)	3.1 (1.4 to 6.7)	0.008
Visual acuity less than counting fingers*	59/60 (98)	10/60 (17)	295.0 (44.9 to 1842.6)	<0.001
Central location of ulcer*	41/60 (68)	14/60(23)	7.1 (3.2 to 15.8)	<0.001
Lack of corneal vascularisation*	41/60 (68)	17/60 (28)	5.2 (2.5 to 11.9)	<0.001
Delay in starting initial treatment	46/60 (77)	8/60 (13)	21.4 (8.3 to 54.8)	<0.001
Failure to start fortified antibiotics	34/41 (83)	8/29 (28)	12.8 (4.1 to 39.7)	<0.001
Monotherapy with fluoroquinolones	28/41 (68)	8/29 (28)	5.7 (2.0 to 15.9)	0.002

OR, univariate odds ratio; CI, confidence intervals.
*Ulcer characteristics at referral or from available previous records.
Risk factors in bold retained association after multiple logistic regression.

corneal ulcers in our study. Unlike earlier reports,[4 5] previous ocular disease was not associated with increased risk of perforation in corneal ulcers. However, a 30% prevalence of trachoma or its sequlae in our patients, make it an important predisposing factor in corneal ulceration.

A failure to implement standard therapy at first contact has been reported to be a marker for poor outcome in microbial keratitis.[10 21 22] Our results show that delay in starting definite treatment is a risk factor for perforation in corneal ulcers. It is likely that delayed treatment underlies the associations with illiteracy, manual labour, and excessive alcohol use. A review of available treatment records shows failure to start combination fortified antibiotics and monotherapy with fluoroquinolones as risk factors for perforation in corneal ulcers. Several studies have reported equal efficacy and better tolerance of fluoroquinolones compared to fortified antibiotics in the treatment of microbial keratitis.[23–25] However, there have been concerns over emergence of resistance to fluoroquinolones.[26] Sixty three per cent of our bacterial isolates were sensitive to fluoroquinolones. Mallari *et al*[27] have described monotherapy with fluoroquinolones as risk factor for corneal perforation independent of bacterial resistance. There have been reports of delayed epithelial healing, keratocyte loss, and recent biochemical evidence of increased metalloproteinases and apoptosis markers with use of fluoroquinolones.[28 29] In spite of these concerns, fluoroquinolones may be a useful alternative considering inherent problems in preparation and storage of fortified antibiotics. It is possible that poor outcome with fluoroquinolones in this study may be related to their use with inadequate frequency.

Unlike previous reports,[5 10] we did not find significant association of topical steroids with perforation in corneal ulcers. However, considering inadequate pre-referral records, it is possible that use of topical steroids was under-reported. The traditional eye medications (TEM) have been associated with corneal ulcers in literature from the developing world.[3 15] The use of TEM may not only delay definite therapy, but non-sterile preparations can introduce pathogenic organisms in already compromised eyes. When asked about previous treatments, none of our patients reported use of TEM.

The central location of corneal ulcer as a risk factor for perforation is in agreement with reports describing poor outcome with central ulcers.[5 21] Hypopyon formation and limbal involvement were not associated with perforation in our study.[5 9] We could not evaluate initial ulcer size[5 18] as a risk factor because of poor documentation. There was a low yield from corneal scrapings performed at referral because of pre-referral treatments. It is possible that the organisms isolated by us represent a secondary infection. Therefore, microbial isolates were not evaluated as risk factors for corneal perforation. Similar to earlier reports,[30] *Staphylococcus epidermis* was the most common bacterial isolate. *Aspergillus* spp were the most common fungal isolates in contrast with predominance of *Fusarium* spp in south India.[6]

There are several limitations to this study conducted in a tertiary hospital. The long delay before referral, varied treatments at pre-referral points, and paucity of treatment records may have introduced a bias in the study. A case-control design is open to bias and confounding and may not identify unsuspected risk factors. The non-masked interviews may have led to an interviewer's bias.

In conclusion, a delay in starting definite therapy is the most important factor associated with increased risk of perforation in corneal ulcers. The primary care health staff should be educated about the diagnosis, appropriate treatment, and referral of corneal ulcer patients. The referral hospitals should liase with the local ophthalmic care providers to introduce standardised protocols for treatment and referral of corneal ulcer patients.

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