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Original Article/นิพนธ์ต้นฉบับ

Safety of Intracameral Levofloxacin Injection on Corneal Endothelial Cell Counts Following Cataract Surgery

ความปลอดภัยของการใช้ยา levofloxaxin ฉีดเข้าในช่องหน้าม่านตาส่วนหน้าเพื่อป้องกันการติดเชื้อหลังการผ่าตัดต้อกระจก

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Abstract

Objective: To determine the safety of prophylactic intracameral levofloxacin 0.5% ophthalmic solution on endothelial cell density in patients having phacoemulsification.

Methods: A prospective blocked randomized control study, 58 eyes were randomized to receive 0.1 ml intracameral levofloxacin 0.5% (cravit®) or an equal volume of balanced salt solution at the last step of phacoemulsification with intraocular lens implantation for endophthalmitis prophylaxis. collected parameters, including best-corrected visual acuity ((BCVA) and intraocular pressure were evaluated preoperatively, 1 month and 3 months postoperatively. Endothelial cell density (EDC) and central corneal thickness were evaluated preoperative and 3 month postoperative.

Results: Fifty eight eyes were included, however forty-three eyes completed the study. At 3 months, mean EDC loss was 17.25% in the intracameral levofloxacin group (n=22) and 12.19% in the control group (n=21) p=0.108. The mean EDC loss was not statistically significant between groups (p>0.05). There were no statistical significant differences in BCVA, IOP, CCT between groups at 3 months (p>0.05). No drug related adverse effects and no endophthalmitis were reported.

Conclusion: Intracameral levofloxacin 0.5% ophthalmic solution demonstrated to be less harmful to visual rehabilitation, central corneal thickness and corneal endothelial cell density. The administration of 0.1 ml intracameral levofloxacin 0.5% ophthalmic solution may be used as a choice for endophthalmitis prophylaxis . A large population may be needed for further study.

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Key words: Intracameral injection, Levofloxacin, Phacoemulsification, Corneal endothelial cell density.

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บทคัดย่อ

ความปลอดภัยของการใช้ยา levofloxacin ฉีดเข้าในช่องหน้าม่านตาส่วนหน้าเพื่อป้องกันการติดเชื้อหลังการผ่าตัดต้อกระจก

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วัตถุประสงค์ เพื่อศึกษาดูผลของการใช้ยา levofloxacin ชนิดยาหยอดตา ฉีดเข้าในช่องหน้าม่านตาส่วนหน้าเพื่อป้องกันการติดเชื้อหลังการผ่าตัดต้อกระจก ต่อเซลล์บุกระจกตาด้านใน(endothelial cell)

วิธีการ โดยการศึกษาแบบ prospective blocked randomization จำนวน 58 ตา แบ่งเป็น 2กลุ่มคือกลุ่มที่ได้ยา levofloxacin ชนิดยาหยอดตา (0.5% cravit®) จำนวน 0.1 มิลลิลิตร (มล.) ฉีดเข้าในช่องหน้าม่านตาส่วนหน้า และกลุ่มที่ 2 ได้รับสารน้ำ balanced salt solution ขนาดเท่ากัน ฉีดตอนสุดท้ายก่อนปิดแผล โดยบันทึกข้อมูลค่าสายตา ความดันตา ก่อนผ่าตัด และหลังผ่าตัดที่ 1 เดือน และ 3 เดือน ส่วนค่าความหนาแน่นเซลล์บุด้านในกระจกตา และ ความหนากระจกตา บันทึกที่ก่อนผ่าตัดปละหลังผ่าตัด 3 เดือน

ผลการศึกษา ผู้ป่วยเข้าเกณฑ์จำนวน 58 ราย แต่มี 43 ราย ที่สามารถรับการตรวจครบตามเกณฑ์ที่กำหนด ที่ 3 เดือน ค่าสายตา ความดันตา ความหนากระจกตา และค่าเฉลี่ยการลดลงของเซลล์บุกระจกตาด้านในระหว่างกลุ่มไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ ($p > 0.05$) โดยการลดลงของเซลล์บุกระจกตาด้านในคิดเป็นร้อยละ 17.25 ในกลุ่มที่ฉีดยา levofloxacin (22 ราย) เทียบกับลดลง ร้อยละ 12.19 ในกลุ่มเปรียบเทียบ (21 ราย) $p=0.108$ ไม่พบภาวแทรกซ้อนและการติดเชื้อในการศึกษานี้

สรุป การใช้ยาหยอดตา 0.5% levofloxacin (cravit®) ขนาด 0.1 มิลลิลิตร ฉีดเข้าช่องม่านตาส่วนหน้า อาจเป็นทางเลือกหนึ่งในการป้องกันการติดเชื้อหลังผ่าตัดต้อกระจก

Background

Phacoemulsification with intraocular lens implantation is the most commonly performed surgical procedure in the elderly population in developed countries. One of the most serious complications of cataract surgery is endophthalmitis. Although post operative endophthalmitis is rare, it can lead to blindness[1-3]. Prevention and elimination of postoperative endophthalmitis, however, is a constant goal of every ophthalmic surgeon.

Many additional prophylactic measures have been tried in an effort to prevent this complication. Among these prophylactic measures, intracameral injection of antibiotics is becoming a popular method, although there is controversy concerning its safety. Increasing attention is drawn to the value of an intracameral injection of antibiotic at the end of cataract surgery to provide immediate, high antibiotic levels in aqueous humor that are sustained for a period of time.[1-8]

In ESCRS, intracameral cefuroxime injection at the end of surgery was reported to decrease the incidence of postoperative endophthalmitis by almost 5-fold.[1-3] However, cefuroxime is available in a systemic preparation that must be reconstituted using saline solution before it can safely be delivered to the eye. Reconstituting the drug for intracameral use may increase the risk for toxic anterior segment syndrome (TASS) because

an undesired concentration of the drug may be inadvertently injected if a mistake occurs during the preparation or dilution process. It is well known that incorrect drug concentration, incorrect pH, and incorrect osmolality can cause TASS [9]. Furthermore, the dose may be contaminated.

Fluoroquinolones have a broad spectrum activity against both gram-positive and gram-negative bacteria, and they penetrate well into the anterior chamber. Levofloxacin is the L (–) optical isomer of racemic ofloxacin. Cravit® (Levofloxacin 0.5%; Santen, Japan) is a self-preserved commercial ophthalmic formulation of a third generation quinolone. It has a broad antimicrobial activity, high solubility in water at neutral pH and shows no significant difference of the corneal thickness and endothelial cell count in rabbits.[10-11] However, few studies have evaluated the efficacy and safety of intracameral levofloxacin.[12] Therefore, we assessed the incidence of endophthalmitis and the complications before and after the introduction of intracameral levofloxacin.

Materials and Methods

A prospective blocked randomized control study was performed at the Department of Ophthalmology, Ramathibodi Hospital, Bangkok, Thailand, during June to December 2014. All patients signed an informed consent for participation in the study and the protocol was approved by the Research Ethics committee of Mahidol University,Thailand.

Fifty eight eyes with senile cataract (NC2 to NC4 grading on the nuclear color of Oxford classification) were randomized to receive 0.1 ml intracameral levofloxacin 0.5% or an equal volume of balanced salt solution at the last step of phacoemulsification with intraocular lens implantation for endophthalmitis prophylaxis. Exclusion criteria included patients with mature cataract, corneal endothelial density less than 1500 cell/mm², complicated surgery or change to other surgical technique, probable or definite case of uveitis, glaucoma, maculopathy or corneal endothelial disease, suspicion of having weakened zonule, pseudoexfoliation syndrome, previous intraocular surgery, previous ocular trauma, cognitive impairment and fluoroquinolone allergy.

Safety parameters including best-corrected visual acuity (BCVA), intraocular pressure (IOP), endothelial cell density (EDC), central corneal thickness (CCT), and patient age and sex were recorded pre and post-operatively.

Surgical technique

All operated eyes were dilated with topical tropicamide 1% and phenylnephrine 2.5%. All surgeries were performed by the same surgeon (P.S.) under peribulbar anesthesia (2% lidocaine with hyarulonidase). Standard phacoemulsification was performed through a 3-mm clear corneal incision using the stop-and-chop technique. Sodium hyarulonate (Healon GV®, AMO,USA) and foldable acrylic IOL were implanted into the capsular bag.

Prophylactic regimen

Preoperatively, patients received povidone-iodine 0.5% instilled into the cul de sac. Intraoperatively, after the IOL was implanted

and the viscoelastic was removed, patients were randomized using a blocked randomization,to receive either an intracameral injection of levofloxacin 0.5% (500 µg/0.1 ml) which was injected through a 27-gauge cannula pointed posteriorly or an equal volume of balanced salt solution at the last step of phacoemulsification. The day after surgery levofloxacin 0.5% was applied as eye drops 4 times daily and 1% prednisolone acetate every 2 hours until bed time until the inflammation subsided in both groups.

Outcome measurement

All patients were scheduled for evaluation at one day, one week, three weeks and three months postoperatively. BCVA (Log MAR), IOP, and adverse events were recorded.

Specular endothelial microscopy of central cornea and measurement of central corneal thickness (CCT) were performed with a noncontact specular microscope (EM-3000, Tomey, Japan) by a masked technician at 3 months postoperatively.

The percentage loss in endothelial density (ECD) was calculated using the following formula (where pre = preoperative; post = postoperative)

$$\text{Loss of ECD \%} = \frac{(\text{ECDpre} - \text{ECDpost}) \times 100\%}{\text{ECDpre}}$$

Statistical analysis

The paired t-test or Mann-Whitney test was used when the distribution of the data was continuous. The chi-square test or Fishers exact test was used for data that were nominal. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 10.0 (SPSS, Chicago). A P value less than 0.05 was considered statistically significant.

Results

Forty-three eyes (43 patients) completed the study. All patients were Asian, 22 eyes in the levofloxacin study group and 21 eyes in the BSS control group. There were 13 men and 30 women. The baseline characteristics are summarized in Table 1. There were no statistically significant differences between patients in the 2 study groups in age, sex and race. Comparisons of the 2 study groups at preoperative baseline evaluations showed no statistically significant differences in the ocular parameters of visual acuity, level of cataract, IOP, endothelial cell counts, or corneal thickness.

At the postoperative evaluations, there were no statistically significant differences between the 2 study groups in BCVA, IOP, CCT and ECD at 3 months postoperatively ($p > 0.05$) (Table 2). All eyes had trace to grade 2 cells and flare only at one week after surgery and all had quiet anterior chamber at subsequent follow-up examination.

At 3 months , mean EDC loss 17.25% in the intracameral levofloxacin group (n=22) and 12.19% in the control group (n=21) p=0.108. The mean EDC loss was not statistically significant between groups. ($p>0.05$).

There were no statistically significant differences in BCVA, IOP, CCT between groups at 3 month ($p>0.05$). No drug related adverse effects

Table 1. Comparison of preoperative baseline parameters

Parameters	Levofloxacin group (n=22)	Control group (n=21)	p-value
Sex			
Female	50%	52.3%	0.82
Age(years)			
Mean ± SD	62.86± 7.62	66.57± 7.18	0.11
Level of cataract			
NC2	8 (36.4%)	9 (42.9%)	0.38
NC3	10 (45.5%)	5 (23.8%)	
NC4	4 (18.1)	7 (33.3%)	
BCVA (LogMAR)			
Mean ± SD	0.28 ± 0.18	0.27 ±0.15	0.86
IOP (mmHg)			
Mean ± SD	15.86 ± 2.75	14.48 ± 3.53	0.16
CCT (μm)			
Mean ± SD	542.32± 30.44	526.52 ± 31.83	0.10
ECD (cell/mm²)			
Mean ± SD	2584.77 ± 278.68	2597.85±386.53	0.89

- BCVA = best-corrected visual acuity; IOP = intraocular pressure; CCT = central corneal thickness; ECD = endothelial cell density
- * statistically significant at p-value < 0.05(Chi square's test)

and no endophthalmitis were reported.

Discussion

Many drugs have been off-label used for intracameral injection at the end of surgery to prevent endophthalmitis.[1-8] However many drugs show numbers of free radicals both in preservative and non-preservative form that may toxic to ocular tissue eg. endothelium.[13-14]

In the ESCRS study, perioperative intracameral cefuroxime in cataract surgery could reduce the number of endophthalmitis infections by almost 5-fold.[15] However, cefuroxime is available in a systemic preparation that must be reconstituted using saline solution before it can safely be delivered to the eye. In this study, we used intracameral levofloxacin instead of cefuroxime because levofloxacin 0.5% is a self-preserved, commercially available, broad spectrum antibiotic against both gram-positive and gram-negative bacteria, penetrates well into the anterior chamber and has been shown to have no significant toxicity on the rabbit corneal endothelial cells count.[10-11] The important concern in intracameral antiobiotics is biocompatibility of the drug with the corneal endothelium. To observe its effects on the cornea

Table 2. Comparison of postoperative parameters at 3 months

Parameters	Levofloxacin group (n=22)	Control group (n=21)	p-value
BCVA (LogMAR) : Mean±SD			
Baseline	0.28 ± 0.18	0.27 ±0.15	0.86
3 months	0.08 ± 0.07	0.09 ± 0.08	0.67
IOP (mmHg) : Mean±SD			
Baseline	15.86 ± 2.75	14.48 ± 3.53	0.16
3 months	13.32 ± 3.05	12.43 ± 3.67	0.39
CCT (μm) : Mean±SD			
Baseline	542.32± 30.44	526.52 ± 31.83	0.10
3 months	545.27± 32.97	528.85 ± 31.85	0.10
ECD(cell/mm²) : Mean±SD			
Baseline	2584.77 ± 278.68	2597.85 ± 386.53	0.89
3 months	2135.36 ± 310.53	2278.71 ± 439.80	0.22
Mean EDC loss	17.25%	12.19%	0.108

BCVA = best-corrected visual acuity; IOP = intraocular pressure; CCT = central corneal thickness; ECD = endothelial cell density
- * Statistically significant at p-value < 0.05

(endothelial cell count and pachymetry), we also excluded patients with corneal problems and ocular pathology to avoid confounding the postoperative outcomes.

The findings of our study were no statistical evidence of reduced endothelial cells or increased corneal thickness at three months postoperatively either comparing to baseline data or comparing between the two groups at the same time period. (table 2)

Because postoperative endophthalmitis is rare (incidence 0.015-0.3%[1-3]), the present study is too small to allow any conclusions to be drawn about the efficacy of the antimicrobial regimens used. Some of limitations in our study include the small sample size, high rate of loss to follow-up of patients, and the short follow-up time.

In conclusion, intracameral levofloxacin 0.5% ophthalmic solution appeared to be less harmful in terms of visual rehabilitation, central corneal thickness, and corneal endothelial cell density at 3 month postoperatively. The administration of 0.1 ml intracameral levofloxacin 0.5% ophthalmic solution may be used as a prophylaxis of endophthalmitis. A large population and longer follow-up time may be needed to prove its safety and effectiveness in preventing endophthalmitis.

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