Comparison of Topical Lomefloxacin 0.3 Per Cent *versus* Topical Ciprofloxacin 0.3 Per Cent for the Treatment of Presumed Bacterial Corneal Ulcers†

WIPAWEE BOORANAPONG, MD*,
PINNITA PRABHASAWAT, MD*,
PAWEENA SUTTIPRAKARN, MD*
PANIDA KOSRIRUKVONGS, MD*,
SABONG SRIVANNABOON, MD*,

Abstract

Purpose : To compare the efficacy and safety of topical lomefloxacin 0.3 per cent with topical ciprofloxacin 0.3 per cent for treating mildly severe suspected bacterial corneal ulcers.

Method : This prospective, randomized, double-masked controlled clinical trial was conducted on 41 patients (41 eyes) with suspected bacterial corneal ulcers who were randomized into 2 groups: 23 patients were in the lomefloxacin group and 18 patients in the ciprofloxacin group. All of these corneal ulcers were scraped for gram's stain, KOH preparation and microbiologic cultures before starting treatment. The clinical success rate, the time to cure, the rates of treatment failures, ocular signs and symptoms and the adverse effects of the study medication were evaluated.

Results : Topical lomefloxacin is equivalent clinically and statistically to topical ciprofloxacin. No statistically significant treatment differences were found between lomefloxacin (100%) and ciprofloxacin (100%) in terms of success rate. Similarly, no differences were noted in the time to cure ($p > 0.05$), the treatment failure, or the resolution of the clinical signs and symptoms ($p > 0.05$). The adverse effects of lomefloxacin were superficial punctate keratitis (26.1%) and irritation (8.7%), whereas those of ciprofloxacin were superficial punctate keratitis (22.2%), white precipitate (11.1%) and irritation (11.1%). However, no statistically significant differences of these adverse effects were found between the two groups ($p > 0.05$).

Conclusion : Lomefloxacin ophthalmic solution (0.3%) is equivalent clinically and statistically to ciprofloxacin ophthalmic solution (0.3%) for the treatment of mildly severe presumed bacterial corneal ulcers without statistically significant differences in the adverse effects and discomfort.

Key word : Corneal Ulcer, Bacterial Keratitis, Lomefloxacin, Ciprofloxacin

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* Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.
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Bacterial corneal ulcer is the most common cause of infectious ulcerative keratitis and can result in severe visual loss[1,2]. The standard conventional broad-spectrum fortified antibiotics, the combination of the first generation cephalosporin or vancomycin and aminoglycosides agent, are administered at high concentrations for the treatment of these ulcers[3-7] instead of commercially available, low concentration ophthalmic antibiotics. The disadvantages of using fortified antibiotics are its possible bacterial contamination during preparation, unstable pH, short storage duration, high cost, inconvenient preparation and administration including the adverse effects especially local toxicity to the ocular surface epithelium[8,9]. Therefore, it will be of great benefit to use the commercially available, topical antibiotics if they can provide broad-spectrum of antibacterial activity, low bacterial resistance rates, and good corneal penetration.

Ciprofloxacin is a fluoroquinolone antibiotic, which has become widely used in the treatment of bacterial corneal ulcers as an alternative to conventional therapy[10-14] because of its broad-spectrum against most aerobic gram-positive and gram-negative bacteria, good ocular penetration, low toxicity, low resistance and is commercially available[15-17]. It was approved by US Food and Drug administration for topical treatment of bacterial corneal ulcer in 1990.

Lomefloxacin, a difluorinated quinolone, is one of the new second-generation fluoroquinolones that is available as a topical ophthalmic preparation. It is a potent bacterial DNA gyrase and topoisomerase IV inhibitor with broad-spectrum of bactericidal activity against a wide variety of gram-negative (including pseudomonas aeruginosa) and gram-positive bacteria [15-21]. In experimental studies, lomefloxacin has been shown to have long lasting concentrations in the tear film as well as excellent and rapid corneal penetration[19-21]. Preclinical and clinical studies have demonstrated the high efficacy of topical lomefloxacin 0.3 per cent in the treatment of acute bacterial conjunctivitis[22-24]. However, there have been no publications evaluating the efficacy of topical lomefloxacin for the treatment of human bacterial corneal ulcer.

The purpose of this study was to determine the clinical efficacy and the adverse effects of topical lomefloxacin 0.3 per cent (Okacin, Novartis Ophthalmics, Thailand) compared with topical ciprofloxacin 0.3 per cent (Ciloxan, Alcon Laboratories, Thailand) in the treatment of suspected mild bacterial corneal ulcer.

The study drug used in this investigation was lomefloxacin 0.3 per cent eye drops (Okacin, Novartis Ophthalmics, Thailand). The active control medication was ciprofloxacin 0.3 per cent eye drops (Ciloxan, Alcon Laboratories, Thailand).

MATERIAL AND METHOD

Study design

This prospective, randomized, double-masked controlled clinical study was conducted at the Department of Ophthalmology, Siriraj Hospital, Faculty of Medicine, Mahidol University from January 2002 to February 2003. An Institutional Review Board/Ethics Committee approval was obtained for this study, and a patient consent form was signed by all subjects before participation in this clinical trial.

Study population

Initially forty-six outpatients (46 eyes) with clinically presumed bacterial corneal ulcer of mild severity[25,26] defined as an epithelial defect $\leq$ 2 millimeters in diameter, stromal infiltration $\leq$ 1/3 of the corneal thickness and no hypopyon were enrolled in the study. Patients were excluded from enrollment if they had corneal ulcers with positive smear of KOH, positive culture for fungus, acanthamoeba or other organisms, moderate and severe degrees of corneal ulcers[25,26], and a past history of herpes or viral keratitis. The patients who were allergic to quinolone group antibiotics, children younger than 1 year of age and pregnant woman were not enrolled.

Clinical procedures

Past and present ocular and medical histories were recorded for each patient. Best-corrected visual acuity was measured in both eyes. Anterior segment examinations were performed using Haag-Streit slit lamp biomicroscopy to determine the location, shape and size of epithelial defect (using fluorescein staining), stromal infiltration and anterior chamber reaction. Corneal ulcer scrapings were performed under slit lamp biomicroscope after topical anaesthesia with 0.5 per cent tetracaine eye drops. Microbiologic identification included gram's stain, KOH preparation and culture in blood agar, chocolate agar, sabouraud dextrose with chloramphenicol agar and sabouraud dextrose without chloramphenicol agar. The patients were randomized (concealed envelope, true randomization) to receive either topical lomefloxacin 0.3 per

cent (Okacin, Novartis Ophthalmics, Thailand) or topical ciprofloxacin 0.3 per cent (Ciloxan, Alcon Laboratories, Thailand). The patients and the examiners (authors WB, PS) did not know the medication, which the patients received. All of the examinations were performed by two investigators (WB, PS) throughout the course of the study. The medication eye drops were delivered to the patients by the nurse who was not involved in the examinations. The dosing regimens were informed by the investigators and were printed in the patient information sheet as follows: instill 1 drop every 15 minutes for the first 6 hours and then 1 drop every hour until midnight on the first day; then 1 drop every hour until bedtime on the following days. The patients were followed-up every 3 days as outpatients.

Physician impression and evaluation of ocular signs and symptoms were performed on the first day and every 3 days. The administration of the medication eye drop was interviewed at every visit. If the dosage of the medication eye drop could not be achieved, the patients would be asked to be admitted in the hospital. Visual acuity of both eyes was determined at each visit including ocular symptoms such as pain, redness and irritation. The following ocular signs were recorded: lid erythema or swelling, conjunctival discharge, bulbar conjunctival hyperemia, corneal epithelial defect, stromal infiltration and anterior chamber reaction. The physicians evaluated the patient's overall clinical conditions and made one of five possible judgments (cured, improved, improving, unchanged, or worse) regarding response of the corneal ulcer to therapy at each follow-up visit (Table 1). A final evaluation was made on cessation of the study treatment.

If the ulcer was improving, the medication eye drop was continued by instilling 1 drop every hour until no epithelial defect (improved ulcer), then reduced to1 drop every 2 hours until no stromal infiltration (cured ulcer), then 1 drop four times a day for 1 week.

If the ulcer became worse at anytime during the study, the study medication was discontinued and corneal scraping was repeated for microbiologic identification. The patient was considered as a treatment failure and an alternate treatment regimen for moderate corneal ulcer was instituted.

In case there was no change in the corneal ulcer after 6 days of treatment, that medication eye drop was revealed and cross-over treatment with another medication eye drop was given with the same dosing and follow-up every 3 days. If the ulcer did not respond to the treatment (as indicated as unchanged or worse), it was judged as a treatment failure.

Statistical method

Chi-square test for independence was used to assess differences between lomefloxacin and ciprofloxacin in age, gender, predisposing factors and prestudy therapies. The independent sample *t*-test was used to assess differences between lomefloxacin and ciprofloxacin in mean age, mean time to cure, mean time to the resolution of ocular signs (bulbar conjunctival injection, corneal epithelial defect and stromal infiltration) and mean ulcer area. To show equivalence between lomefloxacin and ciprofloxacin, 95 per cent confidence intervals were calculated using the percentage of patients with cured *versus* the percentage of treatment failure patients at the final visit. The two treatments were considered equivalent if the absolute value of the lower 95 per cent confidence interval was within 20 per cent of scale range.

Time to cure (number of days that medication eye drops were instilled before the ulcer was 'cured' in the physician's judgment) was compared between the two treatment groups using the independent sample *t*-test. This analysis was performed only

Table 1. Definition of physician judgment of corneal ulcer response to therapy.

Outcome	Category	Description
Clinical success	Cured	No evidence of active bacterial infection, reepithelialization complete, no stromal infiltration and anterior chamber reaction
	Improved	Reepithelialization complete, stromal infiltration or anterior chamber reaction still present
	Improving	Reepithelialization progressing but not complete, stromal infiltration and anterior chamber reaction still evident
Treatment failure	Unchanged	No clinically significant improvement relative to the first day
	Worse	Progressing infection with worsening inflammation

for the patients who were designated as cured by the physician at the final visit. Relative frequencies of treatment failures, location and shape of ulcers including the adverse effects were compared between the two groups using Fisher's exact test. Time to the resolution of ocular symptoms (pain, redness and irritation) were compared using Wilcoxon-Mann-Whitney test.

RESULTS

Patients evaluability

A total of 46 patients were enrolled into the study. Twenty-four patients were randomized to the lomefloxacin treatment group and 22 patients to the ciprofloxacin group. Five patients were lost to follow-up leaving a total of 41 patients who were evaluated per protocol. Of these 41 patients, 23 were treated with lomefloxacin and 18 with ciprofloxacin (active control group).

Patient demographics

There were no statistically significant differences between the treatment groups for any of the demographic or baseline characteristics, including ulcer area, depth of stromal infiltration, location and shape of ulcers ($p > 0.05$) (Table 2, Table 3). The mean ages (± standard deviation) of the lomefloxacin and ciprofloxacin groups were 26.74 (± 10.86) years and 29.72 (± 11.01) years, respectively. The ages of the lomefloxacin group ranged from 4 to 56 years compared with 15 to 57 years for the ciprofloxacin group. Men (47.8% lomefloxacin, 33.3% ciprofloxacin) and women (52.2% lomefloxacin, 66.7% ciprofloxacin) were equally represented in both groups ($p > 0.05$).

Predisposing factors and prestudy treatment

No clinically or statistically significant differences were noted in the predisposing factors (dry eyes, lagophthalmos, trichiasis, contact lens wear, neurotrophic keratopathy) and prestudy treatment before enrollment in the study between the two groups (Table 2). Contact lens wear was the major cause of the corneal ulcer in both groups: 12 (52.2%) patients in the lomefloxacin group and 8 (44.4%) in the ciprofloxacin group (Table 2).

Clinical efficacy

The clinical efficacy response at the final visit was similar for lomefloxacin (100%) compared with ciprofloxacin (100%). No treatment failure was observed in the present study. There was no difference in clinical effectiveness of treatment with lomefloxacin compared with ciprofloxacin in relation to ulcer area and stromal depth.

Table 2. Patient demographics.

	Lomefloxacin (n = 23)		Ciprofloxacin (n = 18)		P-value
	n	%	n	%	
Age (mean ± SD)	26.74 ± 10.86		29.72 ± 11.01		0.391
Gender					0.538
Female	12	52.2	12	66.7	
Male	11	47.8	6	33.3	
Predisposing factors	14	60.9	10	55.6	0.981
Dry eye	-	-	1	5.6	
Lagophthalmos	-	-	1	5.6	
Trichiasis	1	4.3	-	-	
CL wear	12	52.2	8	44.4	
Neurotrophic keratopathy	1	4.4	-	-	
Prestudy treatment	7	30.4	6	33.3	1.000
Eye wash	2	8.7	2	11.1	
Antibiotic eye drop	3	13.0	4	22.2	
Antibiotic + steroid eye drop	1	4.3	-	-	
Steroid eye drop	1	4.3	-	-	
Antibiotic eye ointment	-	-	1	5.6	
Oral systemic antibiotics	1	4.3	-	-	
Antihistamine	1	4.3	1	5.6	

SD = Standard deviation

Table 3. Baseline characteristics of corneal ulcer.

	Lomefloxacin (n = 23)		Ciprofloxacin (n = 18)		P-value
	n	%	n	%	
Mean ulcer area ($mm^2 \pm SD$)					
Epithelial defect	0.81 ± 0.54		0.73 ± 0.78		0.716
Stromal infiltration	1.11 ± 0.50		1.09 ± 0.72		0.922
Location					1.000
Central	4	17.4	3	16.7	
Peripheral	19	82.6	15	83.3	
Shape					0.726
Circular	16	69.6	14	77.8	
Other	7	30.4	4	22.2	

SD = Standard deviation

Table 4. Mean time to cure and mean time to the resolution of ocular symptoms and signs.

Ocular signs and symptoms	Lomefloxacin (Mean ± SD) (Day)	Ciprofloxacin (Mean ± SD) (Day)	P-value
Cure	17.22 ± 3.97	18.67 ± 6.05	0.361
Ocular symptoms			
Eye pain	3.26 ± 0.86	4.00 ± 2.06	0.199
Irritation	4.30 ± 1.77	5.17 ± 4.34	0.867
Red eye	3.13 ± 0.63	3.83 ± 2.01	0.176
Ocular signs			
Conjunctival injection	5.87 ± 2.47	6.67 ± 3.79	0.421
Corneal epithelial defect	6.13 ± 4.09	6.33 ± 2.28	0.852
Stromal infiltration	10.96 ± 5.24	11.33 ± 4.78	0.814

Time to cure

The mean time to cure of a corneal ulcer was clinically equivalent for lomefloxacin relative to ciprofloxacin (17.22 ± 3.97 *versus* 18.67 ± 6.05 days, $p > 0.05$, Table 4).

Clinical symptoms and signs

Lomefloxacin was equivalent clinically and statistically to ciprofloxacin for time to resolution of pain, redness, irritation, conjunctival injection, corneal epithelial defect and stromal infiltration ($p > 0.05$, Table 4).

Microbiologic identification

Positive microbiologic cultures were obtained in 6 (14.6%) of 41 patients. Of these six patients, one patient (4.4%) in the lomefloxacin group had positive culture for pseudomonas aeruginosa, and five patients (27.8%) in the ciprofloxacin group had positive cultures for pseudomonas aeruginosa (3), staphylococcus coagulase negative (1) and serratia marcescens (1). In total, gram-positive bacteria constituted 16.7 per cent of bacterial isolates and gram-negative isolates (83.3%). Pseudomonas aeruginosa was the most common organism found in this study (66.7% of all isolates) Table 5.

Safety and adverse events

Lomefloxacin and ciprofloxacin were safe and well tolerated for treating patients with bacterial corneal ulcers. Adverse events related to lomefloxacin and ciprofloxacin usually were nonserious and resolved without treatment. No serious events related to therapy were reported during the study and no patient was discontinued because of a serious treatment-related event. Eight patients (34.8%) receiving lomefloxacin experienced adverse events, which appeared in eight patients (44.4%) in ciprofloxacin

Table 5. Microbiologic identification.

	Lomefloxacin		Ciprofloxacin		P-value
	n	%	n	%	
Culture result					1.000
Negative	22	95.7	13	72.2	
Positive	1	4.4	5	27.8	
Pseudomonas aeruginosa	1		3		
Staph coagulase negative	0		1		
Serratia marcescens	0		1		

Table 6. Adverse events of lomefloxacin and ciprofloxacin treatment.

Adverse events	Lomefloxacin		Ciprofloxacin		P-value
	n	%	n	%	
Total adverse events	8	34.8	8	44.4	0.759
Irritation	2		2		
SPK	6		4		
White precipitate	-		2		

SPK = Superficial punctate keratitis

treatment. The adverse events reported in lomefloxacin were superficial punctate keratitis (26.1%) and irritation (8.7%), whereas those of ciprofloxacin were superficial punctate keratitis (22.2%), white precipitate (11.1%) and irritation (11.1%). However, no statistically significant differences of these adverse effects were found between the two treatment groups ($p > 0.05$) Table 6.

DISCUSSION

In the current study, ciprofloxacin is proved as an effective and safe ophthalmic antibiotic for the treatment of bacterial corneal ulcer, especially for pseudomonas aeruginosa[10-14]. Lomefloxacin is the new second-generation fluoroquinolone, which has a high efficacy in the treatment of acute bacterial conjunctivitis in clinical studies[22-24]. There have been no clinical reports evaluating the efficacy of topical lomefloxacin in the treatment of bacterial corneal ulcer. Therefore, the Institutional Review Board/Ethics Committee approved this study only for mildly severe corneal ulcers, which are only encountered in a much fewer number of patients. The majority of the corneal ulcers in our university hospital are either moderate or severe degree of severity. Furthermore, the microbiologic identification was limited because of a small amount of tissue available for gram's stain, KOH preparation and cultures, resulting in a low percentage of positive culture for pathogenic organisms. Thus, the ulcers in the present study were presumed to be bacterial in origin by the initial history and clinical examination, especially by the exclusion criteria of the pre-existing signs or histories of other organisms. There were only 6 (14.6%) positive cultures for bacteria. Pseudomonas aeruginosa was the most common isolate in this trial: 1 (4.4%) in lomefloxacin and 3 (16.7%) in ciprofloxacin. Staphylococcus coagulase negative and serratia marcescens were found in the ciprofloxacin group. All ulcers responded very well to either lomefloxacin or ciprofloxacin. The present study supports some previous studies of the efficacy of lomefloxacin and ciprofloxacin against gram-positive bacteria, especially staphylococcus aureus and gram-negative bacteria, especially pseudomonas aeruginosa in the treatment of bacterial keratitis[10-14, 27-29]. However, in the other previous multicenter prospective, but nonmasked evaluation of ciprofloxacin *versus* fortified antibiotics performed by Leibowitz [10] and *in vitro* data[30], streptococcus pneumoniae and anaerobic streptococcus did not respond to fluoroquinolone monotherapy. The present study did not find streptococcus pneumoniae as a cause of the ulcers, that cannot support or be against the latter studies.

Most ocular symptoms (eye pain, ocular irritation, red eye) disappeared before 1 week after

treatment, whereas ocular signs (conjunctival injection, corneal epithelial defect, stromal infiltration) resolved in 6-10 days of treatment in both groups. All ulcers were cured within 3 weeks after treatment with either lomefloxacin or ciprofloxacin. Most patients used only 2 or 3 bottles, each of which contained 5 millimeters of lomefloxacin or ciprofloxacin. This study supports lomefloxacin as an effective, low cost, and safe treatment of corneal ulcers caused by susceptible bacteria compared with ciprofloxacin. Lomefloxacin was found to be well tolerated in treating patients with bacterial corneal ulcers. No serious events related to lomefloxacin were reported during the course of the study. Ocular side effects of lomefloxacin were mild ocular irritation and superficial punctate keratits, which could be spontaneously resolved after stopping medication and there were no statistical differences with those of ciprofloxacin. However, white precipitate was found only in ciprofloxacin treatment, which had no effect on treatment outcome. A potential limitation for routine use of ciprofloxacin is the possibility for the development of resistance to the drug as shown in many reports[31-35]. Thus, lomefloxacin may provide an alternative to ciprofloxacin. In addition, multicenter studies would be required for adequate sample size and further studies of the efficacy of lomefloxacin in moderate and severe degree of corneal ulcer should be encouraged.

SUMMARY

Lomefloxacin ophthalmic solution (0.3%) is equivalent clinically and statistically to ciprofloxacin ophthalmic solution (0.3%) for the treatment of mild severity of bacterial corneal ulcers without statistically significant differences in the adverse effects and discomfort.

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เปรียบเทียบผลของยาหยอดตาโลมีฟล็อคซาซิน 0.3% และยาหยอดตาซิโปรฟล็อคซาซิน 0.3% ในการรักษาแผลกระจกตาติดเชื้อแบคทีเรีย

วิภาวี บูรณพงศ์, พบ, พนิดา โกสีย์รักษ์วงศ์, พบ*, ภิญนิตา ประภาสะวัต, พบ*, สบง ศรีวรรณบูรณ์, พบ*, ปวีณา สุทธิประการ, พบ**

วัตถุประสงค์ : เพื่อประเมินประสิทธิผล และความปลอดภัยของยาหยอดตาโลมีฟล็อคซาซิน และยาหยอดตาซิโปรฟล็อคซาซินในการรักษาแผลกระจกตาติดเชื้อสงสัยเชื้อแบคทีเรีย

วิธีการศึกษา : ทำการศึกษาแบบไปข้างหน้าและสุ่มตัวอย่างในผู้ป่วยที่มีแผลกระจกตาติดเชื้อสงสัยเชื้อแบคทีเรีย จำนวน 41 ราย, 23 รายได้รับยาหยอดตาโลมีฟล็อคซาซินและ 18 รายได้รับยาหยอดตาซิโปรฟล็อคซาซิน ผู้ป่วยทุกรายได้รับการขูดแผลกระจกตาเพื่อตรวจและเพาะเชื้อ หาเชื้อแบคทีเรียและเชื้อราก่อนเริ่มการรักษา ตรวจติดตามผลการรักษาทุก 3 วัน โดยบันทึกอาการ, อาการแสดง, ผลข้างเคียง, จำนวนวันในการรักษา, อัตราการหายและอัตราการล้มเหลว

ผลการศึกษา : ยาหยอดตาโลมีฟล็อคซาซินมีประสิทธิผลดีเท่ากับยาหยอดตาซิโปรฟล็อคซาซิน โดยไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติและทางคลินิก ผู้ป่วยแผลกระจกตาติดเชื้อสงสัยเชื้อแบคทีเรียหายดีทุกราย (100%) ในทั้ง 2 กลุ่ม นอกจากนี้ระยะเวลาที่ใช้ในการรักษาจนไม่มีอาการและอาการแสดง รวมทั้งระยะเวลาที่ใช้ในการรักษาจนหาย ในทั้ง 2 กลุ่ม ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ ผลข้างเคียงของยาหยอดตาโลมีฟล็อคซาซิน คือ กระจกตาอักเสบเป็นจุด พบ 26.1% และอาการระคายเคือง พบ 8.7% ในขณะที่ผลข้างเคียงของยาหยอดตาซิโปรฟล็อคซาซิน คือ กระจกตาอักเสบเป็นจุด พบ 22.2%, ตกตะกอนขาวที่แผล พบ 11.1% และอาการระคายเคือง พบ 11.1% ซึ่งไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติของผลข้างเคียงในทั้งสองกลุ่ม

สรุป : ยาหยอดตาโลมีฟล็อคซาซิน 0.3% มีประสิทธิผลดีเท่ากับยาหยอดตาซิโปรฟล็อคซาซิน 0.3% ในการรักษาแผลติดเชื้อกระจกตาสงสัยเชื้อแบคทีเรีย โดยไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติและทางคลินิก และไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติในด้านผลข้างเคียง หรือความไม่สบายตาในระหว่างยาหยอดตาทั้ง 2 ชนิด

คำสำคัญ : แผลกระจกตา, แผลกระจกตาติดเชื้อแบคทีเรีย, โลมีฟล็อคซาซิน, ซิโปรฟล็อคซาซิน

วิภาวี บูรณพงศ์, พนิดา โกสีย์รักษ์วงศ์, ภิญนิตา ประภาสะวัต, สบง ศรีวรรณบูรณ์, ปวีณา สุทธิประการ
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* ภาควิชาจักษุวิทยา, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10700