Original Article

A 5-YEAR RETROSPECTIVE REVIEW OF CORNEAL ULCERS IN NORTHERN MALAYSIA

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ABSTRACT

Corneal ulcer is a common ocular infection which may result in devastating visual impairment and significant morbidity. In view of the paucity of local corneal ulcer data, we aim to evaluate the predisposing factors, disease patterns and clinical outcomes of corneal ulcer in northern Malaysia. A retrospective review of medical and microbiological records of all patients treated for corneal ulcer from 2015 to 2019 at Hospital Sultanah Bahiyah was performed. Socio-demography, predisposing factors, clinical characteristics, causative organisms and final visual outcome were analysed. A total of 408 patients were treated as corneal ulcer during our study period. The most common predisposing factor was ocular trauma (n=212, 52.0%), followed by contact lens-related (n=47, 11.5%), bullous keratopathy (n=30, 7.4%), corneal-suture related (n=25, 6.1%), ocular surface disease (n=21, 5.1%), eyelid pathology (n=14, 3.4%), exposure keratopathy (n=13, 3.2%) and pre-existing cornea dystrophy or degeneration (n=11, 2.7%). Positive yield from corneal scrapping was acquired in 213 eyes (52.2%). The commonest bacteria isolated was Pseudomonas sp. (85, 20.8%) while fungal growth contributed to 9.6% of cases. Corneal ulcer size of more than 4mm (p<0.001), centrally located ulcer (p<0.001) and presence of hypopyon (p<0.001) were significantly related to worse final visual acuity. Majority (n=364, 89.22%) of the patients healed while 16 (3.9%) patients required penetrating keratoplasty, 16 (3.9%) underwent evisceration and 12 (2.9%) was treated with glue and bandage contact lens. In conclusion, ocular trauma and contact lens were the commonest cause for corneal ulcer in this study. Pseudomonas sp was the commonest bacteria isolated. By understanding the local statistics, preventive measures can be identified and prompt intensive treatment can be initiated to reduce the morbidity related to corneal ulcer and improve visual outcome.

INTRODUCTION

Corneal ulcer is a leading cause of preventable corneal blindness. It is estimated that 1.5 to 2 million corneal ulcer cases resulted in unilateral blindness annually worldwide [1]. In developing countries, limited access to health care services and lack of eye-care awareness were the major obstacles to early medical treatment. This subsequently led to higher morbidity, increased disease burden, longer duration of treatment and hospitalization, and surgical intervention. Predisposing factors and causative organisms of corneal ulcer varies between developed and developing countries, with bacterial infection being the predominant causative organism in developed countries compared to fungal infection in developing countries [1].

Based on the largest single-centre study on corneal ulcer in Malaysia, contact lens was the commonest predisposing risk factors followed by ocular trauma, with *Pseudomonas* sp being the commonest causative organisms in Malaysia [2]. There are limited studies on corneal ulcer in the northern part of Malaysia especially in the state of Kedah. This study is designed to investigate the predisposing factors, disease patterns, causative organism, and clinical outcomes of corneal ulcer in Hospital Sultanah Bahiyah, a tertiary referral centre for the northern region of Malaysia.

MATERIALS & METHODS

This is a retrospective study involving patients treated as corneal ulcer and investigated with corneal scrapping in Hospital Sultanah Bahiyah between January 2015 and December 2019. This study was approved by the Malaysian National Institute of Health and was registered in the

National Medical Research Registry (NMRR -20-1473-55317).

Data acquired via the electronic hospital information systems (EHIS) of Hospital Sultanah Bahiyah were reviewed. Data collected include patients' demographic information, referral source, onset of first symptoms prior to presentation, predisposing factors, clinical features of corneal ulcer, result of culture from corneal scraping, duration of hospitalization and final visual outcome.

Snellen visual acuity was used to evaluate the presenting and final vision and categorised into good (6/6 to 6/12), moderate (6/15 to 6/60) and severe (worse than 3/60) [2] visual acuity. The location of the ulcer was determined based on 3 zones of the cornea. The central zone is 1 to 3 mm in diameter at the center of the cornea, bordered by the paracentral zone, a 3 to 4 mm area from the margin of the central zone; and the peripheral zone which is the remaining cornea outside of the paracentral zone [3]. The corneal ulcer size was defined as the largest diameter of the cornea ulcer measured prior to corneal scraping which is divided into small (0 to 2 mm), medium (2 to 4 mm) and large (5 or more). Corneal smear was sent for gram stain and in vitro cultures on blood agar, chocolate agar, Sabouraud dextrose agar, and McConkey agar.

According to the local hospital's practice, bacterial corneal ulcers were mostly treated with intensive combined topical fortified gentamicin 0.9% and ceftazidime 5% eye drops or combined topical fortified gentamicin 0.9% and cefuroxime 5% as empirical treatment. The treatment would be revised based on clinical response and culture and sensitivity results. Intensive topical amphotericin B 0.15% and fluconazole 2% were the empirical treatment for clinically-appearing fungal ulcer. Systemic antibiotic or antifungal were considered in limbal involvement, impending perforation, perforated ulcer, scleral extension or endophthalmitis. Surgical interventions like evisceration, penetrating keratoplasty, glue with bandage contact lens and temporary tarsorrhaphy were done when indicated.

Patients were either treated as an outpatient or admitted to the eye ward based on the clinical severity. They then underwent regular follow-ups at the eye clinic until the corneal ulcer healed and final visual outcome achieved.

SPSS 22.0 were used to analyse the data. Categorial data is presented as frequency and percentage, whereas continuous data is presented as mean and standard deviation. Pearson's chi square was used to determine the difference between categorical data. A *p* value of less than 0.05 is considered as statistically significant.

RESULTS

There were 408 patients treated with corneal ulcer in Hospital Sultanah Bahiyah from January 2015 to December 2019. The female to male ratio was 1:2. The mean age of the patients was 49.6 years (range: 9 to 87 years). Majority of the patients were Malay (80.4%), followed by Chinese (12.5%) and Indian (2.9%), conforming to the local ethnicity distribution. Most of the patients were referred from government health clinic or emergency department of Hospital Sultanah Bahiyah (52.5%). The complete data on the socio-demographic is shown in Table 1.

Table 1: Socio-demoghraphic data.

Sociodemographic		n (%)
Gender	Female	273 (33.1)
	Male	135 (66.9)
Age	<21	25 (6.1)
	21-40	131 (32.1)
	41-60	112 (27.5)
	61-80	124 (30.4)
	>80	16 (3.9)
Ethnicity	Malay	328 (80.4)
	Chinese	51 (12.5)
	Indian	12 (2.9)
	Foreigner	17 (4.2)
Source of referral	Emergency department/ Government health clinic	214 (52.5)
	Private health clinic	8 (2.0)
	Private ophthalmologist	71 (17.4)
	Other specialties	7 (1.7)
	Walk-in cases	78 (19.1)
	Unknown	30 (7.4)

Slightly more than half of the patients (n=229, 56.1%) sought medical attention relatively early within three days after onset of symptoms, while 179 (43.9%) patients presented after three days. A total of 153 (37.5%) patients had an ulcer size of less than 2 mm, 128 (31.4%) had ulcer size of 2 to 4 mm and 127 (31.1%) had ulcer diameter of more than 4 mm. Most corneal ulcers were located paracentrally (181, 44.4%) followed by central (140, 34.3%) and peripheral zone (87, 21.3%). Hypopyon was present in one third (60 eyes, 33%) of the study population. Slightly more than half (207, 50.7%) of the patients required hospitalization for more than seven days for optimal treatment while 63 (15.4%) patients was treated as outpatient including those who refused hospital admission. Ocular trauma was the main predisposing factor of corneal ulcer (n=212 eyes, 52%) followed by contact lens related (n=47, 11.5%), bullous keratopathy (n=30, 7.4%) and corneal suture related (n=25, 6.1%). Thirty five (8.6%) cases had no known predisposing factor. Almost half of the patients (191, 46.8%) presented with severe vision loss with visual acuity of less than 3/60. Clinical characteristics were summarised in Table 2.

There was no significant difference between the presenting intervals of initial symptoms with visual outcome in this study. Marked Improvement of vision was observed in corneal ulcers of less than 4 mm in diameter. Central location of corneal ulcers, presence of hypopyon and high intraocular pressure (IOP) (more than 21 mmHg) was significantly related to poorer visual outcomes (p <0.001) (Table 3). Patients with bullous keratopathy, ocular surface disease and pre-existing corneal pathology also showed lesser degree of visual improvement after treatment.

Pseudomonas sp. was the commonest causative bacteria isolated (20.8%), followed by *Staphylococcus aureus* (7.1%), *Streptococcus pneumonia* (4.9%), Coagulase-negative staphylococci (*CoNS*) (1.5%), *Bacillus sp.* (1.2%) and *Hemophilus Influenza* (1.0%). Thirty cases (9.6%) had fungal growth while no pathogen was isolated in 195 of samples (47.8%). Table 4 summarised the causative organism of corneal ulcer.

DISCUSSIONS

In this study, male predominance was similar to other studies conducted in Indonesia and Thailand [4,5]. Studies in Malaysia found that male has higher incidence compared to female and predominantly in those aged 21 to 40 years (32.1%) [2,6]. This may be due to the fact that young males are the main work force, rendering themselves to higher risk of industrial ocular injury. Eighty per cent of corneal ulcer patients were Malays corresponding to the ethnicity composition of Kedah. [7].

We received most of our referrals from government clinics and emergency department, followed by private ophthalmology clinics. About 43.9% of patients presented later than three days. Hooi et al showed the average time to presentation was 4.7

Table 2: Clinical characteristics, complications and surgical intervention.

	n (%)
Presentation interval	
≤3 days	229 (56.1)
>3 days	179 (43.9)
Laterality	
Right eye	216 (52.9)
Left eye	192 (47.1)
Size, largest diameter	
≤2mm	153 (37.5)
2-4mm	128 (31.4)
>4mm	127 (31.1)
Location	
Central	140 (34.3)
Paracentral	181 (44.4)
Peripheral	87 (21.3)
Hypopyon	
Present	60 (33.3)
Absent	120 (66.7)
Hospitalization duration	
≤ 7 days	138 (33.8)
> 7 days	207 (50.7)
Not admitted	63 (15.4)
Predisposing risk factors	
Ocular trauma	212 (52)
Contact-lens related	47 (11.5)
Unknown	35 (8.6)
Bullous keratopathy	30 (7.4)
Corneal-suture related	25 (6.1)
Ocular surface disease	21 (5.1)
Eyelid pathology	14 (3.4)
Exposure keratopathy	13 (3.2)
Pre-existing corneal opacity/ Dystrophy/ Degeneration	11 (2.7)
Presenting visual acuity	
Good : 6/6 – 6/12	91 (22.3)
Moderate : 6/15 – 3/60	126 (30.9)
Severe loss : < 3/60	191 (46.8)
Final visual acuity	
Good : 6/6 – 6/12	156 (38.2)
Moderate : 6/15 – 3/60	117 (28.7)
Severe loss : < 3/60	135 (33.1)
Complication	
Corneal perforation	30 (7.4%)
Exogenous endophthalmitis	19 (4.7%)
Surgical intervention	
Evisceration	16 (3.9%)
Penetrating keratoplasty	16 (3.9%)
Glue and bandage contact	9 (2.2%)
lens (BCL)	3 (0.7%)
Temporary tarsorrhaphy	

Table 3: Presenting and final visual acuity vs clinical features.

Parameters	Final visual acuity[a], n (%)			p Value[b]
	Good	Moderate	Severe	
Presenting Interval				
≤ 3 days	94 (41.1)	63 (27.5)	72 (31.4)	0.416
> 3 days	62 (34.6)	54 (30.2)	63 (35.2)	
Size, largest diameter				
≤ 2 mm	85 (55.5)	44 (28.8)	24 (15.7)	<0.001
2-4 mm	59 (46.1)	40 (31.2)	29 (22.7)	
> 4 mm	12 (9.4)	33 (26.0)	82 (64.6)	
Location				
Central	28 (20.0)	32 (22.9)	80 (57.1)	<0.001
Paracentral	88 (48.6)	61 (33.7)	32 (17.7)	
Peripheral	40 (46.0)	24 (27.6)	23 (26.4)	
Hypopyon				
Present	45 (23.4)	51 (26.6)	96 (50.0)	<0.001
Absent	111 (51.4)	66 (30.5)	39 (18.1)	
Intraocular pressure (IOP)				
10 - 21 mm Hg	152 (45.0)	108 (32.0)	78 (23.0)	<0.001
> 21 mm Hg	4 (5.7)	9 (12.9)	57 (81.4)	
Predisposing ocular factors				
Ocular trauma	102 (48.1)	63 (29.7)	47 (22.2)	<0.001
Contact lens-related	22 (46.8)	17 (36.2)	8 (17.0)	
Bullous keratopathy	0 (0.0)	2 (6.7)	28 (93.3)	
Corneal suture-related	6 (24.0)	12 (48.0)	7 (28.0)	
Ocular surface disease	4 (19.1)	5 (23.8)	12 (57.1)	
Eyelid pathology	6 (42.9)	2 (14.2)	6 (42.9)	
Exposure keratopathy	5 (38.5)	5 (38.5)	3 (23.0)	
Pre-existing corneal Opacity/ Dystrophy/ Degeneration	0 (0.0)	3 (27.3)	8 (72.3)	
Unknown	11 (31.4)	8 (22.9)	16 (45.7)	

Table 4: Causative Organisms.

Causative organisms	n (%)
Pseudomonas spp	85 (20.8)
Staphylococcus aureus	29 (7.1)
Streptococcus pneumonia	20 (4.9)
Coagulase-negative staphylococci	6 (1.5)
Bacillus spp	5 (1.2)
Hemophilus Influenza	4 (1.0)
Fungal	30 (9.6)
Others	34 (6.1)
Unknown	195 (47.8)

Table 5: Presenting and final visual acuity vs clinical features.

Year	Aurthors	Study Period	Region	Patients	Risk factors (%)	Positive cultures (%)	Organisms		Microbiological profiles
							B(%)	F(%)	
Malaysia									
2017	Nazri O et al. (2)	2006-2013	Selangor	174	CL (47.2)	46.8	38.6	1.3	Pseudomonas (31.6%); S.aureus (5.7%)
2019	Yap YJ et al (6)	2015-2017	Kelantan	137	Ocular trauma (70.8)	75.9	51.1	24.8	Pseudomonas (27.1%); S.aureus (9.5%); Fusarium (9.5%)
2005	Hooi SH et al. (8)	1999-2002	Johor	100	Ocular trauma (41%)	-	39.6	-	Pseudomonas (58.8%); S.aureus (10.5%).
2008	Kursiah et al. (11)	2003-2004	Perak	28	Ocular trauma （32%）	70	64	36	Pseudomonas (30%)
Other countries									
2012	Napaporn T et al. (14)	2003-2006	Thailand	305	Ocular trauma (43.9%)	25.6	49.3	46.3	Fusarium(26.9%); Pseudomonas(14.9%)
2015	Asroruddin et al. (4)	2008-2011	Indonesia	216	Ocular trauma (45.8)	46.7	100	-	Pseudomonas (24.7%); S.epidermidis (18.4%)
2019	Weihan T et al. (10)	2012-2016	Singapore	230	CL (64.3)	100			Pseudomonas (51.7%); CoNS
2015	Lalitha et al. (13)	2002-2012	India	23897	-	59	24.7	34.3	Fusarium (14.5), Aspergillus (8.8); S.pneumoniae(7)
2019	Lin et al.(15)	2010-2018	China	7229	-	42.8	52.7	57.6	CoNS (28.6); Fusarium (23.5), Aspergillus (12.2)
2018	Khor et al. (12)	2012-2014	Asia	6626	Ocular trauma (34.7)	70.7	38	32.7	Fusarium (18.3); Pseudomonas (10.7); Aspergillus (8.3)
2017	Tan et al.(16)	2004-2015	Manchester, UK	4229	-	32.6	90.6	7.1	CoNS (24.4); S.aureus (15.1);Streptococci (13.3)
2020	Asbell et al. (17)	2009-2018	US	6091	-	100	100	0	S. aureus (35.9); CONS(29); H.influenza (13)

days in a tertiary hospital in Johor, Malasia [8]. The factors that delay patients from seeking medical help include lack of awareness, self-remedy, alternative treatment and over-the-counter medication as well as transportation problems [9]. For that, the public should be educated regarding the risk factors and severity of corneal ulcers and importance of early medical attention.

Predisposing factors vary in different populations. Our study found ocular trauma to be the most common predisposing risk factor (52.0%) followed by contact lens use (11.2%). Yap et al. showed ocular trauma (70.8%) was the main risk factors of corneal ulcer in East coast, Malaysia as well, where primarily agriculture activities was predominant, resembling the socioeconomic background of our study location [6]. In a similar sociodemographic background in central part of Thailand where agriculture is the main source of income, Saratorn et al found that ocular trauma (47.8%) was the commonest risk factors for corneal ulcer [10]. Nazri et al. reported that contact lens-related corneal ulcers tend to be more in the urban area (59.2%) as contact-lens are more readily available and used [2]. Contact lens were the commonest predisposing factors in Singapore (64.4%), followed by ocular trauma as contact lens are widely used by young females [11].

We found ulcers larger than 4 mm, central location and presence of hypopyon upon presentation resulted in a significantly ($p < 0.001$) poorer final visual outcome. Although ocular trauma and contact lens usage appeared to be the main predisposing factors, the overall visual improvement after treatment were better compared to those with underlying ocular pathologies and pre-existing poor visual. Weihan T et al reported that poorer visual outcome was associated with older age, non-contact lens wearer, larger corneal ulcers and trauma [11].

A total of 213 (52.2%) corneal scrapping samples yielded positive cultures. This culture yield is slightly low compared to findings by Yap et al in Kelantan (75.9%) and Kursiah et al in Perak (70%) [6,11]. Local studies in different states in Malaysia also recorded *Pseudomonas sp* as the commonest causative organism, [2,6,8,12] agreeing with studies from Singapore and Indonesia [4,11]. These can be explained by similar geographical and socioeconomic characteristics in these locations. *Fusarium sp* was found to be the main

causative organism in Asia particularly Thailand and India [13,14,15]. Coagulase-negative staphylococci *(CoNs)* was more common in China and United Kingdom (UK) while studies from the United States revealed *Staphylococcus aureus* as the main causative organism [16,17,18].

Our patients were empirically treated with combined topical aminoglycoside (gentamicin) and cephalosporin (ceftazidime or cefuroxime) after being clinically diagnosed as bacterial ulcers while topical amphotericin B and fluconazole were prescribed to those with presumed fungal keratitis. More specific antibiotics or antifungal were administered according to the culture and sensitivity results. Only 30 eyes (7.4%) were complicated with corneal perforation while 19 eyes (4.7%) developed exogenous endophthalmitis. Sixteen (3.9%) patients required penetrating keratoplasty and another 16 (3.9%) had to undergo evisceration.

We found 135 patients (33.1%) had final visual acuity worse than 3/60, almost similar to the results by Nazri et al, 21.9% [2]. Visual impairment has significant impact on individuals and society. It is important to raise public awareness regarding the risk factors of corneal ulcer, the preventive measures especially in high-risk occupation, and the urgency to seek treatment to achieve better visual outcome.

Being a retrospective design, this study has limited more thorough correlation to be established with regards to specific demographic features such as occupation, education level, financial status, smoking status, comorbidities and disease control. Duration of treatment and hospitalisation was not analysed in view of multiple confounding factors such as patient's compliance and refusal for hospital admission.

CONCLUSIONS

Ocular trauma was the main predisposing factor in our cohort of corneal ulcer patients and *Pseudomonas* sp was the commonest causative organism. Large corneal ulcer, central ulcer location, presence of hypopyon and underlying ocular pathologies contributed to worse visual outcome. The awareness of eye disease and prevention need to be emphasize in community health promotion. Routine ophthalmology training programme for primary healthcare practitioners is indeed crucial for early referral and definitive treatment in order to achieve better visual outcome.

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