Original Research Article

Clinical implication of microbiological evaluation of corneal ulcer and its correlation with outcome: A follow up study from a central Indian tertiary health care center

Ravi Chauhan[1], Sachin Agrawal[2], Rahul Dagwar[3], Nidhi Lalwani[4*]

[1]Professor, Department of Ophthalmology, Indira Gandhi Government Medical College, Nagpur, Maharashtra, India

[2]Associate Professor, Department of Ophthalmology, Indira Gandhi Government Medical College, Nagpur, Maharashtra, India

[3]Associate Professor, Department of Ophthalmology, Indira Gandhi Government Medical College, Nagpur, Maharashtra, India

[4]Junior Resident, Department of Ophthalmology, Indira Gandhi Government Medical College, Nagpur, Maharashtra, India

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Abstract

Objective: To find out the incidence of different types of corneal ulcers and outcome of target-specific treatment based on microbiological evaluation. **Materials and methods:** In a hospital based prospective studies spanning over 2 years, 50 cases of corneal ulcer underwent microbiological evaluation of corneal scrapings and were started on culture-guided antimicrobial therapy. **Result:** Most ulcers were found to be prevalent in age between 51-70 years. 72 % were males, 28% females, 52% from rural areas, 50% were labourers (agricultural 28% and manual 22%), with ocular trauma and vegetative foreign body being the commonest predisposing factors. Among culture positive cases, 58.6% and 41.4% were positive for fungi and bacteria, respectively. *Aspergillus* was the most commonly isolated fungal species and *Pseudomonas aeruginosa* was the most common bacterial isolate. Moxifloxacin and tobramycin were effective in treating a majority of bacterial corneal ulcers, and hence can be considered to be the drugs of choice for the same. Complete healing of corneal ulcer with treatment was seen in 82.8% of culture positive patients. **Conclusion:** Infective keratitis should be managed as an ophthalmic emergency. Instantaneous administration of culture-guided antimicrobial therapy to patients with infective keratitis can avert disabling ocular morbidity and sequential blindness.

Keywords:cornea,ulcer,clinical

Introduction

Diseases of cornea are a major cause of blindness worldwide and in most cases, they represent a preventable or treatable ophthalmic disease. In India, 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[1,2]. Corneal ulceration is a major cause of monocular blindness in developing countries[3] and has been identified as a 'silent epidemic' in the developing world[2].

Infectious keratitis is a broad term for corneal diseases due to an infective agent. Corneal ulcer is a manifestation of infectious keratitis due to organisms that cause tissue death[4]. Untreated corneal ulcer can cause corneal perforation, corneal scarring, endophthalmitis and even corneal blindness in a few cases. Delayed presentation and improper microbiological diagnosis of infectious keratitis makes timely treatment very difficult.

*Correspondence
Dr. Nidhi Lalwani
Junior Resident, Department of Ophthalmology, Indira Gandhi Government Medical College, Nagpur, Maharashtra, India.
E-mail: nidhilalwani14@gmail.com

In approximately 60% of cases, corneal scar or adherent leucoma is the outcome of neglected or improperly treated corneal ulcers[5]. Microbiological investigation is, therefore, essential to detect the causative organism of corneal ulcer, and is a necessary guide to start target specific antimicrobial therapy for its optimum management[6].

The aim of this study is to evaluate the risk factors associated with causation of infective keratitis, their microbiological profile and antibiotic susceptibility, in order to improve and optimize diagnosis and treatment of this potentially blinding disease and determine the outcome of treatment based on microbiological evaluation.

Subjects and methods

The present study was conducted at a tertiary care centre from September 2018 to December 2020.

Inclusion criteria

Patients with infective keratitis irrespective of age and gender were enrolled in the study.

Exclusion criteria

Following patients were excluded from our study-

- non-infectious keratitis
- dendritic, geographic ulcers and clinical suspicion of viral etiology
- chronic, non-healing ulcer
- impending perforation and perforated corneal ulcers.
- immune-compromised patients

- systemic autoimmune diseases

Methodology

Selection of subjects

All patients presenting with infectious keratitis were evaluated. Detailed history including age, sex, economic status, occupation, ocular symptomatology, exposure to chemicals UV light, previous history of trauma, mode of injury or nature of foreign body damaging cornea were enquired. History of contact lens wear, systemic diseases like diabetes, Hypertension, HIV was obtained.

Detailed slit-lamp biomicroscopic examination, with special attention to cornea was done. The details of the corneal ulcer including the location, size, shape, depth of the ulcer, nature of infiltrate, margins of the ulcer, presence of any satellite lesions, immune ring, corneal vascularization and hypopyon were noted. Ocular adnexa were examined to rule out meibomianitis, trichiasis, lagophthalmos, and chronic dacryocystitis.

Ocular investigations including fluorescein stain, lacrimal syringing and corneal sensation were carried out.

After detailed ocular examination, under topical anaesthesia, corneal scraping samples were collected for culture and sensitivity from base and margins of ulcer with number 15 surgical blade. Scraping was inoculated into Blood agar, Chocolate agar, MacConkey media, and Sabouraud's Dextrose Agar (SDA) media. Material from corneal scraping was also smeared on two separate glass slides: one for Gram stain and other for microscopic examination as a KOH wet mount.

Relevant systemic investigations, CRP, ESR and blood glucose levels were performed.

Management was decided on basis of smear report / culture sensitivity report. When negative, appropriate antimicrobial therapy was initiated based on the clinical appearance of the ulcer. Suspected fungal ulcers were treated with Natamycin 5% drops were, and systemic anti-fungal in deeper penetration. if bacterial ulcers were suspected, treatment with moxifloxacin eye drops or combination of fortified tobramycin and fortified cephazolin eye drops. The therapy was modified based on culture report and response of the patient. The antimicrobial susceptibility pattern was determined for each of the bacterial isolates. If the ulcer showed no sign of improvement, then therapy was changed or reviewed after obtaining the culture and sensitivity report and target specific antimicrobials were started.

The patients were followed up at 1 week, 3 weeks, 6 weeks and 3 months, respectively, to look for clinical response. Treatment outcome was evaluated in the form of signs of healing, final visual acuity achieved, surgical intervention required or not and complication if any. Treatment was considered successful where the corneal infiltrates resolved (with consequential scarring) and where the overlying corneal epithelium healed completely. Clinical outcome was said to be poor either if corneal perforation developed despite antimicrobial therapy, or where a penetrating keratoplasty was performed for visual restoration or for infection control, or where an eye destructive procedure such as enucleation or evisceration was required. At the last follow up, Best Corrected Visual Acuity, condition of cornea, presence/absence of complications and surgical interventions, if done were recorded systematically.

Results

50 patients with infective keratitis were studied.

The incidence of infective corneal ulcers was greater between 51 – 70 years, which accounted for 50 % of the total cases. The mean age was 55.8 years.

Corneal ulcers were more frequent in males (72%) than females (28%).

Higher incidence was observed in illiterate population (76%).

Rural population (52%) has moderately higher incidence of corneal ulcers.

Farmers, manual labourers (50%), industrial workers (12%) were more predisposed to corneal ulcers due to increased incidence of injury to the eye. 12% of patients were household workers.

Ocular trauma or foreign body accounted for 62% of the cases of corneal ulcer in present study. Ocular trauma was the most frequent risk factor. Among that, injury with vegetative material like grass, paddy stalk, plant twigs were the most common type (42%), followed by sand (16.1%), metallic foreign bodies (16.1%) and chemical injury with lime in 1 case (3.2%). The nature of ocular injury remained undetermined in 7 cases (22.6%).

16% of the cases of infective keratitis had diabetes mellitus as the predisposing systemic condition. Co-existing ocular disorders, such as chronic dacryocystitis and lid margin disorders, were observed in 8% and 12% patients, respectively. Among lid margin abnormalities, severe blepharitis and meibomianitis were frequently associated. In 16% patients, there was a history of incautious use of topical steroids. Use of self-medications was seen in 4% and history of contact lens usage was seen in 2% of the participants. In 11 (22%) patients, no ocular predisposing factor was observed.

In our study the most common presentation was with watering from eyes (76%), followed by ocular pain (64%), diminution of vision (60%), redness (50%), photophobia (50%) and foreign body sensation (40%).

We found that 40% patients had an unaided visual acuity of less than 6/60 in the affected eye at the time of presentation while 60% patients had visual acuity of greater than 6/60 in the affected eye.

Ulcer was considered central if it was present in the central 5 mm diameter and peripheral if it was present within 3 mm from the limbus. Out of the 50 patients, 28% patients had an ulcer involving the centre of the cornea leading to marked visual impairment in these patients. 16% patients had peripheral ulcers while 56% patients had ulcers involving the paracentral cornea.

Corneal ulcers were graded as mild, moderate and severe, depending upon size of epithelial defect (mm), depth of ulcer (%), depth of infiltrate and scleral involvement. Ulcer was of mild grade in 11 (22%) patients, moderate grade in 23 (46%) patients and severe in 16 (32%) patients.

Hypopyon at the time of presentation, was present in 34% patients and it was absent in 66% patients.

Out of the 50 patients of infective corneal ulcer, growth in culture was seen in 29 (58%) patients. Among them 12 cases (41.4%) had a pure bacterial growth and 17 (58.6%) patients had pure fungal growth on culture. fungi were the most commonly isolated causative agents in our study.

We found statistically significant association between nature of corneal injury and the etiology of infective keratitis, wherein fungal keratitis was found to be more in cases who had a history of trauma by vegetative matter as compared to cases with trauma by other agents. (Chi square = 11.02, d.f.=1, p=0.0008).

The predominant fungal isolate belonged to the genus *Aspergillus* (20.69%), followed by *Fusarium* (13.79%), *Curvularia* species (13.79%) and *Candida* species (10.33%). Out of the 12 bacterial isolates, 7 were found to be Gram positive cocci and 5 were Gram negative bacilli. *Pseudomonas aeruginosa* was the predominant bacterial isolate in the present study (17.24%), followed by *Staphylococcus aureus* (10.33%), *Streptococcus pneumoniae* (6.90%) and *Staphylococcus epidermidis* (6.90%).

All the gram-positive bacteria isolated in this study were sensitive strains except for one strain of *Staphylococcus aureus* which was resistant to penicillin and ciprofloxacin. All the gram negative isolates were also sensitive. However, among the 5 cases where *Pseudomonas aeruginosa* was isolated, one was resistant to gentamicin. Antibiotic susceptibility testing showed majority of bacterial isolates sensitive to tobramycin, moxifloxacin, amikacin and ceftazidime.

Out of 50 patients, 32 (64%) patients attained complete healing of corneal ulcer with or without corneal scarring. Poor outcome in the form of perforation/ adherent leucoma was seen in 8 patients (16%), non-healing corneal ulcers in 6 patients (12%) and therapeutic penetrating keratoplasty was required in 4 patients (8%).

40% of the patients had visual acuity below 6/60 on initial presentation whereas 36% had visual acuity below 6/60 at the time of 3 months follow up. The percentage of patients who had vision more

than 6/60 at 3 months follow up (64%) was significantly more than the percentage of patients who had vision more than 6/60 at the time of presentation (60%). (Fischer exact test P 0.000) Percentage of culture positive patients who had better outcomes in the form of healed scar (82.8%) was significantly more than percentage of culture negative patients who had healed scar (38.1%). (Chi square = 10.54, d.f.=1, p=0.001)

Table 1: Culture results of corneal scraping samples

Culture	Number		
Fungal (culture positive)	17 (34%)	KOH Positive	10 (58.82%)
		KOH Negative	7 (41.18%)
		Aspergillus	6 (20.70%)
		Fusarium	4 (13.80%)
		Candida	3 (10.3%)
		Curvularia	4 (13.80%)
Bacterial (culture positive)	12 (24%)	Gram positive stain	3 (25%)
		Gram negative stain	2 (16.67%)
		No stain	7 (58.33%)
		Staphylococcus aureus	3 (10.33%)
		Staphylococcus epidermidis	2 (6.90%)
		Streptococcus pneumoniae	2 (6.90%)
		Pseudomonas aeruginosa	5 (17.24%)
No growth	21(42%)		

Table 2: Antibiotic sensitivity results of the samples

Antibiotic	Staphylococcus aureus	Staphylococcus epidermidis	Streptococcus pneumoniae	Pseudomonas aeruginosa
Gentamicin	100%	100%	Not tested	80%
Tobramycin	100%	100%	Not tested	100%
Moxifloxacin	100%	100%	100%	100%
Ciprofloxacin	66.66%	100%	100%	100%
Vancomycin	100%	100%	100%	Not tested
Amikacin	100%	100%	100%	100%
Ceftazidime	100%	100%	Not tested	100%

Table 3: Treatment outcome of corneal ulcer patients

Treatment outcome	Number	Percentage
Healed scar	32	64%
Adherent leucoma / perforation	8	16%
Evisceration	0	0
Therapeutic penetrating keratoplasty	4	8%
Non healing ulcer	6	12%
Total	50	100%

Table 4: Visual acuity of patients (Baseline v/s 3 months follow up) Fischer exact test is used. P=0.000

Vision	No. of patients at presentation	Percentage	No of patients at 3 months	Percentage
6/60 or more	30	60%	32	64%
<6/60	20	40%	18	36%
Total	50	100%	50	100%

Table 5: Outcome of patients based on culture reports. Chi square = 10.54, d.f.=1, p=0.001

Culture	Number	Number of cases with Healed scar	Percentage of culture positive / negative who had healed scar
Positive	29	24	82.8%
Negative	21	8	38.1%
Total	50	32	

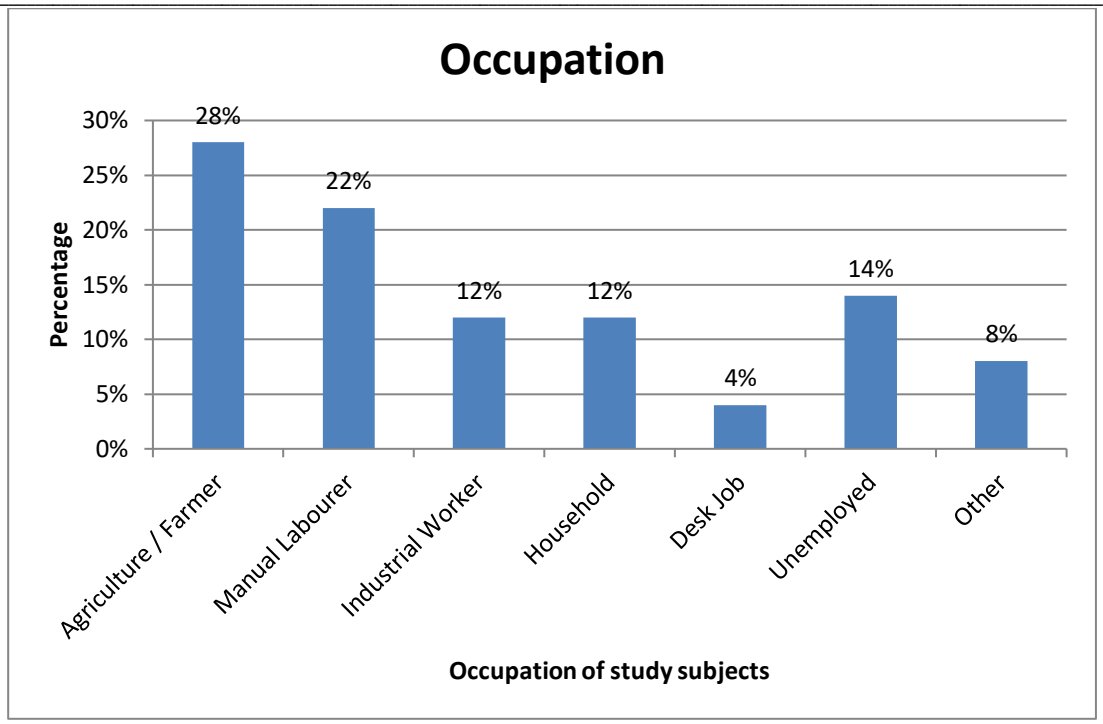

Fig 1: Occupation of study subjects

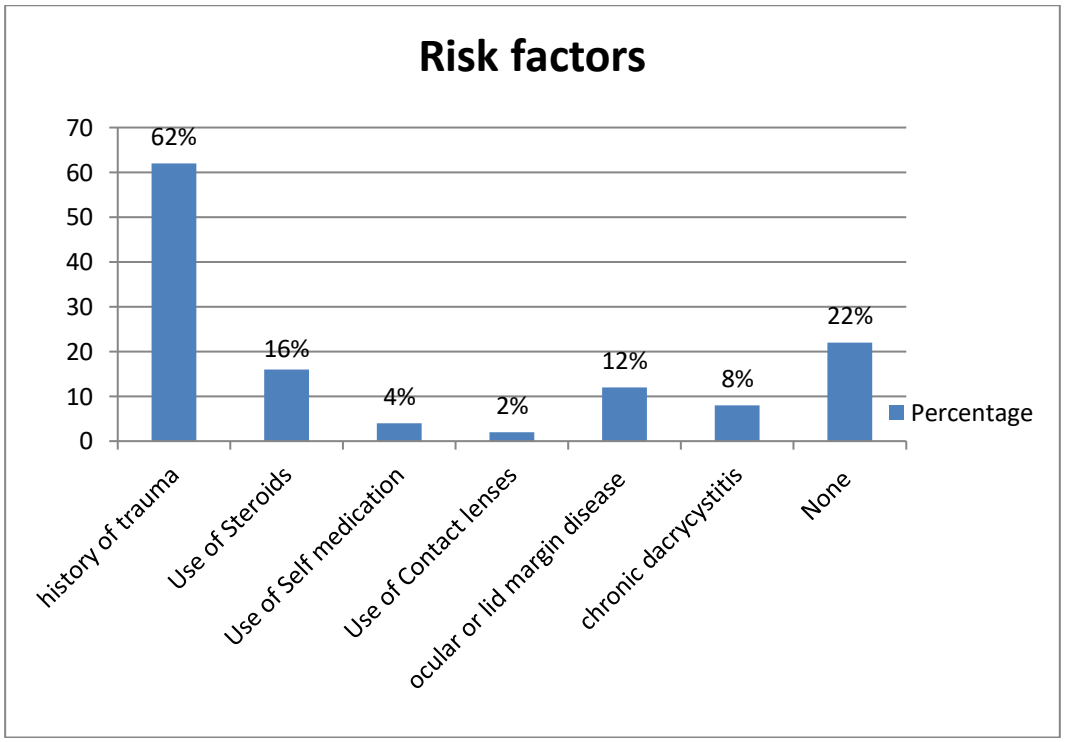

Fig 2: Risk factors

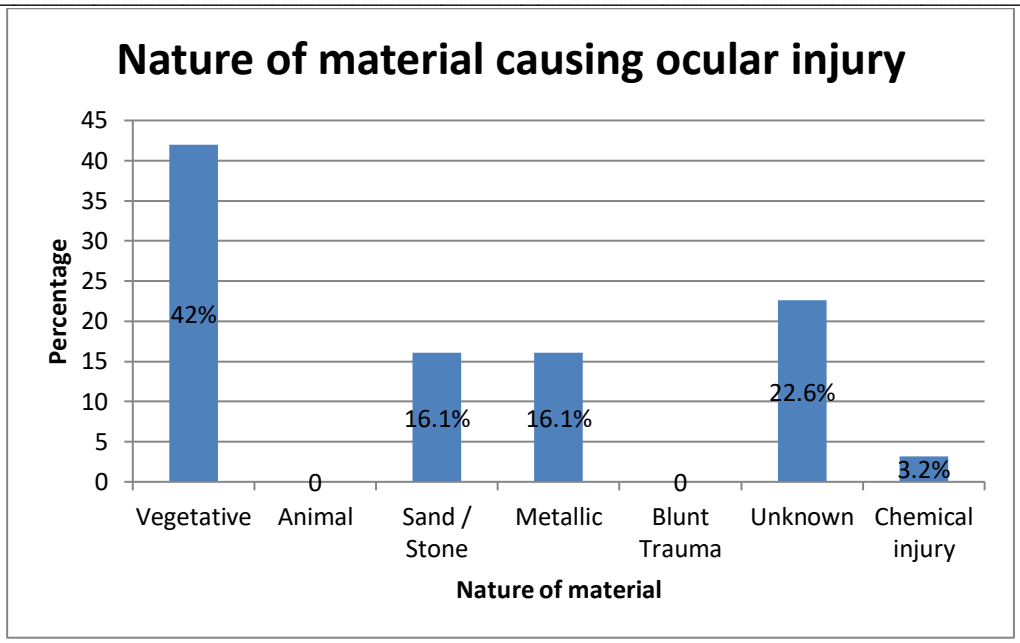

Fig 3: Nature of material causing ocular injury in 31 cases presenting with ocular trauma

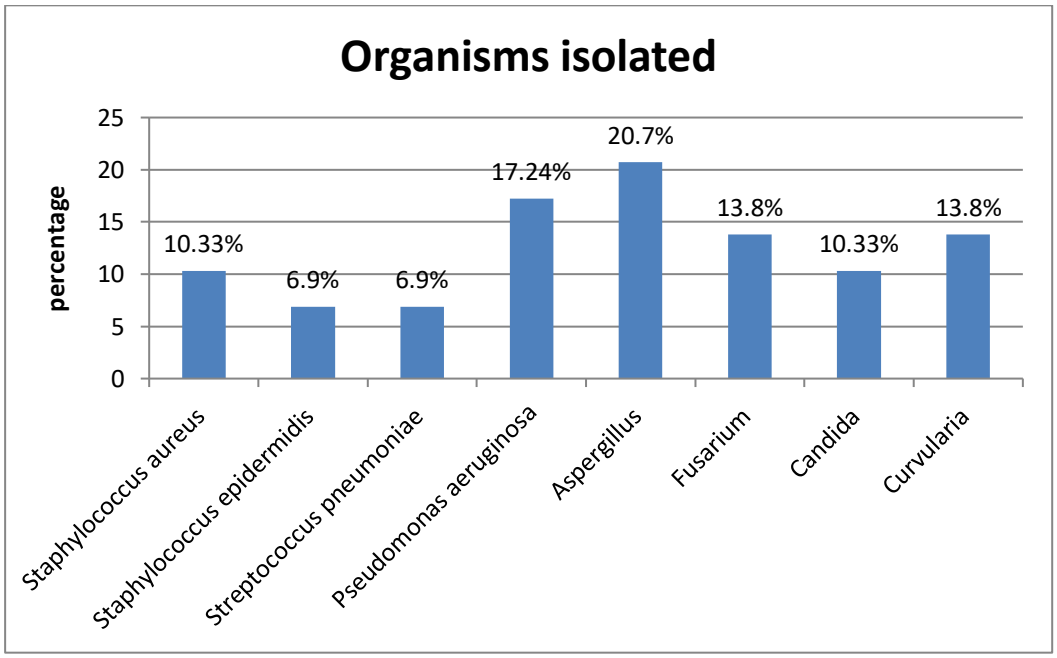

Fig 4: Organisms isolated

Discussion

Infective keratitis is a significant public health problem in developing nations. Precise and prompt diagnosis is the essence of management of corneal ulcers. Incorrect diagnosis can result in rapid progression of ulcers, thereby threatening the integrity of the globe and vision. It may lead to loss of sight, if not diagnosed timely or if managed ineffectively.

Patient demographics

Age Increased incidence of infective keratitis in the age group of 51-70 years is supported by a similar South Indian study[7]. This may be seen as an additive effect of underlying predisposing diseases, either systemic or local that are more prevalent in the older age group.

Sex Males were affected 2.57 times more than females which is in concordance with other Indian studies[8,9].

Occupation Majority of the patients were manual labourers which includes construction, factory and industrial workers, and agriculture related workers. 12% of total patients in our study with infective corneal ulcers were housewives. Similar distributions have been noted by other researchers[6,10,11,12]. Vegetative matter was the most common pre-disposing traumatic factor in causation of corneal ulcer. In countries like India, agriculture is the single most common occupation of the adult population among both the sexes. Inadequate ocular protection and lack of awareness about ocular injury during farming, results in high incidence of corneal ulcers in farmers.

Residence Higher incidence of infective keratitis among rural patients found in our study has been corroborated by other Indian studies as well[13,14,15,16]. This may be due to the fact that patients hailing from rural set areas have a higher chance of exposure to agricultural products and vegetative matter. Most of the rural area attached to our tertiary care centre is urbanised. Hence, the occurrence of corneal ulcers was found to be comparable in our study.

Risk factors

Ocular trauma History of antecedent ocular trauma in a predominant proportion of our study population was revealed in other studies as well[6,10,17,18]. Trauma may break down the normal defence mechanism and allow the resident flora of the conjunctiva, pathogenic organisms inoculated at the time of injury or those from the infected lacrimal sac to colonize the damaged corneal tissue.

Nature of ocular trauma Our finding of vegetative trauma being the commonest mode replicates a similar observation by Basak et al.[17]. Trauma as a predisposing factor for fungal corneal ulcers has been reported by various researchers[19,20,21]. In our study as well, we found a statistically significant association between a history of trauma by vegetative matter and microbiologically proven fungal keratitis. This is agreeable with the observations of Gopinathan U et al[8] and Jose et al[22].

Other local and systemic risk factors

Similar to our study, Chang YS et al.[23] and Jose et al.[22] also found diabetes to an important systemic risk factor.The finding of local predisposing factors as mentioned in the results corroborated with that of other studies[8,22,24]. Ocular surface disorders disturb the tear film dynamics and may compromise the local ocular defence system, thereby increasing the risk of corneal ulceration. Contact lens use has been found to be a major predisposing factor causing infective ulcerative keratitis in a large number of studies conducted among the Western population. However, the decreased prevalence of the same in our study could be due to the fact that the majority of patients in our study group belonged to rural areas. This finding is similar to another Indian study[17].

Clinical profile Khadka S et al.[18] observed that 55.8% ulcers were in paracentral region followed by 27.4% central and peripheral 16.8%. On the contrary, in a study by Mehta et al.,[2,4] 78.3% patients had an ulcer involving the centre of the cornea. This is comparable to our findings mentioned in the results.

In an Indian study, 39% of the cases were diagnosed severe, followed by mild 34% to moderate 27% among all corneal ulcer patients,[25] whereas in our sample, majority of the patients had moderate severity. In a study by Gupta R et al.,[13] hypopyon on presentation was seen in 57.5% cases, against 34% seen in our study.

Corneal ulcers profoundly affect the visual function of an individual, and if appropriate treatment is not administered in time, irreversible loss of vision might occur. Size, severity and location of corneal ulcer are also known to influence the final visual outcome as central corneal ulcers with deeper infiltrates are usually associated with marked visual impairment.

Microbiological profile An accurate smear diagnosis is important in achieving optimum treatment outcome. In a study by Gupta et al.,[13] 87.5% cases showed growth on culture media. In a study by Mehta et al.,[24] among the 43 culture-positive patients, 67.44% patients were positive for fungi, while 32.56% patients gave a positive yield for bacteria. Srinivasan et al.[10] isolated equal numbers of bacterial (47.1%) and fungal (46.8%) agents causing infectious keratitis with 5.1% cases having mixed infections. On the other hand, in a study conducted in Nepal by Upadhyay et al.,[6] microorganisms were grown from 80% of the ulcers. Pure bacterial cultures were obtained from 63.2% of the patients, whereas pure fungal cultures were obtained from 6.7% of the patients.

The preponderance of culture positive fungal corneal ulcers in our study can be ascribed to hot and humid climatic conditions that are conducive to the growth of fungi and agriculture being the main occupation of the large farming population in our study group.

Microbial isolates Among the culture positive cases, in our study the prevalence of various fungal species is in concurrence with findings of Basak et al.[17] and Mehta et al.[24].

The prevalence of various bacterial species and the gram positivity rate in our study are in concurrence with the isolates of other national and international studies[26,27,28].

In our study, the predominance of fungi can be due to agriculture and manual labour being the main occupation in our study, the hot and humid climatic conditions and fact that cases of trauma leading to corneal ulcers were large in number (62%).

Antibiotic sensitivity As per the results of our study, moxifloxacin and tobramycin can be considered as the drugs of choice for bacterial corneal ulcer. Antibiotic susceptibility testing in a study by Biradar S et al.,[29] showed gram positive cocci were more susceptible to ciprofloxacin and vancomycin, whereas gram-negative isolates were more susceptible to amikacin and ciprofloxacin. Few studies[30,31] have mentioned about gentamicin, but in our study, we found 100% sensitivity to moxifloxacin and tobramycin.

Treatment outcome A majority of patients responded to our line of management with only 18 cases showing signs of progression/worsening. In a study done by BR Keshav et al.,[32] 69.14% patients recovered with treatment, 4.78% worsened, perforation was seen in 17% of the cases and 65% had a visual acuity of less than 3/60 in the affected eye. In a study by Mehta et al.,[24] 6.66% patients worsened despite appropriate medical line of management. 3.33% patients underwent therapeutic keratoplasty due to non-responsiveness to treatment. 83.4% patients had a visual acuity of less than 3/60 in the affected eye. Gopinathan U et al.,[8] found that 46.6% of their patients required surgical intervention. Jitendra Kumar et al.[16] observed favourable clinical outcome of healed scar in 42.59% patients, deteriorating (non-healing) ulcers in 55.55%, out of which 2 cases had perforated corneal ulcer and panophthalmitis (3.70%), requiring evisceration. Shoja et al.,[7] found that 36.2% of their patients achieved visual acuity of 6/36 or better at the final follow-up. 17.5% required surgery and 5% eventually needed evisceration. Successful medical treatment of microbial keratitis was also evidenced in various other studies based on microbiological evaluation,[8,17] and early presentation accounted for good visual outcome in these studies. The poor vision was attributed to the ulcer itself, corneal degeneration, corneal opacity or cataract.

Conclusion

In cases with corneal ulcer, identification of the exact causative microbial organism, along with prompt, accurate and early initiation of appropriate treatment modalities are the most important goals for healing of corneal ulcer and good anatomical and visual outcome. Hence, direct microscopy and microbiological evaluation are of utmost importance for ophthalmologists in managing this clinical emergency that remains a therapeutic challenge. Instantaneous administration of culture-guided antimicrobial therapy to patients with infective keratitis can avert disabling ocular morbidity and sequential blindness.

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