Endophthalmitis after cataract surgery despite intracameral antibiotic prophylaxis with licensed cefuroxime

Charles Mesnard, MD, Laurence Beral, MD, Rabih Hage, MD, Harold Merle, MD, PhD, Selim Farès, MD, Thierry David, MD, PhD

PURPOSE: To report a case series of post-phacoemulsification endophthalmitis despite antibiotic prophylaxis with an intracameral injection of a licensed cefuroxime formulation (Aprokam).

SETTING: University Hospitals of Pointe-à-Pitre, Guadeloupe, and Fort-de-France, Martinique, French West Indies.

DESIGN: Retrospective case series.

METHODS: Patients who had cataract surgery with licensed cefuroxime prophylaxis between March 1, 2013, and July 31, 2015, and developed endophthalmitis were included. Bacteriologic findings and final corrected distance visual acuity 6 months after treatment were collected.

RESULTS: Five patients developed endophthalmitis within 15 days after surgery, which was performed in different settings by different cataract surgeons. All patients had no-stich cataract surgery. Surgery was uneventful in 4 cases. One patient had a posterior capsule rupture. An anterior chamber paracentesis with analysis of the aqueous humor was performed to confirm endophthalmitis. Bacteriologic tests showed α-hemolytic streptococcus in 2 cases, *Staphylococcus epidermidis* in 1 case, and *Serratia marcescens* in 1 case. Two strains of bacteria showed cefuroxime resistance on the antibiogram. Despite parenteral and intravitreal injections of antibiotics, 4 of 5 cases had a poor outcome, with a visual acuity of less than 20/200. Retinal detachment (RD) was the most frequent complication observed in the following months.

CONCLUSIONS: Although licensed cefuroxime has proven to be efficient in reducing the incidence of endophthalmitis, it has not eradicated this potentially severe complication of cataract surgery. Endophthalmitis occurring after the use of licensed cefuroxime can still result in very poor visual outcomes related to the infection itself or to its delayed complications such as RD.

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In 2007, the European Society of Cataract and Refractive Surgeons (ESCRS) study[1] showed that intracameral injection of cefuroxime at the end of cataract surgery resulted in a 5-fold reduction in the incidence of postoperative endophthalmitis ($P = .001$ for presumed endophthalmitis; $P = .005$ for proven endophthalmitis). Since then, many centers started using intracameral cefuroxime to prevent endophthalmitis. However, many studies[1–10] have reported the occurrence of endophthalmitis despite the use of antibiotic prophylaxis with intracameral injection of unlicensed cefuroxime. Furthermore, the fact that no approved commercial preparation was available before 2012 discouraged some surgeons from using it because of potential dilution errors.[11]

In September 2012, the European Medicines Agency approved a specific preparation of cefuroxime for intracameral injection (Aprokam) as a prophylaxis to postoperative endophthalmitis after cataract surgery. This licensed cefuroxime formulation aimed to reduce the risk for dilution errors and contamination. It is available in 50 mg vials that must be reconstituted as

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a solution for intracameral injection of 1.0 mg cefuroxime in 0.1 mL. Each vial of Aprokam is for single-patient use. The French National Authority for Health approved this formulation in March 2013, as did several other European countries, and it became the first-line antibiotic prophylaxis in cataract surgery at all French ophthalmologic centers. Since March 1, 2013, all patients who have cataract surgery in the French Caribbean islands of Martinique and Guadeloupe have received antibiotic prophylaxis with the licensed intracameral cefuroxime at the end of surgery (0.1 mL of reconstituted solution; 1.0 mg of cefuroxime). The dose is prepared by a nurse adhering to strict aseptic procedures.

On both islands, all patients with a suspicion of endophthalmitis are referred to the University Hospitals (Martinique University Hospital and University Hospital of Pointe-à-Pitre) because no other healthcare centers on either island are able to admit patients for appropriate endophthalmitis treatment.

We report 5 cases of endophthalmitis after cataract surgery with intracameral injection of Aprokam licensed cefuroxime that occurred in Guadeloupe and Martinique, French West Indies, between March 1, 2013, and July 31, 2015.

PATIENTS AND METHODS

A retrospective review was performed of billing codes between March 1, 2013, and July 31, 2015, at Martinique University Hospital and Pointe-à-Pitre University Hospital to identify endophthalmitis cases (Code CIM-10 H44 and H44.1) in patients who had a history of cataract surgery during that period (Code CIM-10 H25) and who had no history of other types of eye surgery. Another retrospective review of the same billing codes was performed for patients who were admitted in 2012, when no intracameral antibiotics were used during cataract surgeries.

Once identified, the charts of the patients were reviewed and the following data were recorded: age, sex, medical history, date of surgery, date of onset of decreased vision, position of corneal incision, type of intraocular lens (IOL) used, the occurrence of complications during surgery, visual acuity at presentation, slitlamp and fundus examination findings, intraocular pressure (IOP), treatment of endophthalmitis, bacteriologic culture findings, results of antibiograms, visual acuity at 1 month and 3 months, and the occurrence of delayed complications.

In both hospitals, the usual care of endophthalmitis includes bacteriologic analysis of a sample of aqueous humor obtained by anterior chamber paracentesis. Treatment consists of intravenous levofloxacin and imipenem for 5 days in Guadeloupe and fosfomycin and ofloxacin for 5 days in Martinique and intravitreal vancomycin and ceftazidime every other day for 5 days performed in a dedicated room. Fluoroquinolones were used because of their good bioavailability. Carbapenem and fosfomycin were added to broaden the spectrum of activity (specifically against streptococcus, pyocyanic bacteria, and anaerobic bacteria) and prevent the emergence of resistant mutations. Repeat intravitreal injections were administered when the fundus examination showed persistent inflammation or when there was no improvement or poor improvement in visual acuity. In Guadeloupe, vitrectomy was not considered a first-line treatment option because no experienced vitreoretinal surgeons were available.

Subconjunctival or intravitreal steroids were used only at the medical team's discretion after 2 days of treatment. All therapeutic strategies contained steroid eyedrops (1 drop per hour for 2 days, then tapered over 1 month or until resolution of the intraocular inflammation).

RESULTS

Between March 1, 2013, and July 31, 2015, 23 244 cataract surgeries were performed in Martinique (7257 cases) and Guadeloupe (15 987 cases). Five cases of endophthalmitis after cataract surgery with the use of licensed cefuroxime were seen during this period at the 2 hospitals. The incidence of post-phacoemulsification endophthalmitis after antibiotic prophylaxis by intracameral injection of licensed cefuroxime in the French Caribbean was then 0.02%.

In 2012, 9464 cataract surgeries were performed on both islands (3118 in Martinique and 6346 in Guadeloupe). Twelve patients in Guadeloupe and 4 patients in Martinique had billing codes of cataract surgery and endophthalmitis (incidence 0.17%). There was an 8.5-fold reduction in endophthalmitis between 2012 and the time of this study.

The patients in Cases 1 to 4 were seen at Pointe-à-Pitre University Hospital. The fifth patient (Case 5) was seen at the University Hospital of Martinique. All patients had cataract surgery at an outside facility except patient 3, who had surgery at University Hospital of Pointe-à-Pitre.

All patients had microincision cataract surgery with no corneal wound stitching. All patients developed eye pain, dramatically decreased visual acuity, and severe anterior chamber inflammation that obscured the view of the fundus during the examination. All patients had B-scan ultrasonography that showed vitreous opacities and overall attached retina. In the context of post-cataract surgery,

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From the Ophthalmology Department (Mesnard, Beral, David), Pointe-à-Pitre University Hospital, Guadeloupe, and the Ophthalmology Department (Mesnard, Hage, Merle, Farès), Martinique University Hospital, Martinique, French West Indies.

Corresponding author: Rabih Hage, MD, Centre Hospitalier Universitaire de Martinique, Hôpital Pierre Zobda-Quitman, Service d'ophtalmologie, BP 632, 97261 Fort-de-France Cedex, French West Indies. E-mail: rabih.hage@chu-fortdefrance.fr.

endophthalmitis was suspected and all patients were treated according to the usual protocol described previously. In all cases, 2 intravitreal injections of antibiotics were performed every other day for 5 days. Table 1 shows the details of the examinations and treatments.

Case 1

A 78-year-old man with no significant medical history developed pain and decreased visual acuity in the right eye 1 week after uneventful cataract surgery with posterior chamber hydrophilic IOL implantation performed at an outside facility. On arrival, the visual

Table 1. Clinical characteristics, bacteriology findings, and outcomes of the 5 patients.

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5
Age at surgery (y)	78	86	69	66	49
Sex	Male	Male	Male	Male	Male
Medical history	Not significant	HBP	HBP, diabetes mellitus	HBP, POAG	POAG
Ocular laterality	Right	Left	Right	Left	Left
Position of the corneal incision	Temporal	Superior	Temporal	Nasal	Superior
IOL used	CT Asphina, Carl Zeiss Meditec AG	Akreos Adapt AO, Bausch & Lomb, Inc.	Micro-AY, Physiol S.A.	Akreos Adapt AO, Bausch & Lomb, Inc.	Acrysof SN60WF, Alcon Laboratories, Inc.
Complication of surgery (n)	None	None	None	PCR	None
Delay of decreased vision after surgery (d)	7	7	13	1	5
CDVA at presentation	Light perception	Light perception	Hand motion	Light perception	Hand motion
Slitlamp examination	Pupillary membrane with hypopyon	Corneal edema with hypopyon	Pupillary membrane with hypopyon	Corneal edema with hypopyon	Corneal edema with hypopyon
Intraocular pressure (mm Hg)	10	25	9	35	19
Treatment*					
Intravenous levofloxacin and imipenem	Daily from D1 to D5	Daily from D1 to D5	Daily from D1 to D5	Daily from D1 to D5	No
Intravitreal vancomycin and ceftazidime	D1, D3, and D5	D1, D3, and D5	D1, D3, and D5	D1, D3, and D5	D1, D3, and D5
Intravenous fosfomycin and ofloxacin	No	No	No	No	Daily from D1 to D5
Intravitreal steroids	No	No	Yes	No	No
Subconjunctival steroid injection	No	No	Yes	No	No
Steroid eyedrops	Yes	Yes	Yes	Yes	Yes
Bacteriologic culture	Negative	α-hemolytic streptococcus	*Staphylococcus epidermidis*	α-hemolytic streptococcus	*Serratia marcescens*
Antibiogram (resistances)	NA	No cefuroxime resistance	Methicillin resistance	No cefuroxime resistance	Cefuroxime resistance
CDVA at 1 month	Count fingers	Light perception	Hand motion	No light perception	Hand motion
CDVA at 3 months	20/50	Light perception	Hand motion	No light perception	Hand motion
Complications	None	Retinal detachment, NVG	Retinal detachment	Retinal detachment, NVG	None
Final outcome	VA 20/50	Enucleation	VA limited to hand motion	No light perception	VA limited to hand motion

CDVA = corrected distance visual acuity; HBP = high blood pressure; IOL = intraocular lens; NA = does not apply; NVG = neovascular glaucoma; PCR = posterior capsular rupture; POAG = primary open-angle glaucoma; VA = visual acuity
*Day 1 represents the day of the hospital admission

acuity in the right eye was limited to light perception (LP). A bacteriologic analysis of the aqueous humor was negative. The patient was treated according to the usual endophthalmitis care protocol, despite negative bacteriologic samples. No vitrectomy was performed because a vitreoretinal surgeon was not available. Fortunately, the patient's visual acuity improved to 20/50 4 months after treatment.

Case 2

One week after cataract surgery with hydrophilic IOL implantation, an 86-year-old man presented with a red, painful left eye with decreased visual acuity. The initial visual acuity was light perception. The IOP was elevated (25 mm Hg with applanation tonometry). The diagnosis of endophthalmitis was confirmed by bacteriologic analysis of the aqueous humor, which showed the presence of α-hemolytic *Streptococcus*. The antibiogram showed specific resistance to norfloxacin, a second-generation quinolone. There were no specific resistances to other antibiotics, including penicillin, cephalosporin, third-generation quinolone, aminoglycoside, glycopeptide, rifampicin, tetracycline, and cefuroxime. Two months after the onset of the symptoms, the patient developed retinal detachment (RD) and neovascular glaucoma, which led to phthisis bulbi. An enucleation was performed 3 months later.

Case 3

A 69-year-old man presented with decreased visual acuity in the right eye 2 weeks after uneventful cataract surgery with posterior chamber hydrophilic IOL implantation. The visual acuity in the operated eye was limited to hand motion (HM). The bacteriologic samples showed the presence of methicillin-resistant *Staphylococcus epidermidis* (MRSE). The patient developed an RD 2 months after the onset of the symptoms. A vitrectomy with silicone oil tamponade was scheduled at an outside facility. The patient did not develop postsurgical complications, and the visual acuity remained limited to the HM until 1 year after the onset. The surgeon decided not to remove the silicone oil to prevent a recurrence of the RD.

Case 4

One day after phacoemulsification with hydrophilic IOL implantation, a 66-year-old man presented with pain in the left eye. The operative report stated that posterior capsule rupture occurred before the intracameral injection of licensed cefuroxime. An ophthalmologic examination showed that the patient's visual acuity was limited to LP and the IOP was 35 mm Hg. Bacteriologic sample test results showed α-hemolytic streptococcus. The antibiogram showed specific resistance to norfloxacin. There were no specific resistances to other antibiotics (same antibiotics tested as in Case 2). The visual outcome was poor, with RD and neovascular glaucoma caused by severe retinal ischemia. Three months after the cataract surgery, the eye had lost its LP and a retrobulbar chlorpromazine injection was given to alleviate the eye pain.

Case 5

A 49-year-old man presented 1 week after cataract surgery with posterior chamber hydrophobic IOL implantation. On arrival, the visual acuity in the patient's left eye was limited to HM. The bacteriologic samples were positive for *Serratia marcescens*, a gram-negative bacteria resistant to cefuroxime. Two months later, the outcome was poor, with a visual acuity of worse than 20/200, although no complications occurred.

DISCUSSION

To our knowledge, these are the first reported cases of endophthalmitis after cataract surgery despite intracameral injection of licensed cefuroxime (Aprokam). Endophthalmitis after antibiotic prophylaxis with cefuroxime prepared in compounding hospital pharmacies has been reported in several studies.[1–9,12]

In our series, all patients were men. The mean age was 69.6 years, and a medical history review showed cardiovascular risk factors in 3 cases and primary open-angle glaucoma in 2 cases. Hydrophilic IOLs were used in 4 of the 5 cases, and only 1 surgery was complicated by a posterior capsule rupture.

Bacteriologic sample analyses showed the presence of gram-positive bacteria in 3 patients (2 α-hemolytic streptococci with no specific resistance and 1 MRSE) and gram-negative bacteria in 1 patient. These microbial species have also been found in endophthalmitis after antibiotic prophylaxis with unlicensed cefuroxime.[1–9,12] In the present study, only 1 bacteriologic sample was negative. Several studies[2,5,6] have reported presumed endophthalmitis after antibiotic prophylaxis by unlicensed cefuroxime with negative bacteriologic culture. In the current study, toxic anterior segment syndrome (TASS) was considered in the patient with the negative aqueous humor culture. The delayed onset of symptoms (1 week after surgery), the absence of corneal edema or ocular hypertension, and the improvement in intraocular inflammation after treatment (without intravitreal steroids) confirmed the diagnosis of endophthalmitis. Moreover, no similar cases were diagnosed in the same period, which refutes the epidemic characteristic of TASS.

Finally, 2 microorganisms showed cefuroxime resistance on the antibiogram, 1 of them being an MRSE, which was found in the ESCRS study.[1] The 2 others were sensitive to penicillin and cefuroxime. Possible explanations are that the infection occurred after the surgery or that the cefuroxime was misused, especially for the patient in Case 4 who developed early postoperative endophthalmitis.

The efficiency of cefuroxime has been proven.[1–9,12] Several hypotheses can be made regarding the cause of the endophthalmitis in this study. A break in surgical asepsis should be considered, and this can occur at any step of the surgery, including during the preparation of licensed cefuroxime. Aprokam is a formulation that still requires a dilution step, and even with the use of povidone–iodine 5.0% ophthalmic solution before surgery, the rate of surgical fluid contamination remains high (up to 50%).[13] A rupture of the posterior capsule, as in 1 of this study's patients, also increases the risk for endophthalmitis.[1,2] Elderly (<85 years) and male patients seem to be more at risk for developing endophthalmitis.[4,12] Postoperative contamination caused by poor hygiene could also be suspected.[8] However, it should only affect eyes with corneal wound abnormalities, which was not the case with the patients in our study. Four of the 5 implanted IOLs were hydrophilic, which are less likely to allow bacterial adhesion than hydrophobic IOLs.[14] Our study did not show a left eye or right eye predilection. All surgeons were right-handed, and incision placement was temporal in 2 right eyes and superior in 3 left eyes.[15]

Four of the 5 cases had a poor outcome, with a final visual acuity of less than 20/200. This is different from other studies of endophthalmitis after unlicensed cefuroxime that show a better final visual acuity[2,6]; however, those were performed in countries (United States and Spain) with different climate conditions and thus different bacterial flora than ours. Moreover, no bacteriologic sample was positive in these previously reported cases, which can challenge the endophthalmitis diagnosis and explain the better visual outcomes. In India, a study also found poor visual outcomes with endophthalmitis after unlicensed cefuroxime.[8] That study found 1 gram-positive bacterium and 2 gram-negative bacteria. The authors concluded the poor mean visual outcome could be linked to RD that occurred after endophthalmitis treatment, which is what we observed in our series.

Finally, endophthalmitis severity depends on many factors, such as the involved microorganism. For instance, poor outcomes usually occur in endophthalmitis associated with *Streptococcus* and gram-negative species, which were found in our series.[3,10] Antibiotic resistance can also explain the infection severity, as in the patient with MRSE infection in our study. Furthermore, the prognosis depends on a diagnostic delay after the onset of the symptoms and a treatment protocol that varies depending on hospitals. In our series, 3 patients (Cases 1, 2, and 4) with visual acuity limited to LP at presentation could have benefited from an emergency vitrectomy, as recommended by ESCRS guidelines. Unfortunately, those 3 patients were admitted to Pointe-à-Pitre University Hospital at a time when no experienced vitreoretinal surgeons were available. Transferring the patients to another hospital was considered inappropriate because it would have delayed intravenous and intravitreal antibiotic treatment. The poor final outcome in 2 cases (enucleation in patient 2 and no LP in patient 4) can be related to the lack of vitrectomy at the time of presentation. Indeed, those 2 patients eventually developed RD and a delayed vitrectomy was performed at an outside facility. Compliance with treatment is also a poor outcome risk factor to be considered.

The positive effect of combining intracameral antibiotic prophylaxis with cefuroxime is well documented.[1–9,12] Intracameral injection of licensed cefuroxime at the end of the cataract surgery remains the first-line prophylaxis of endophthalmitis postoperatively in all French ophthalmology departments, which is not the case outside Europe. The American Society of Cataract and Refractive Surgery and ESCRS surveys stated that the most frequent reasons for not using an intracameral injection of cefuroxime were the lack of an approved commercial preparation and the risks for dilution and contamination errors.[11] The use of Aprokam aims to reduce those risks. Furthermore, its economic impact seems to be better than the use of unlicensed cefuroxime.[16] However, this cefuroxime preparation still requires 1 dilution before injection. Even if this step is unlikely to cause endophthalmitis, there is still a risk for perioperative contamination when the injection is administered. New formulations without an additional dilution step would be safer and would lead to more widespread use of this antibiotic prophylaxis, although such use is not possible with cefuroxime. Although other antibiotics might be used, none has the scientific background of cefuroxime.

Although licensed cefuroxime has proved to be efficient at preventing endophthalmitis, it has not eradicated this potentially severe complication of cataract surgery. Other preventive methods (preoperative blepharitis treatment, perioperative aseptic measures, postoperative patient education) still reduce the incidence of this devastating complication.

WHAT WAS KNOW

- Intracameral injection of cefuroxime at the end of cataract surgery allows a 5-fold reduction in the occurrence of postoperative endophthalmitis.
- Use of the first licensed cefuroxime formulation for post-cataract antibiotic prophylaxis has led to no reports of endophthalmitis.

WHAT THIS PAPER ADDS

- Despite the use of licensed cefuroxime, virulent germs can still cause severe endophthalmitis after cataract surgery. Aggressive treatment combining early vitrectomy and intravitreal antibiotics should be performed in emergency to prevent devastating complications, such as RD and permanent visual loss.

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