Clinical Research

Various factors affecting the bacterial corneal ulcer healing: a 4-years study in referral tertiary eye hospital in Indonesia

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ABSTRAK

Latar belakang: *Ulkus kornea merupakan salah satu penyebab utama gangguan penglihatan dan kebutaan di seluruh dunia. Penelitian ini bertujuan mengevaluasi faktor-faktor yang mempengaruhi penyembuhan ulkus kornea bakteri, termasuk faktor predisposisi, organisme penyebab, sensitivitas antibiotik, dan hasil terapi.*

Metode: *Semua data diambil secara retrospektif berdasarkan rekam medis pasien ulkus selama 4 tahun (2008-2011) di Rumah Sakit Cipto Mangunkusumo, Jakarta. Dilakukan apusan kornea untuk pemeriksaan gram dan/atau kultur. Hasil terapi ulkus dianalisis menggunakan uji kai kuadrat dan* one-way ANOVA*, serta* post-hoc analysis*.*

Hasil: *Sebanyak 220 kasus ulkus kornea bakteri ditemukan berasal dari 216 pasien. Faktor risiko ulkus yang paling sering ditemukan adalah trauma okuler (45,8%). Kokus gram-positive ditemukan pada 65,7% kasus. Pseudomonas sp. (25,0%) dan Staphylococcus epidermidis (18,4%) merupakan spesies yang paling banyak ditemukan, dan sensitif terhadap hampir semua jenis antibiotik. Sekitar 83,0% (106 kasus) membaik dengan pemberian antibiotik saja, sisanya tidak membaik dan memburuk. Rerata masa penyembuhan ulkus yang sempurna adalah 17,5 ± 8,9 hari dan ulkus ringan mengalami masa penyembuhan tercepat. Ulkus yang diterapi dengan tetes mata fluorokuinolon menyembuh lebih cepat dari regimen lain yaitu dalam waktu 14 hari.*

Kesimpulan: *Trauma okuler merupakan faktor risiko ulkus kornea yang paling sering. Penyebab mikroorganisme tersering adalah Pseudomonas sp. Sebagian besar kasus membaik dengan pemberian antibiotik saja. Kasus yang diberikan fluorokuinolon menyembuh lebih cepat dibanding jenis lain. Rerata masa penyembuhan ulkus adalah sekitar 17,5 hari.*

ABSTRACT

Background: Corneal ulcer is one of the most common causes of visual acuity impairment and blindness all over the world. The aim of the study was to evaluate various factors affecting the bacterial corneal ulcers healing, including the predisposing factors, causative organisms, antibiotic sensitivity, as well as the treatment outcomes.

Methods: All data were taken retrospectively from medical records of patients who underwent corneal scraping for Gram examination and/or culture over a-4-year period (2008-2011) at the Cipto Mangunkusumo Hospital Jakarta. Treatment outcome were analyzed using Chi-square test, one-way ANOVA, and post-hoc analysis. Mean time required for complete epithelial healing was also investigated.

Results: 220 cases of bacterial corneal ulcers in 216 patients were included. The most common risk factors were ocular trauma (45.8%). Gram-positive coccus were found in 65.7% cases other than other microbes. *Pseudomonas sp.* (25,0%) and *Staphylococcus epidermidis* (18.4%) were the most common isolates, sensitive to almost all kinds of antibiotics. About 83.0% (106 cases) were improved with antibiotics only, the rest were not improved and worsened. Mean time for complete epithelial healing was 17.5 ± 8.9 days with mild ulcer had the most rapid recovery. Eyes treated with fluoroquinolone eyedrops were healed in 14 days, faster than other regiments.

Conclusion: Ocular trauma was the most common risk factor for corneal ulcer, and the most commonly isolated organism was *Pseudomonas sp.* Most cases were improved with antibiotics, and fluoroquinolone showed faster healing. Complete epithelial healing occurred in about 17.5 days.

Keywords: bacterial corneal ulcer, fluoroquinolone, *Pseudomonas sp.*

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Bacterial keratitis is now a world-wide leading cause of visual loss and blindness. Ulcerative keratitis (corneal ulcers) can be caused by bacteria, fungi, viruses, or parasites.[1-4] The incidence or number of cases varies between western and developing countries due to different predisposing factors. For example, Cipto Mangunkusumo Hospital (CMH) Jakarta has recorded 88 cases of 202 new corneal ulcers (43.6%)[5] and 132 cases of 262 new cases (50.38%)[6] in different terms. These numbers slightly differ from Thailand[7] and India.[8,9] The most leading causes of corneal ulcers are *Streptococcus*, *Pseudomonas*, and *Staphylococcus*. Study at CMH in last 20 years found *Pseudomonas aeruginosa* (49%) and *Staphyloccus epidermidis* (24%) as the causes.[10] However, in last ten years, ulcer was dominated by *Staphylococcus epidermidis*.[5,6,11]

Predisposing factors of bacterial corneal ulcers are commonly ocular trauma, contact lens users, ocular surface diseases, and as well systemic factors like diabetes mellitus and immunocompromise. Corneal ulcers are emergency cases, sight-threatening, and sometimes progressive, and also potentially resulting complications such as corneal perforation and endoftalmitis, that would need immediate surgery. Thus, this needs early diagnosis-including Gram examination and culture of corneal scraping-and agressive prompt treatment.[1-4,12,13]

This study was aimed to periodically evaluate the predisposing factors, patient demographics, clinical characteristics, causative organisms, antibiotic sensitivity and resistance, as well as the treatment outcomes of bacterial corneal ulcers at CMH. This study would obtain the empirical evidences that would be the guidelines in treating bacterial corneal ulcer.

METHODS

A retrospective analysis of all patients with positive results of gram examination and/or culture proven bacterial corneal ulcer of corneal scraping was performed. A total of 216 patients (220 eyes) registered during period of November 2012 to January 2013 at CMH were analyzed. Ulcers caused by mixed infection or immunological type were excluded.

We collected all data related to socio-demographic features, duration of symptoms, predisposing factors (history of trauma, diabetes mellitus, steroid use), prior therapy received including traditional medicine, contact lens use, and ocular and systemic disease. Initial visual acuity at the time of presentation, laterality, and all clinical findings including ulcers size and depth, inflammation reaction in anterior chamber, hypopion, and corneal scraping results were also collected. Disease severity was graded to mild, moderate, and severe based on modified Jones criteria.[14] Antibiotics resistance and treatment outcomes including mean time required for of complete epithelial healing were also assessed. The data were analyzed using SPSS 16.0 and Microsoft Excel 2007. Chi-square test and one-way ANOVA were used to analyze the treatment outcome, which p-value less than 0.05 regards as statistically significant. All data taken from medical records of patients. Confidentiality of subjects identity were guaranteed.

RESULTS

Two hundred and sixteen cases (220 eyes) or 32.9% of 656 new corneal ulcers cases were identified as bacterial ulcers during 1 January 2008 – 31 December 2011 at CMH. Others were caused by fungi, virus, *Achantamoeba*, and noninfectious ulcers.

Demographics, predisposing factors, and clinical features

Out of 216 patients, 145 (67.1%) were males and 71 (32.9%) were females. Age of patients of over 40 years old (48.6%) dominated, with range between three months old to 83 years. Demographic and clinical features are described in table 1.

Most patients did not have systemic predisposing factors (91.6%), but there were patients with diabetes mellitus, leukemia, and human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS).

Causative bacteria

Table 2 shows that microbial culture of corneal scraping were dominated by Gram-negative rods, *Pseudomonas sp* in 19 (24.7%) isolates and Gram-

Table 1. Demographics, predisposing factors, and clinical features of bacterial corneal ulcers at CMH

Variables	Number of patients/eyes	Percentage (%)
Sex (n=216 patients)		
Male	145	67.1
Female	71	32.9
Age		
< 18 years	27	12.5
19 – 40 years	84	38.9
> 40 years	105	48.6
Local predisposing factors (n=216 patients)		
External		
Surgical and non-surgical trauma	99	45.8
Contact lens use	22	10.2
Eyelid and tears dysfunction	29	12.4
Abnormal cornea	3	1.3
Topical drugs	2	0.1
Unspecified (red eye, pain, etc)	10	4.6
No records	51	23.6
Systemic predisposing factors		
Diabetes mellitus	10	4.6
HIV/AIDS	3	1.4
Immunological disorders	5	2.3
No influencing factors	198	91.67
Laterality (n=220 eyes)		
RE (right eye)	111	51.4
OU (both eyes)	4	1.9
LE (left eye)	101	46.8
Ulcer location		
Central	121	54.6
Paracentral	67	30.6
Peripheral	26	12.0
No records	6	2.8
Ulcer size		
< 2 mm	45	20.4
2 – 6 mm	118	54.2
> 6 mm	43	19.4
No records	14	6.0
Mean (n=203 eyes) 4.1 mm ± 0.2		
Ulcer depth (stromal)		
< 1/3	41	19.0
1/3 - 2/3	108	49.1
> 2/3	10	4.6
Perforation	43	19.9
No records	18	8.3

positive coccus, *Staphylococcus epidermidis,* 14 isolates (18.42%). Culture was not performed in eight patients because of small lesion and evidence of clinical improvement after given prior therapy.

Pattern of bacterial resistance and sensitivity to some antibiotics are shown in table 3 below.

Treatment outcome

Topical antibiotic was given to all subjects in this study as the initial therapy. Treatment outcome of bacterial corneal ulcer is classified into improved, not improved (steady), and worsen. Clinical improvement was noted in 106 patients, in which 62 of them followed the treatment until corneal ulcers healed. The remaining 44 patients were lost to follow up. No improvement and clinical worsening were experienced by four and 18 patients, respectively, and they were further underwent surgery such as amniotic membrane transplantation (AMT) one patient, penetrating keratoplasty eight patients, periosteal graft three patients, and evisceration two patients (Table 4).

Out of 62 patients who followed the treatment until formation of corneal scarring, mean days of epithelial healing or corneal scarring form could

Table 2. Microbial culture of corneal scrapping in 76 samples

Bacteria	Samples (n=76)	Percentage (%)
Gram-positive *coccus*		
Staphylococcus epidermidis	14	18.42
Streptococcus anhaemolytic	2	0.26
Staphylococcus saprophyticus	2	0.26
Staphylococcus aureus	2	0.26
Streptococcus viridians	2	0.26
Methicillin-resistant *Staphylococcus epidermidis*	1	0.13
Gram-positive rods		
Bacilus sp	3	0.39
Gram-negative rods		
Pseudomonas sp	19	24.7
Acinetobacter sp	7	0.92
Acinetobacter calcoaceticus	3	0.39
Escherichia coli	2	0.26
Klebsiella pneumonia	1	0.13
Proteus mirabilis	1	0.13
Enterobacter aerogenes	1	0.13
No microbial growth	16	20.8

Table 3. Culture pattern of bacteria with some antibiotics

Culture results	Gentamycin			Ciprofloxacin			Ceftazidime			Gatifloxacin			Levofloxacin		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Acinetobacter calcoaceticus	1	-	2	3	-	-	3	-	-	2	1	-	3	-	-
Acinetobacter sp	7	-	-	5	1	-	4	-	-	5	1	1	5	-	1
Bacilus sp	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Enterobacter aerogenes	-	1	-	-	1	-	-	-	1	-	-	1	-	-	1
Escherichia coli	3	1	-	2	1	-	2	1	-	1		1	1		
Klebsiella pneumonia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MR Staphylococcus epidermidis	-	-	-	1	-	-	-	-	1	1	-	1	1	-	-
Proteus mirabilis	1	-	-	1	-	-	-	-	-	1	-	-	1	-	-
Pseudomonas sp	14	1	2	15	-	2	13	-	1	8	3	2	12	-	1
Staphylococcus aureus	1	-	-	2	-	-	1	-	1	2	-	-	2	-	-
Staphylococcus epidermidis	-	-	1	9	1	2	7	2	2	6	1	1	11	-	1
Staphylococcus saprophyticus	-	-	-	2	-	-	2	-	-	2	-	-	2	-	-
Streptococcus anhaemolytic	1	-	-	1	-	1	-	-	1	-	1	-	1	1	-
Streptococcus viridians	-	-	2	-	1	1	1	-	1	1	-	1	1	-	1

S : Sensitive; I : Intermediate; R : Resistent

Table 4. Treatment outcomes of corneal ulcer according to disease severity and types of antibiotics

Ulcers Grading	Treatment Outcome			Total
	Improved (%)	Not improved (%)	Worsen (%)	
Mild	11 (100)	0 (0)	0 (0)	11
Moderate	59 (89)	2 (3)	5 (8)	66
Severe	36 (71)	2 (4)	13 (26)	51
Total	106 (83)	4 (3)	18 (14)	128
Antibiotics				
Fluoroquinolone	73 (88)	2 (2)	8 (10)	83
Aminoglycoside	20 (69)	2 (7)	7 (24)	29
Cephalosporine	10 (100)	0 (0)	0 (0)	10
Combination	3 (50)	0 (0)	3 (50)	6

Table 5. Mean time for epithelial healing based on ulcers grading and antibiotics group

Variable	Patients (n=48)	Mean time (days)
Ulcer grading		
Mild	5	7 (3-30)
Moderate	28	15.8 ± 8.4
Severe	15	21.9 ± 7.9
Total	48	17.5 ± 8.9
Antibiotics group		
Fluoroquinolone	29	14 (3-30)
Aminoglycoside	11	19.2 ± 8.6
Cephalosporine	7	19.6 ± 1.08

be analyzed in 48 patients (mild 25 pts, moderate 28 pts, severe 15 pts) whose. Fourteen patients were excluded because they had predisposing factors that could inhibit healing process such as lagophtalmus and corneal exposure, diabetes mellitus, HIV/AIDS, persistent trichiasis, chemical injury, and immunocompromise in leukemic patients.

Regardless of disease severity, it is shown that the fastest time for corneal healing was found in fluoroquinolone group (14 days), followed by aminoglycoside group (19.2 + 8.6 days), and cephalosporine group (19.6 ± 1.08 days, table 5).

DISCUSSION

Microbial corneal ulcers are the major cause of visual loss and blindness in Indonesia. The male versus female ratio in this study was 2:1. This was similar to other study conducted by Sirikul, et al[7] in Thailand. This is probably men have more outdoor activities than women, so that the higher the risk to have ocular trauma and exposure of foreign body. This also explains that the most

common predisposing factor in our study was ocular trauma. However, our ratio was different from other study that conducted by Fong, et al[15] in Taiwan dan Marangon, et al[16] in New York (1:1), Bharathi, et al[8] in southern India (1.5:1), and Shalchi, et al[17] (1:1.5). Corneal ulcer in our study affected mostly aged over 40 years of old and young adults. This study was quite similar to study performed by Srinivasan, et al[9] (61.3%), and Narsani, et al[18] in Pakistan.

Ocular trauma was the leading predisposing factor for corneal ulcer in our study. This result was similar to study by Damayanti and Sitompul[5], Bharathi, et al[8], and Srinivasan, et al.[9] However, our result was different from study by Fong, et al[15] and Keay, et al[19] in Australia that found contact lens use (44.3%) as the most common factor, and trauma (23.8%), as well as by Mah-Sadorra, et al[13] and Bourcier, et al.[20]

The causative bacterium found in our study was *Pseudomonas sp*. This finding was similar to study performed by Damayanti and Sitompul[5] and Fong, et al.[15] However, Narsani, et al[18] in Pakistan found *Staphylococcus aureus* as the most common isolate, followed by *Pseudomonas aeruginosa* dan *Streptococcus pneumoniae.* On the other way, Chawla, et al[21] found *Staphylococcus epidermidis* (77,0%) as the predominant isolate. *Pseudomonas sp.* as the most commonly found bacterium, mostly sensitive to gentamycin, ciprofloxacin, ceftazidime, gatifloxacin, dan levofloxacin. This result was different from study by Sitompul, et al[10] in last decade that 27% Pseudomonas had already resistant to gentamycin. *Staphylococcus epidermidis* was also dominantly sensitive to vancomycin, levofloxacin, dan gatifloxacin except gentamycin. Resistance to fluoroquinolone group had been partly encountered, primarily to ciprofloxacin, levofloxacin, dan gatifloxacin. This supports similar result in study by Damayanti and Sitompul[5], Shalchi, et al[17], and Maske, et al.[22]

Our treatment outcome which gained up to 80% patients with clinical improvement was better than study conducted by Hussain, et al[23] that reached 68.4% patients, and Damayanti and Sitompul[5] during 2005-2007 that reached 74,0%. The most common used antibiotics in our study were topical fluoroquinolone and aminoglycoside eyedrops with proper concentration. Single used antibiotics (monotherapy) was given more than combined formula. The standard dose was also given more than fortified dose. Fluoroquinolone is used frequently because of its good sensitivity for all groups of bacteria, Gram-positive and Gram-negative, including good ocular penetration and longer half-life. In our study, most patients treated with fluoroquionolone revealed better clinical improvement than treated by other groups. Type of antibiotics were commonly ofloxacin and levofloxacin, other than moxifloxacin as fourth generation quinolones. However, Shah, et al[24] dan Kowalski, et al[25] in their clinical trial found that moxifloxacin or gatifloxacin gave better potency in combating bacteria, even for resistent bacteria by second and third generation quinolones.

Besides fluoroquinolones, some patients in our study were also given combined therapy of cefazolin 10% + tobramycin 1.5%. This therapy suits WHO guidelines for bacterial corneal ulcer in Southeast Asia region. Study by Khokhar, et al[26] found that this combination compared to ofloxacin had no different clinical outcomes. Mean day for epithelial healing was approximately 15 days, as well as study by Panda, et al[27] dan Constantinou, et al[28]. However, these two groups were not applicable to our study since only one patient included. Nevertheless, regarding the efficacy and safety, good availability and cost-effective, and issue of kitchen pharmacy, clinicians prefer to give fluoroquinolones as initial empirical therapy for bacterial corneal ulcers in last decades. The mean days of epithelial healing in our study, 17.5 days, was better than results in study of Damayanti and Sitompul[5] which was 19 days. Healing in moderate corneal ulcer was 15.8 days, which is also better than study of Damayanti and Sitompul[5], 17 days. Our result was quite similar to study of Khokhar, et al[26] and Panda, et al[27] with the similar method.

This study has some limitations including the design as retrospective study, in which not all medical records can be included, high rate of lost to follow-up (35.2%), and low rate of bacterial culture (< 50%).

In conclusion, the most common risk factor for bacterial corneal ulcers in this study was trauma, and the most commonly isolated organism was *Pseudomonas sp*. Most cases were improved with antibiotic only, and fluoroquinolones showed

faster healing. Complete epithelial healing occurred in 17.5 days. These factors affected features of the corneal ulcers healing in this study.

Conflict of Interest

The authors affirm there is no conflict of interest in this study.

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