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ORIGINAL RESEARCH

Randomized controlled trial on the safety of intracameral cephalosporins in cataract surgery

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Objective: To compare the safety profiles of intracameral cephalosporins in cataract surgery.

Patients and methods: In this controlled trial, 129 patients were randomized to one of four groups to receive 1 mg of one of three cephalosporins – cefazolin, cefuroxime, or ceftazidime, or normal saline – given intracamerally during cataract surgery. Central endothelial cell density (ECD) and retinal center point thickness (CPT) were determined by specular microscopy and ocular coherence tomography, respectively, before and at 3 months after surgery.

Results: There were no statistical significant differences in the changes of ECD and CPT between eyes receiving intracameral cephalosporin and control.

Conclusion: The use of intracameral cefazolin, cefuroxime, or ceftazidime (1 mg in 0.1-mL solution) at the time of cataract surgery had no significant effect on ECD and CPT postoperatively.

Keywords: intracameral cephalosporin, endophthalmitis, phacoemulsification

Introduction

Postoperative endophthalmitis is a serious complication of cataract surgery that can lead to loss of sight or even loss of the eye. Peroperative topical application of 5% povidone–iodine or an antibiotic to the conjunctival sac was commonly used as prophylaxis against infection.[1] Commensal bacteria could not be totally eliminated from the ocular surface and could contaminate the anterior chamber during cataract surgery.[2–4] Peroperative intracameral application of antibiotics might eliminate bacteria that gained access to the anterior chamber. Antibiotics could be infused continuously during surgery along with the irrigating solution given either as a variable dose[5] or as a fixed-dose bolus injection at the end of surgery. Cephalosporins and vancomycin were studied extensively in retrospective series and prospective trials providing evidence on clinical efficacy of intracameral cephalosporins.[6–10] Safety aspects were studied via the effects on endothelial cell loss and macular thickening. Intracameral drug toxicity could lead to endothelial cell loss or diffuse into the posterior segment of the eye resulting in macular edema. In a nonrandomized trial, Montan et al[11] showed the use of 1-mg intracameral cefuroxime did not lead to endothelial cell loss. Gupta et al[12] also showed the same dose of intracameral cefuroxime did not lead to macular thickening. The effects of cefazolin and ceftazidime on endothelial cell loss and macular thickening were not reported in the European clinical studies. In this prospective randomized trial, we directly compared the safety profiles of three intracameral cephalosporins – cefazolin, cefuroxime, and ceftazidime – given via the intracameral route.

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Materials and methods

This study was approved by the hospital clinical research ethics committee. Patients aged 50 years or above with senile cataract were recruited from the ophthalmic outpatient clinic of the hospital. Only one eye in a patient with bilateral cataract would be recruited into this study. At the recruitment visit, a comprehensive ocular examination was conducted, followed by optical biometry, and central endothelial density and central macular thickness measurements. These three measurements were conducted by trained technicians. Patients' steady fixation and cooperation were required for acquisition of reliable data. Patients giving a history of intraocular surgery or showing signs of ocular pathologies detected at the examination were excluded. Systemic conditions leading to exclusion were diabetes mellitus, uncontrolled hypertension, and heart or renal failure. Patients who would not consent to surgery under local or topical anesthesia were also excluded. Written informed consent to the study was obtained from those who satisfied inclusion criteria.

Central corneal endothelial cell density (ECD) was evaluated by fixed-frame analysis with a noncontact specular microscope (NonCon ROBO SP-8000; Konan Inc, Hoyogo, Japan). The area selected within each frame included 50 or more cells to qualify for manual analysis. Photographic evaluation of the cell image of the entire frame was also conducted. An ECD below 2000 cells/mm^2 or the presence of corneal guttata led to exclusion. Macular thickness was determined using time-domain optical coherence tomography (OCT). With the fast macular scan protocol provided with the Stratus OCT (Carl Zeiss Meditec, Dublin, CA), six equally spaced 6-mm radial scans each consisting of 100 sequential measurements were centered on the patient's fixation point. The software averaged the six scans to give the central area thickness. The center point thickness (CPT) was adopted as another primary outcome variable.

The sample size was calculated to have 80% power to detect a 5% significant difference of ECD or CPT between a cephalosporin and control. Patients were randomized to the operating lists of four participating surgeons. To control for variations, the randomization scheme was designed such that each surgeon would operate on around 32 eyes, about 8 eyes from each treatment group. Surgery was conducted within 14 days after the recruitment visit. Each surgeon used his or her most preferred lens removal and irrigation-aspiration technique, the same ophthalmic viscosurgical device, intraocular lens model, and lens delivery system to all eyes randomized to his or her surgical list. Intraocular lenses were to be implanted into the capsular bag. The use of a capsular stain or an intracameral miotic, posterior capsular break with or without vitreous presentation into the anterior chamber would lead to exclusion. To allow comparison of ultrasound energy used in the surgery, the effective phaco time (EPT) was calculated by multiplying the total phaco time by the average percentage power used. The EPT would be the phaco duration if 100% power continuous mode was used.

Three cephalosporins were compared – cefazolin (1-g vial; Chung Hwa, Suzhou, China), cefuroxime (750-mg vial, Zinacef®; GlaxoSmithKline, Brentford, UK), and ceftazidime (1-g vial, Fortum®; GlaxoSmithKline). Solutions were prepared from the powder supplied in vials for intravenous use. The powder was first dissolved with normal saline (NS) (0.9% NaCl; B Braun, Penang, Malaysia) to a concentration of 100 mg/mL in a 10-mL syringe. The solution was further diluted to the concentration of 10 mg/mL with NS. Water for injection or balanced salt solution (BSS) was not used in the process. A hypotonic solution could result from dissolution and dilution with water for injection. Precipitations could form by mixing cephalosporin with BSS. Solutions were discarded 4 h after reconstitution.

The surgeons were supplied with a tuberculin syringe containing 1 mg (in 0.1 mL) of one of the three cephalosporins – cefazolin, cefuroxime, and ceftazidime – drawn from the diluted drug in the 10-mL syringe, or 0.1 mL of NS, which was to be injected into the anterior chamber at the end of surgery. The surgeons were masked as to which treatment was given until the surgery had been completed and patient had left the theater.

A standard topical antibiotic–steroid regime (dexamethasone and chloramphenicol) was commenced on the first postoperative day. Patients were seen again at 1 week, 1 month, and 3 months after operation by a masked observer. Central ECD and CPT were measured at 3 months (±2 weeks) postoperatively by the same trained technician masked to the treatment, previous specular microscopy, and OCT data.

The primary outcome variables were changes in ECD and CPT. Change in ECD was expressed as a percentage, obtained by dividing the difference between postoperative and preoperative values by the preoperative value. Similarly, the percentage change in CPT was obtained by dividing the difference between post- and preoperative thickness by the preoperative value. Using a statistical package (SAS version 9.1; SAS Institute, Cary, NC), the percentage changes in ECD and CPT with analysis of variance at an alpha value of 0.05 and the correlation between change in EPT and improvement of visual acuities were determined. Post hoc comparisons

of the outcome variables with the Bonferroni *t* tests among surgeons were also conducted.

Results

A total of 129 patients, comprising 49 males and 80 females, were recruited in this study. Mean age of the patients was 74.5 years (SD = 7 years). They were randomized to be operated by one of the four participating surgeons. Details of their surgical preferences and the number of patients randomized are listed in Table 1. One patient in the cefuroxime group withdrew before the final follow-up visit. The four groups were comparable with regard to their mean age, biometry values, visual acuities, baseline ECD and CPT, and EPT (Table 2). The mean preoperative unaided visual acuity was 0.6 (±0.27) logMAR. There was a mean improvement of 0.25 (±0.33) logMAR after cataract surgery.

The mean pre- and postoperative ECD were 2546 ± 334 and 2286 ± 463 cells/mm^2, respectively. The mean change was −9.9% (±17.1%). The mean pre- and postoperative CPTs were 172 ± 31 and 179 ± 40 µm. There was a small increase of foveal thickening at around 4.6%. One patient in the cefazolin group developed clinical macular edema with a drop in visual acuity at the final visit. She required treatment with topical nonsteroidal anti-inflammatory agent.

We were unable to detect a statistically significant change in ECD ($P = 0.74$) and CPT ($P = 0.36$) between cephalosporins and control (Table 2). There was no significant correlation of changes in CPT and improvement in visual acuities after surgery (Pearson correlation = 0.07, $P = 0.43$). Post hoc analysis using the Bonferroni *t* test showed the patients operated by one surgeon had a higher rate of endothelial cell loss ($P < 0.0001$) than the other three surgeons. This accounted for the larger standard deviation for postoperative endothelial density (463 cells/mm^2) compared with the preoperative value (334 cells/mm^2). No statistical difference was detected between the groups after patients operated by the surgeon were excluded from analysis.

Discussion

Effectiveness of intracameral cephalosporins as prophylaxis for postoperative endophthalmitis after cataract surgery was shown in large case series and randomized trials. Results from the European Society of Cataract and Refractive Surgeons (ESCRS) multicenter randomized control trial on 16,211 subjects showed the risk of endophthalmitis could be reduced by 4.9-fold with an intracameral injection of cefuroxime.[6] Another prospective study conducted in Spain involving 13,652 cataract patients concluded the efficacy of intracameral cefuroxime in reducing the risk of postoperative endophthalmitis.[7] The choice of cefuroxime was based on the microbiological spectrum in the Swedish series of endophthalmitis cases from 1996 to 2000.[10] In this series, 55 of 59 strains of pathogens isolated were sensitive to cefuroxime. Use of cefazolin was described in smaller retrospective case series from Spain.[8,9] Cefazolin is a first-generation cephalosporin that has bactericidal effect against Gram-positive cocci, particularly staphylococci. Ceftazidime, a third-generation cephalosporin, was used in Sweden following an epidemic caused by a Gram-negative bacterium.[10] Antibiotics chosen for prophylaxis were targeted toward either pathogens isolated

Table 1 List of participating surgeons' preferences on surgical methods, ophthalmic viscosurgical devices, intraocular lenses, implantation devices, and the number of eyes randomized to each surgeon

Surgeon	Surgical methods[1]	Ophthalmic viscosurgical devices[2]	Intraocular lenses and implantation devices[3]	Number of eyes				
				Cefazolin	Cefuroxime	Ceftazidime	Normal saline	Subtotal
A	Stop and chop Single coaxial I&A	Vitrax II and Healon	AcrySof SA60AT Monarch C cartridge	8	9	7	8	32
B	Stop and chop Bimanual I&A	VisCoat and ProVisc	Tecnis Z9003 Emerald C cartridge	8	9[4]	9	7	33
C	Stop and chop Single coaxial I&A	VisCoat and ProVisc	AcrySof SA60AT Monarch C cartridge	8	8	8	8	32
D	Stop and chop Bimanual I&A	VisCoat and ProVisc	AcrySof SA60AT Monarch C cartridge	8	8	8	8	32
			Subtotal	32	34	32	31	129

Notes: [1]Irrigating solution: To each 500-mL bottle of balanced salt solution (Alcon Laboratories, Forth Worth, TX), 5 mL of 1:10,000 nonpreserved adrenaline acid tartrate (DBL, Mulgrave, Australia) was added; [2]Vitrax II (sodium hyaluronate 30 mg/mL), Healon (sodium hyaluronate 10 mg/mL; Abbott Medical Optics, Santa Ana, CA), VisCoat (sodium hyaluronate 16.5 mg/mL, sodium chrondoitin sulfate 40 mg/mL), ProVisc (sodium hyaluronate 10 mg/mL; Alcon Laboratories); [3]AcrySof SA60AT one-piece intraocular lenses and Monarch delivery system (Alcon Laboratories), Tecnis Z9003 three-piece intraocular lenses and Emerald delivery system (Abbott Medical Optics); [4]One patient in the cefuroxime group withdrew before the final visit.

Table 2 Effects of intracameral cephalosporins versus normal saline (control) on endothelial cell density and central point thickness

	Cefazolin	Cefuroxime	Ceftazidime	Normal saline	*P*[1]
Number of eyes	32	34[2]	32	31	–
Mean ± SD					
Age, years	74.0 ± 7.8	73.9 ± 7.4	75.8 ± 6.9	74.2 ± 6.1	0.65
Axial length, mm	23.70 ± 0.98	23.44 ± 0.91	23.42 ± 0.70	23.64 ± 1.16	0.55
Average keratometry, D	44.13 ± 1.55	44.33 ± 1.36	44.04 ± 1.28	43.69 ± 1.30	0.31
Visual acuities, logMAR					
Preoperative	0.56 ± 0.22	0.63 ± 0.28	0.64 ± 0.31	0.56 ± 0.25	0.31
Change	–0.15 ± 0.28	–0.31 ± 0.35	–0.31 ± 0.30	–0.21 ± 0.36	0.15
Effective phaco time, sec	31.0 ± 15.3	28.1 ± 19.2	34.3 ± 17.7	26.7 ± 15.6	0.31
Endothelial cell density, cells/mm^2					
Preoperative	2555 ± 349	2567 ± 327	2536 ± 385	2528 ± 280	0.97
Postoperative	2352 ± 476	2326 ± 481	2206 ± 455	2257 ± 447	–
Change, %	–7.7 ± 18.0	–9.0 ± 17.0	–12.0 ± 18.0	–11.0 ± 15.7	0.74
Central macular thickness, µm					
Preoperative	171.9 ± 23.8	174.4 ± 36.0	172.1 ± 32.4	171.8 ± 31.8	0.99
Postoperative	176.8 ± 31.1	178.7 ± 51.5	176.3 ± 32.8	187.1 ± 45.7	–
Change, %	2.9 ± 10.7	2.8 ± 22.4	3.3 ± 13.0	9.9 ± 21.0	0.32

Notes: [1]Analysis of variance, $P < 0.05$ is considered statistically significant; [2]One patient in the cefuroxime group withdrew before the final visit.

from cases of endophthalmitis[10] or conjunctival cultures of patients undergoing cataract surgery.[13] Methicillin-resistant staphylococci were resistant to cephalosporins, but not to vancomycin. Vancomycin was preferred by some groups for intracameral use after cataract surgery.[14] The US Centers for Disease Control and Prevention cautioned against prophylactic use of vancomycin to reduce the risk of emergence of vancomycin-resistant organisms.[15]

Commercial preparations of cephalosporins for intracameral use had not been available. Solutions were reconstituted from the powder supplied for intravenous or intramuscular use. The manufacturers recommended the use of water for injection for reconstitution.[16] For intracameral use, we used NS to reconstitute the solutions to avoid hypotonicity, as in the majority of clinical studies.[9–11,17] In a study on the safety of intracameral cefuroxime, Gupta et al[12] used BSS as control. We used NS as control in an attempt to differentiate the effect between cephalosporins, if such existed, and to avoid the confounding effect of a control that was different from the diluent. Risk of drug toxicity leading to toxic anterior segment syndrome could arise from dilution and dosing errors. Lockington et al[17] compared two protocols for diluting cefuroxime and found errors could arise from using small (1.0-mL) syringes. The preparations used in this study were reconstituted from 1-g vials of cefazolin and ceftazidime and 750-mg vials of cefuroxime using 10-mL syringes, avoiding incomplete dissolution of drug powder and inaccuracies with small syringes. We discarded cephalosporin solutions 4 h after reconstitution to avoid possible loss of efficacy, despite the manufacturers confirmed compatibility with NS and retaining potency more than 12 h after reconstitution.[16]

In this study design, control for sources of variations was addressed. We excluded patients with long axial lengths (thin maculae) and any ocular or systemic conditions that could lead to postoperative macular edema. In clinical trials comparing effects of phacoemulsification methods or irrigating solutions on the cornea, variations arising from surgeons could be controlled by limiting the procedure to be conducted by a single surgeon.[17,18] In this trial, four surgeons participated, and the number of eyes randomized to each treatment and control were closely matched for every surgeon, even though a perfect 4×4 allocation was not achieved. This design allowed the differentiation of treatment (drug) effect from the surgeon effect through statistical analysis. The mean endothelial cell loss of 9.9% in this study compared favorably with the results in two recent studies on endothelial cell loss in phacoemulsification. Using fortified BSS as irrigating solution, the mean cell loss at 2 months was 13.2% (±2%) in Lucena's study[19] and 22.9% (±14%) at 3 months in the Richard et al study.[20] In eyes operated by one participating surgeon, the mean cell loss was 19.8%. This value was comparable to the mean cell loss by Richard et al.[20]

There was an inherent variability in the measurement of ECD. Variations could be reduced by cell analysis over a larger area or with repeated measurements. In practice, the area of endothelial cells available for counting was limited by magnification and the area brought under focus of the specular microscope. In this study, 50 or more endothelial cells

per frame were accepted for analysis. We did not compare the absolute cell loss as Montan et al[10] did in their study on the safety of intracameral cefuroxime. Anticipating a wide range of preoperative cell densities (ranging from 2005 to 3683 cells/mm^2), we analyzed the percentage changes rather than the absolute differences between the pre- and postoperative ECD values. The percentage values could convey the magnitude of cell loss with regard to the baseline ECD. We measured ECD at one single time point, namely at 3 months, postoperatively. In a study comparing corneal changes after phacoemulsification using fortified BSS versus lactated Ringer's solution, Lucena et al[19] observed endothelial cell count stabilized after 2 weeks postoperatively. It was less likely that the drugs could cause continual endothelial cell loss, and these effects could be picked up if the measurements were conducted at a later date.

To study the effect on macular thickness, we used CPT as our primary outcome variable similar to the study by Kim et al.[21] No topical nonsteroid anti-inflammatory agent was used in the pre- and immediate postoperative stage. This could have masked the difference in change of macular thickness, if any, between the groups. We were unable to detect any statistical difference in CPT between treatment and control groups. Our result showed a mean increase of 4.6% (or 7.0 μm) in CPT in the postoperative period. This value concurred with other OCT studies on changes of retinal thickness with cataract surgery using Stratus OCT. Kurz's group demonstrated a 6–8-μm increase in CPT at 8 weeks after microincisional cataract surgery.[22] Kim et al showed a mean 9-μm increase in CPT at 12 weeks.[21] Biró et al advocated using the 6-mm perifoveal retinal thickness for a more sensitive measure for detecting macular edema.[23,24] They showed 5.3% increase in 6-mm perifoveal values at 2 months after phacoemulsification. The increase was maximal at 1 month and had not resolved at 6 months postoperatively.

Conclusion

This study could not detect any statistical difference in changes in ECD or CPT between cephalosporins and control. The magnitude of endothelial cell loss and macular thickening detected in this study was not in excess of that after uneventful cataract surgery, and thus it could not be ascribed to the use of any one of the three intracameral cephalosporins. Cefazolin, cefuroxime, and ceftazidime could be considered safe for intracameral use when 1 mg in 0.1 mL was given during cataract surgery.

Disclosure

The authors report no conflicts of interest in this work.

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