Topical Ciprofloxacin for Bacterial Corneal Ulcer

PANIDA KOSRIRUKVONGS, M.D.*,
WIPAWEE BURANAPONGS, M.D.*

Abstract

Objective : To assess topical ciprofloxacin in patients with moderate severity of suspected bacterial corneal ulcers.

Study Design : Randomized, controlled clinical trial.

Setting : Inpatient at Siriraj Hospital.

Participants : All patients with suspected corneal ulcers. Patients with fungal cause known before admission and an allergy to any medication, were excluded.

Intervention : Topical ciprofloxacin 0.3 per cent or cefazolin (50 mg/ml) and fortified gentamicin (14 mg/ml) were given every 15 minutes for the first 6 hours, then every half hour on the first day, and every hour while awake till midnight until complete recovery without staining of fluorescein and no culture growth.

Main Outcome Measures : The primary outcomes were the success rate and duration of the healing of the ulcer after treatment in each group.

Results : Forty-one patients were enrolled. Twelve (70.6%) of 17 patients in the ciprofloxacin group were therapeutically successful while 15 (62.5%) of 24 patients in the control group showed similar outcome without a statistically significant difference. However, the mean duration for healing after treatment was not significantly different being 14.6 days in the control group and 15.6 days in the ciprofloxacin group. Visual improvement in the success cases of the control and ciprofloxacin groups was 46.7 per cent, and 66.7 per cent, respectively.

Conclusion : Treatment with topical ciprofloxacin in suspected bacterial corneal ulcer should be considered as an alternative to standard therapy.

Key word : Bacterial Corneal Ulcer, Topical Ciprofloxacin

KOSRIRUKVONGS P & BURANAPONGS W
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* Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Unsuccessful treatment of bacterial corneal ulcers may lead to blindness from perforation, endophthalmitis, panophthalmitis and cavernous sinus thrombosis which is a serious complication and cause of death(1). Because of the high negative result of Gram's stain and culture from corneal scraping, or delayed report, standard broad-spectrum antibiotics cefazolin and fortified gentamicin are widely used for initial treatment instead of commercially available low concentration topical antibiotics(2,3). The small number or absence of organism may be caused by prior treatment or other causes such as virus, parasite or fungus(4). Prompt recognition, accurate diagnosis, and proper management are essential for successful treatment. However, many varieties of organisms may be resistant to these broad spectrum antibiotics. In addition, a study of standard treatment regimen at Siriraj Hospital revealed that their efficacy had only a 65 per cent success rate in moderate severity of corneal ulcer patients(5). The cost of this treatment is approximately two hundred and fifty baht and is inconvenient to prepare as an intravenous drug mixed in tear substitutes for cefazolin and commercial bottles with low concentration for gentamicin with the risk of contamination and adverse reactions. These are the main reasons for seeking an inexpensive but highly effective commercial eye drop on the market which is ready to use. Leibowitz and others have reported that new broad spectrum antibiotics, 0.3 per cent ciprofloxacin or fluorinated quinolone, have a high efficacy of 91.9 per cent which is an interesting development in the new trend of treatment(6,7). Studies have demonstrated that ciprofloxacin inhibits DNA gyrase with excellent ocular penetration and activity against gram positive and negative bacteria including methicillin-resistant *Staphylococcus aureus* and gentamicin-resistant *Pseudomonas aeruginosa* (8-12). In addition, bacteria with resistance to ciprofloxacin have been shown to occur at a low rate by chromosomal mutations rather than exchanges of resistant genes(13,14). Because no study has been carried out on ciprofloxacin in the treatment of corneal ulcers in Thailand, and because of the low cost of ciprofloxacin compared with standard regimens, it may be the suitable choice as treatment to diminish the complications of corneal ulcer in Thailand and permit patients to quickly return to normal life.

The purpose of this study was to evaluate the efficacy of topical ciprofloxacin 0.3 per cent compared with standard regimens of fortified gentamicin-cefazolin for treatment of bacterial keratitis.

MATERIAL AND METHOD

Forty-one patients with moderate bacterial corneal ulcers (2-6 mm in diameter) diagnosed clinically with a negative smear of KOH preparation at Siriraj Hospital were studied from February 1996 to September 1997 with informed consent. Exclusion criteria was one eye, pregnant women, and those patients who stopped the treatment. All patients had thorough history-taking, best-corrected visual acuity, intraocular pressure measurement, eye examination on a slit lamp biomicroscope to measure the size and depth of the lesion, and anterior chamber cell reaction performed before and after treatment everyday, after staining the cornea with fluorescein. Corneal scrapings were performed under a slit lamp biomicroscope for Gram's stain, 10 per cent KOH preparation, bacterial culture on blood agar, chocolate agar, and thioglycollate broth, mycobacterium culture on Lowenstein Jensen media and fungal culture on Sabouraud dextrose agar. The patients randomly received topical cefazolin (50 mg/ml) and fortified gentamicin (14 mg/ml) in the control group, or ciprofloxacin 0.3 per cent as ciprofloxacin group every 15 minutes for 6 hours, then every half hour on the first day, later every hour till midnight until healing occurred. Clinical success was defined as the absence of symptoms and signs, no staining of fluorescein, negative smear and no growth on culture. At each clinical observation, ocular signs and symptoms were graded by the following scale: 0=absent, 1=mild, 2=moderate and 3=severe. Final grading of treatment efficacy was defined as successful (cured or improved) or failed (unchanged or worse). Signs of clinical improvement were decreased or stopped progression of lesion, blunt edges, neovascularization and decreased anterior chamber cell reaction. Both groups of patients were treated with atropine sulfate 1 per cent, twice daily. When a negative smear and no growth result were initially reported, the ulcer was scraped again for re-identification and acanthamoeba culture. If the ulcer did not respond well to the test drug within 3 days, the alternative drug was given. If it also failed, we used other antibiotics such as vancomycin and amikacin or following the result of culture and sensitivity. If all medication failed, surgery such as penetrating keratoplasty or enucleation was finally performed. Chi square test and Student's *t* test were used to assess differences in demographic variables and treatment outcomes.

RESULT

Forty-one patients with moderate corneal ulcer were randomly administered topical cefazolin and fortified gentamicin in the control group (n=24), and topical ciprofloxacin in the ciprofloxacin group (n=17), as shown in Table 1. Most patients were labourers in 13 cases, retired personnel in 9 cases, and farmers in 5 cases. There were no statistically significant differences between the groups with respect to sex, injury before presentation, associated systemic diseases, mean duration of ulcer before treatment and mean ulcer size, although associated systemic diseases in the control group was less frequent than in the ciprofloxacin group, including shorter duration of ulcer and smaller size. The mean age in the control group was significantly younger than in the ciprofloxacin group (P=0.021). Males were predominantly affected in both groups. Twenty (48.8%) of 41 patients had injury caused by metal (7 cases), splinters (6 cases), dust (5 cases), soil (1 case) and chemical (1 case). Predisposing factors in the control group (16.7%) were significantly less than in the ciprofloxacin group. (47%, P=0.045). In the control group there were 2 entropions, 1 lagophthalmos, and 1 with contact lenses. In the ciprofloxacin group, there were 2 lagophthalmos, 1 entropion, contact lenses, lattice corneal dystrophy, pseudophakic bullous keratopathy and glaucoma, dry eye and glaucoma, and graft failure with aphakic bullous keratopathy. Eight (19.5%) of 41 patients had systemic diseases, including 2 HIV infection, 2 allergy, 1 hypertension, myasthenia gravis, hyperthyroidism and bone tumor.

Bacteria were found in 21 (51.2%) of 41 patients evidenced from positive Gram's stain 9 cases (21.9%) and culture-proven 17 cases (41.5%). Gram positive diplococci 6 cases, positive cocci 2 cases and negative bacilli 1 case were found in our study. Thirteen (54.2%) of 24 control patients had positive culture results for *Pseudomonas aeruginosa*, the most frequently isolated organism, whereas five (29.4%) of 17 ciprofloxacin treated patients had positive cultures for 2 *Staphylococcus aureus*, 2 *Pseudomonas aeruginosa* and 1 Fusarium species (late report), P=0.210, as shown in Table 1. In the control group, there were mixed bacterial infections with *Citrobacter freundii* and *Pseudomonas aeruginosa* was found in one patient. Mixed bacterial and fungal infections (nonfermentative gram negative bacilli and candida nonalbicans) were also found in one patient in the control group.

Table 1. Characteristics of patients.

	Control n = 24		Ciprofloxacin n = 17		P-value
	no	%	no	%	
Sex : male	15	62.5	12	70.6	0.839
Mean age (yr±SD)	39.9±21.5		55.2±16.9		0.021*
Injury	13	54.2	7	41.2	0.615
Predisposing factors	4	16.7	8	47.0	0.045*
Systemic diseases	3	12.5	5	29.4	0.241
Mean duration (days±SD)	11.9±18.5		24.1±56.3		0.328
Mean ulcer area (mm^2±SD)					
epithelium	13.2±11.9		16.6±10		0.358
stroma	21.6±13.1		24.4±11.9		0.634
Culture result					
Gram positive cocci					
S. aureus (MSSA)	-		2		
S. pneumoniae	2		-		
Gram negative bacilli					
Citrobacter freundii	1		-		
Klebsiella pneumoniae	1		-		
Nonfermentative negative bacilli	1		-		
Pseudomonas aeruginosa	9		2		
Fungus					
Candida non-albicans	1		-		
Fusarium species	-		1		

Table 2. Response to treatment.

	Control* (%)	Ciprofloxacin (%)	P-value
Clinical success	15/24 (62.5)	12/17 (70.6)	0.839
Mean time to heal (days±SD)	14.6±5.8	15.6±8.6	0.726
(min, max)	(6, 27)	(6, 31)	
Visual improvement	7/15 (46.7)	8/12 (66.7)	0.516
In success cases			
> 2 line	4	8	
> 1 line	3	-	
Final visual acuity in success cases			
$^6/_6$	0	1	
$^6/_9$-$^6/_{12}$	1	1	
$^6/_{18}$-$^6/_{36}$	4	6	
$\leq ^6/_{60}$	9	4	

* visual acuity measurement could not be done in one case aged one year old.

The average time to heal in 15 successful cases (62.5%) in the control group was 14.6 ± 5.8 days *versus* 15.6 ± 8.6 days in 12 successful cases (70.6%) of the ciprofloxacin group with visual improvement of 46.7 per cent and 66.7 per cent, respectively (Table 2). Final best corrected visual acuity under $^6/_{60}$ in the control group was 9 (64.3%) of 14 cases, but 4 (33.3%) of 12 cases in the ciprofloxacin group. The overall clinical efficacy of treatment with ciprofloxacin was better than the standard therapy.

Nine (37%) of 24 patients in the control group required ciprofloxacin and other antibiotic regimens because of poor results with conventional therapy, whereas only 5 (29%) of 17 ciprofloxacin-treated patients required a change in their antibiotic regimen.

Failure in the control group caused from unknown causes numbered 5 cases, *Streptococcus pneumoniae* 2 cases, *Klebsiella pneumoniae* 1 case, and nonfermentative gram negative bacilli and candida nonalbicans 1 case. Whereas culture results in cases of failure in the ciprofloxacin group were no growth 4 cases, and Fusarium species 1 case with late report. Three (33.3%) of 9 failures in the control group were successful with ciprofloxacin (2 no growth, and 1 *Streptococcus pneumoniae* with response to treatment in 7, 12 and 13 days). One case of *Klebsiella pneumoniae* responded to other antibiotic regimens (vancomycin and amikacin) in 11 days. Three cases with unknown causes responded to a topical antifungal drug (0.2% amphotericin B) in 16, 19 and 24 days. One (20%) of 5 failures in the ciprofloxacin group from unknown cause responded to topical cefazolin and fortified gentamicin in 29 days. One unknown cause and Fusarium case of 2 failures in the ciprofloxacin group were successful with topical antifungal in 20 days and 58 days, respectively.

Surgery was performed in 2 cases of failure in each group, 1 conjunctival flap from perforation caused by *Streptococcus pneumoniae*, and 1 enucleation due to lack of response to treatment in the control group caused by candida nonalbicans. Keratoplasty was performed in two cases of the ciprofloxacin group from perforation. A white crystalline precipitate, the only adverse effect of ciprofloxacin, was noted on the cornea between 1-2 weeks after medication in 3 (17.6%) of 17 patients. This precipitate remained on the cornea and dissolved after reducing or discontinuation of medication without sequelae. No severe adverse effects were noted in the ciprofloxacin group.

DISCUSSION

Initial therapy was carried out in bacterial keratitis with intensive fortified antibiotic treatment designed to sterilise the cornea and limit further inflammatory damage, preventing superinfection and promoting epithelial healing[15]. The fluorinated quinolone antibiotic, ciprofloxacin which is a new broad spectrum antimicrobial activity with low toxicity, low resistance rate, low minimum inhibitory concentration and stability in aqueous solution and good ocular penetration was used[10,16,17]. Monotherapy with ciprofloxacin may be the most appropriate treatment in pseudomonas with resistance to aminoglycosides which has become a significant problem[18]. Moreover, ciprofloxacin is less toxic and causes less discomfort than aminoglycosides[19-21].

This randomised clinical trial has shown slightly better results with the use of ciprofloxacin than with conventional therapy, similar to many previous studies[6,21-23]. However, late treatment associated with greater severity and larger initial mean ulcer area in our study may be the cause of our lower clinical success (70.6%) compared with others that have reported success rates of 72.7 per cent to 91.9 per cent with different geographic location, climate and humidity[6,21,23]. There was no statistically significant difference in clinical effectiveness of treatment with ciprofloxacin compared with standard therapy. The average time to cure the ulcer in the ciprofloxacin treated patients was approximately 2 weeks relative to standard therapy (15.6 *versus* 14.6 days, P=0.726, Table 2). As was found in other studies, time to cure ulcer was clinically equivalent for ciprofloxacin relative to fortified tobramycin and cefazolin (14.0 days *versus* 13.5 days, 15.7 days *versus* 29.9 days)[21,24]. However, contrary to Parks' report, the average time to heal in the ciprofloxacin group was 34 days *versus* 45 days in the control group which is longer than our study[25]. The frequency of drug application in our study, every hour till healing after the second day is different from every 4 hours for 12 days in Parks' study, and this may result in the faster recovery in our patients. However, the longer time for recovery in ciprofloxacin treated patients in our study may be due to older age, more predisposing factors and systemic diseases, longer duration before treatment and larger initial mean ulcer area. The slow reparative process in older age might be a contributing factor and important to healing because of statistically significant differences in age between the two treatment groups.

Comparing visual results with standard regimens, ciprofloxacin appears to give more improvement and to be suitable for treatment of corneal ulcer. It provides antibacterial efficacy against the most common ocular pathogens isolated in patients with bacterial corneal ulcers. It was safe and well tolerated. No adverse events were reported related to ciprofloxacin, except the white precipitate, similar to other reports,[21,23] but less than in Parks' study (42%)[24].

This study indicates that ciprofloxacin monotherapy is an effective and safe treatment for bacterial corneal ulcers compared with fortified gentamicin and cefazolin.

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ผลการรักษาแผลกระจกตาด้วยยาหยอดตาซิโปรฟล็อคซาซิน

พนิดา โกสียรักษ์วงศ์, พ.บ., วิภาวี บูรณพงศ์, พ.บ.**

วัตถุประสงค์ เพื่อศึกษาผลการรักษาแผลกระจกตาที่สงสัยติดเชื้อแบคทีเรียในโรงพยาบาลศิริราช ด้วยยาหยอดตาซิโปรฟล็อกซาซิน แบบสุ่มตัวอย่าง เปรียบเทียบกับยามาตรฐานที่เตรียมจากยาฉีด cefazolin (50 มก/มล) และ gentamicin (14 มก/มล) ในรายที่ทราบมาก่อนว่าติดเชื้อราหรือแพ้ยาตัวทดสอบ จะคัดออกจากการศึกษา

วิธีการ ให้ยาหยอดตาบ่อยทุก 15 นาทีใน 6 ชั่วโมงแรก หลังจากนั้นทุก 30 นาทีในวันแรก วันรุ่งขึ้นหยอดทุก 1 ชั่วโมงจนถึงหลับ จนกระทั่งแผลหาย ย้อมไม่ติดสี fluorescein และไม่พบเชื้อ ถือว่าประสบความสำเร็จและบันทึกระยะเวลาที่หาย หลังจากรักษาในแต่ละกลุ่ม

ผล ผู้ป่วยในกลุ่มรักษาด้วยซิโปรฟล็อกซาซิน 17 ราย หาย 12 ราย คิดเป็นร้อยละ 70.6 มากกว่า ผู้ป่วยที่รักษาด้วยยามาตรฐาน 24 ราย หาย 15 ราย คิดเป็นร้อยละ 62.5 โดยระยะเวลาที่หายในกลุ่มยามาตรฐานและยาซิโปรฟล็อกซาซินใกล้เคียงกันประมาณ 2 สัปดาห์ ระดับการมองเห็นหลังรักษาในกลุ่มยามาตรฐานน้อยกว่า กลุ่มซิโปรฟล็อกซาซิน คิดเป็นร้อยละ 46.7 และ 66.7 ตามลำดับ

สรุป การรักษาแผลกระจกตาที่สงสัยติดเชื้อแบคทีเรียด้วยซิโปรฟล็อกซาซิน ได้ผลดีใกล้เคียงกับยามาตรฐาน

คำสำคัญ : แผลกระจกตา, ยาหยอดตาซิโปรฟล็อกซาซิน

พนิดา โกสียรักษ์วงศ์, วิภาวี บูรณพงศ์,
จดหมายเหตุทางแพทย์ ฯ 2543; 83: 776–782

* ภาควิชาจักษุวิทยา, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10700