Clinical features and microbiology of post-cataract surgery endophthalmitis with and without intracameral moxifloxacin prophylaxis: Endophthalmitis prophylaxis study report 3

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Purpose: This study aimed to analyze the clinical presentations, microbiology, and management outcomes of post–cataract surgery endophthalmitis, with and without intracameral moxifloxacin prophylaxis. **Methods:** This study was designed as a retrospective, consecutive, comparative case series. Records of consecutive cataract surgery from January 1, 2015, till June 30, 2020, were analyzed. The cases that developed endophthalmitis were analyzed. The endophthalmitis cases were divided by their prophylaxis treatment into two groups: with intracameral moxifloxacin (ICM) and without (N-ICM). Inclusion criteria were (1) age ≥ 18 years, (2) cataract surgery with intraocular lens implantation, (3) endophthalmitis within 6 weeks of cataract surgery, and (4) cataract surgery in the institute by any of the three methods—phacoemulsification, manual small incision cataract surgery, and extracapsular cataract extraction. **Results:** In the study period, 66,967 cataract surgeries were performed; 48.7% ($n = 32,649$) did not receive ICM. There was no difference between the N-ICM and ICM groups in the incidence of clinical ($n = 21$, 0.064% and $n = 15$, 0.043%; $P = 0.23$) and culture proven ($n = 19$, 0.033% and $n = 11$, 0.023%; $P = 0.99$) endophthalmitis, respectively. Greater number of patients in the N-ICM group had lid edema (76.2% vs. 40%; $P = 0.03$), corneal edema (71.4% vs. 33.3%; $P = 0.03$) and lower presenting vision with available correction (logMAR [logarithm of the minimum angle of resolution] 1.26 ± 1.2 vs. logMAR 0.54 ± 0.85; $P = 0.02$). The final best-corrected visual acuity following treatment was worse in the N-ICM group (logMAR 1.26 ± 1.2 vs. 0.54 ± 0.85; $P = 0.02$). **Conclusion:** Endophthalmitis after intracameral moxifloxacin may have relatively milder signs and symptoms and may respond better to treatment.

Key words: Endophthalmitis, intracameral antibiotics, intracameral moxifloxacin, prophylaxis

Post–cataract surgery endophthalmitis is a grave complication that can result in severe vision loss and, occasionally, loss of globe integrity.[1] In recent decades, improvement in the understanding of the aseptic techniques and applying the protocols for surgical prophylaxis has considerably reduced this complication. The currently reported incidence of post–cataract surgery endophthalmitis is from 0.06% to 0.36%.[2-4] A review of the published literature on post–cataract surgery endophthalmitis in India has reported the incidence of clinical endophthalmitis from 0.04% to 0.15% and culture-proven endophthalmitis from 0.02% to 0.08%.[5]

Today, presurgical prophylaxis remains a proven measure for reducing the incidence of endophthalmitis. Povidone-iodine (PI) preparation of the eye and periocular skin is the current standard of care for endophthalmitis prophylaxis.[6,7] A randomized control trial in Europe demonstrated the benefit of intracameral cefuroxime (1 mg in 0.1 mL) with a fivefold reduction in the incidence of post–cataract surgery endophthalmitis.[8-10] A multicenter

trial in India reported a three- to sixfold decrease in post–cataract surgery acute endophthalmitis with intracameral moxifloxacin (0.5 mg in 0.1 mL).[11] In a comparative study between the two intracameral antibiotics, we have shown a 3.6-fold reduction in the incidence of postcataract acute endophthalmitis; there was no statistically significant difference between cefuroxime and moxifloxacin in the rate of decrease of infection.[12] A study in India has also shown that intracameral moxifloxacin is used more often because it is readily available and is less expensive.[13]

However, not every ophthalmic surgeon uses intracameral antibiotic routinely in cataract surgery. Furthermore, the use of intracameral antibiotics has reduced endophthalmitis incidence, although it has not eliminated it. We do not have many reports on the clinical profile, microbiology, and antibiotic susceptibility of endophthalmitis after intracameral antibiotic in cataract surgery with an intraocular lens (IOL). In

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this communication, we have analyzed the clinical features, microbiological profile, and outcomes of post–cataract surgery acute endophthalmitis that occurred after intracameral moxifloxacin and compared these with the ones that occurred without intracameral prophylaxis in the same period.

Methods

This study is a retrospective analysis of prospectively collected data of cataract surgery complications, including endophthalmitis. All patients were operated on for cataract in the institute. The study was approved by the Institutional Review Board/Ethics Committee (LEC 08-16-066), and it adhered to the tenets of the Declaration of Helsinki. Medical records of all patients who received cataract surgery from January 1, 2015, till June 30, 2020, were evaluated. The case records of those who developed endophthalmitis were segregated and divided into two groups: one in which intracameral moxifloxacin prophylaxis was given (ICM group) and the other where it was not given (N-ICM group). The inclusion criteria were (1) age ≥ 18 years, (2) cataract surgery with IOL, (3) endophthalmitis within 6 weeks of cataract surgery, and (4) cataract surgery done in the institute by any of the three methods—phacoemulsification, manual small incision cataract surgery (MSICS), and extracapsular cataract extraction (ECCE). The exclusion criteria were (1) underage, <18 years; (2) aphakia without IOL; (3) occurrence of endophthalmitis >6 weeks of primary surgery; and (4) cataract surgery performed outside the institute.

In all eyes, the primary cataract surgery and IOL implantation were done as per the institute protocol. Briefly, it was a sterile preparation of skin around the eye (10% PI) and the operating field (5% PI), standard cataract surgery by one of the three methods (phacoemulsification, MSICS, or ECCE), filling the anterior chamber with viscoelastic, and insertion of predetermined IOL. The decision on the type of cataract surgery was left to the discretion of the operating surgeon. Because routine use of intracameral antibiotic was not a standard protocol of the institute during the study period, the decision to use intracameral moxifloxacin was left to the operating surgeon's discretion. When used, moxifloxacin 0.5 mg in 0.1 mL was injected into the anterior chamber in front of the IOL after washing out the viscoelastic material and before the corneal or scleral or limbal incision closure.

After surgery, all patients received topical corticosteroid (1% prednisolone acetate, tapered over a month) and topical antibiotic (moxifloxacin 0.5%, ciprofloxacin 0.3%, and ofloxacin 0.3% four times daily for a week). Clinical endophthalmitis was diagnosed from a constellation of symptoms (injection of the eye, reduction of vision, pain) and signs (lid edema, corneal edema, hypopyon, pupillary exudative membrane, and hazy vitreous). The patients suspected of having endophthalmitis clinically were referred to the retina service and were reviewed in this service until complete resolution of inflammation or the eye worsened to phthisis. The specific treatment consisted of the Endophthalmitis Vitrectomy Study (EVS)–recommended two intravitreal antibiotics (ceftazidime 2.25 mg and vancomycin 1.0 mg, each in 0.1 mL) with or without vitrectomy at the same time or later.[1] At the beginning of the surgery, undiluted vitreous, 0.5 to 1.0 mL was collected using a syringe and processed in microbiology as per the institute protocol.[14]

Microbiology

The microbiological processing of the vitreous sample included direct microscopy and culture. Smears were examined after staining with Gram and Giemsa stains and 0.1% calcofluor white. The vitreous sample was inoculated in a combination of culture media that included 5% sheep blood agar, chocolate agar (aerobic and anaerobic), thioglycolate broth, brain heart infusion broth, Sabouraud's dextrose agar, and potato dextrose agar. All media were incubated aerobically at 37°C except Sabouraud's dextrose agar and potato dextrose agar, which were incubated at 27°C for 2 weeks. Chocolate agar was incubated anaerobically in 5% CO_2 at 37°C. The antibiotic susceptibility testing was done by the minimum inhibitory concentration (MIC) method.

Clinical management

The treatment of clinically suspected endophthalmitis was as per the institute protocol. The primary treatment in less severe cases (presenting vision ≥ 20/400, relatively clearer cornea and pupillary area, and relatively better vitreous view in highest illumination on indirect ophthalmoscopy) was a vitreous biopsy and intravitreal antibiotics injection; the primary treatment in severe cases (presenting vision <20/400, corneal edema, vitritis, poor or no fundus view in highest illumination on indirect ophthalmoscopy, vitreous exudates on B scan) was pars plana vitrectomy and intravitreal antibiotics. The primary intravitreal antibiotics were vancomycin (1 mg/0.1 mL) and ceftazidime (2.25 mg/0.1 mL) injected using two separate syringes. A repeat intravitreal antibiotic (culture and susceptibility adjusted) and/or surgery (vitrectomy) was repeated in 48 to 72 hours for eyes not responding favorably (clinical judgment) to primary therapy.

The collected data of the patients were as follows: demography (age, gender, laterality), cataract surgery (type, incision site, complication, suturing), surgeon's profile (ophthalmology fellow/faculty), symptoms (time to symptoms, pain, presenting vision), ophthalmic signs (lid edema, corneal edema, presence of hypopyon), interventions (type, intravitreal antibiotic and vitrectomy, number), and outcome (time to resolution of endophthalmitis, vision at last follow-up, total follow-up duration, and the globe salvage rate). The best-corrected visual acuity was converted to logarithm of the minimum angle of resolution (logMAR) as per the previously described methods in the literature.[15]

The resolution of endophthalmitis was defined as an absence of inflammation, judged by the treating ophthalmology faculty at the last visit. Anatomic salvage was defined as the absence of inflammation, hypotony (Intraocular pressure <5 mmHg), and retinal detachment at the last visit.

Statistical analysis

The collected data were arranged on an Excel spreadsheet. The statistical analysis was done using MedCalc Version 19.4.1 (Ostend, Belgium). All normative data were compared using the paired *t*-test. Nonnormative data were compared using the Mann–Whitney test. Means with standard deviation were reported for normative, and medians were reported for nonnormative data. Univariate and multivariate linear regression analysis was performed to assess various factors on the final visual outcome. A *P* value of <0.05 was

considered significant and was reported with appropriate 95% confidence intervals.

Results

A total of 66,967 consecutive cataract surgery records were reviewed. In this cohort, 48.7% (*n* = 32,649) eyes had not received intracameral moxifloxacin (N-ICM) prophylaxis, and 51.3% (*n* = 34,318) eyes had received intracameral moxifloxacin (ICM) prophylaxis. Thirty-six eyes developed clinical endophthalmitis (incidence 0.05%) and included 0.064% (21 of 32,649) endophthalmitis in the N-ICM group and 0.043% (15 of 34,318) in the ICM group. This difference, *P* = 0.2, was not statistically significant.

The analysis showed a greater use of intracameral moxifloxacin in relatively older people (56.5 vs. 39.9 years; *P* = 0.04), in eyes secured with suture (86.7% vs. 33.3%; *P* = 0.001); longer surgical time (≥ 30 minutes, 66.7% vs. 28.6%; *P* = 0.02), and surgery by ophthalmology fellows (73.3% vs. 33.3%; *P* = 0.02) [Table 1]. There was no statistical difference in gender, the technique of cataract surgery (phacoemulsification and others), and the location of incision (corneal and limbal/scleral) [Table 1].

The symptoms and signs of endophthalmitis were less in eyes that received intracameral moxifloxacin: time to infection (13.13 vs. 6.78 days; *P* = 0.01); lid edema (40% vs. 76.2%; *P* = 0.03); corneal edema (33.3% vs. 71.4%; *P* = 0.03); presence of hypopyon (53.3% vs. 71.4%; *P* = 0.03); and presenting logMAR vision (1.44 vs. 1.93; *P* = 0.008) [Table 1]. There was no statistical difference in pain.

The eyes in the N-ICM group received vitrectomy more often and a greater number of intravitreal antibiotic injections than the ICM group, although there was no statistical difference. Following the standard of care (laid down by the institute), endophthalmitis resolved earlier in eyes that had received intracameral moxifloxacin (3.7 vs. 6 weeks; *P* = 0.008), regained more vision (logMAR 0.54 vs. 1.26; *P* = 0.02) and higher globe salvage rate (80% vs. 47.6%; *P* = 0.05). None of the patients in either group had posterior capsular dehiscence during surgery or any eventful surgical course.

On multivariate regression analysis, a favorable final visual outcome was seen for the scleral incision (vs. corneal; *P* = 0.02), surgery by ophthalmology faculty surgeon (vs. ophthalmologist fellow; *P* = 0.01), intracameral moxifloxacin prophylaxis (vs. no intracameral antibiotic; *P* = 0.04), and better presenting vision (*P* = 0.008) [Table 2].

There was no difference in culture positivity of vitreous in either group; but gram-positive cocci grew more often in

Table 1: Comparison of the nonprophylaxis (N-ICM) and the prophylaxis (ICM) groups

	Total	N-ICM	ICM	*P* for difference	95% CI
Cataract surgeries, *n*	66,967	32,649 (48.8%)	34,318 (51.2%		
Clinical endophthalmitis, *n* (incidence)	36 (0.05%)	21 (0.064%)	15 (0.043%)	0.23	
Culture-proven endophthalmitis, *n* (incidence)	19 (0.03%)	11 (0.033%)	8 (0.023%)	0.99	
Age in years (median)		39.95±26.04 (47)	56.53±96.44 (59)	0.04*	1-33
Male gender (%)		13 (61.9%)	8 (53.3%)	0.61	
Number of phacoemulsification surgeries (%)		17 (81%)	10 (66.7%)	0.33	
Cases with corneal surgical incision		13 (61.9%)	7 (46.7%)	0.37	
Cases where suture was applied		7 (33.33%)	13 (86.7%)	0.001*	20.87%-72.13%
Duration of surgery (minutes)	<15	4 (19%)	1 (6.7%)	0.29	
	16-30	11 (52.4%)	2 (13.3%)	0.01	0.43%-60.6%
	31-60	6 (28.6%)	10 (66.7%)	0.02	5.24%-64.29%
	>60	0	2 (13.3%)7.	0.09	
Surgeries by trainees		7 (33.3%)	11 (73.3%)	0.02*	6.94%-62.57%
Days from surgery to symptoms (median)		6.78±10.33 (7)	13.13±9.34 (12)	0.003*	0-1
Pain		16 (76.2%)	11 (73.3%)	0.84	
Lid edema		16 (76.2%)	6 (40%)	0.03*	3.93%-60.3%
Corneal edema		15 (71.4%)	5 (33.3%)	0.03*	5.24%-61.49%
Presence of hypopyon		15 (71.4%)	8 (53.3%)	0.27	
Primary vitrectomy		14 (66.7%)	8 (53.3%)	0.42	
Mean number of repeat interventions (median)		2.66±1.49 (3)	1.86±1.55 (1)	0.06	
Culture positivity, *n* (%)		11 (52.4%)	7 (46.6%)	0.73	
Gram-positive organisms isolated		9 of 11 (81.8%)	3 of 7 (42.8%)	0.01*	7.3%-62.65%
Gram-negative organisms isolated		2 of 11 (18.2%)	4 of 7 (57.2%)	0.001*	7.3%-62.65%
Baseline presenting vision in logMAR (median)		1.93±0.44 (2)	1.44±0.68 (1.7)	0.008*	−1-0
Time to resolution in weeks		6±2.58 (6)	3.76±1.73 (4)	0.008*	−4-0
Final best-corrected vision in logMAR (median)		1.26±1.2 (1)	0.54±0.85 (0.3)	0.02*	−1.28-0
Total follow-up		11.72±11.84 (5)	9.53±9.84 (4)	0.64	
Globe salvage (%)		10 (47.6%)	12 (80%)	0.05	0.23%-55.62%

*Significant values. logMAR=logarithm of the minimum angle of resolution; CI=confidence interval

Table 2: Multiple linear regression for potential factors that may influence final visual outcome

Variable	P (bivariate)	P (multivariate)
Age	0.06	0.22
Gender	0.85	0.5
Type of surgery	0.23	0.17
Scleral incision (vs. corneal incision)	0.06	0.02*
Nonusage of suture	0.008	0.09
Duration of surgery	0.47	0.95
Surgeon experience	0.61	0.01*
Use of prophylaxis	0.04	0.04*
Days to symptoms	0.64	0.83
Prompt PPV	0.33	0.07
Presenting vision	0.008	0.008*

*Significant value. PPV=pars plana vitrectomy

eyes without intracameral moxifloxacin (81.8% vs. 42.8%; $P = 0.01$), and gram-negative bacilli grew more frequently in eyes with intracameral moxifloxacin (57.2% vs. 18.2%; $P = 0.02$). The culture was positive in 18 vitreous samples. These included 12 gram-positive cocci (66.6%) and six gram-negative bacilli (33.3%). There was no fungal growth in either group. *Streptococcus pneumoniae* and *Staphylococcus epidermidis* were the common gram-positive cocci; *Haemophilus influenzae* and *Pseudomonas stutzeri* were the common gram-negative bacilli. The antibiotic susceptibility pattern to two currently commercially available intracameral antibiotics, moxifloxacin, and cefuroxime is tabulated. In the ICM group, four organisms (one gram-positive and three gram-negative) were resistant to moxifloxacin; five organisms (one gram-positive and four gram-negative) were resistant to cefuroxime. In the N-ICM group, all organisms (seven gram-positive and two gram-negative) were sensitive to both moxifloxacin and cefuroxime [Table 3].

Discussion

Prophylactic treatment, be it preparation of the eye with topical betadine or intraoperative intracameral (IC) injection of antibiotic, has reduced the incidence of endophthalmitis after cataract surgery.[6,11,12] The current study showed a reduction in the incidence of endophthalmitis using IC moxifloxacin, although it did not reach statistical significance in a low incidence of endophthalmitis setting. But there was a significant reduction in the constellation of symptoms and signs of endophthalmitis. Additionally, with IC moxifloxacin, the acute endophthalmitis occurrence was delayed, the presenting vision was relatively better, and the outcome was superior with the standard operating protocol of the institute compared with eyes with no IC moxifloxacin prophylaxis.

Periocular fluid may ingress into the anterior chamber despite hydration of the incisions in cataract surgery. The intraocular bacterial contamination rate could be as high as 31% despite the preparation of the operative field with PI and other aseptic measures.[16] Intracameral antibiotic prevents the spread of infection caused by this situation. Several retrospective studies have documented the efficacy of intracameral antibiotic prophylaxis.[17-23] This also prevents

endophthalmitis even in certain surgical accidents such as the rupture of the posterior capsule.[11,23] Despite these pieces of evidence, the earlier surveys with the members of the American Society of Cataract and Refractive Surgery (ASCRS) and the All India Ophthalmological Society (AIOS) have not shown a universal acceptance of IC antibiotic.[10,13] This was the precise reason the routine use of IC antibiotic was not included in the standard protocol of the institute and was left to the decision of the operating surgeon through a general advisory.

Both intracameral cefuroxime and moxifloxacin protect from post–cataract surgery acute endophthalmitis.[23] Both are available commercially, but moxifloxacin is often used in India because of its reduced cost and easy availability.[13] Studies from India have shown the efficacy of intracameral moxifloxacin.[11,12,16,24] One study from India had shown higher culture-positive endophthalmitis when ICM was not used (37.4% vs. 17.2%) and a lower incidence of gram-positive cocci infection.[11] In the current study, we did not find such a difference in culture positivity.

Intriguingly, we found endophthalmitis was more often caused by gram-positive cocci when ICM was not used (81.8% vs. 42.8%; $P = 0.01$) and caused by gram-negative bacilli when ICM was used (18.2% vs. 57.2%; $P = 0.02$). It is possible that gram-positive cocci infection was inhibited when intracameral moxifloxacin was used, but it did not explain the lower incidence of gram-negative bacilli infection in the eye that did not receive ICM prophylaxis. Post–cataract acute endophthalmitis is also reported after intracameral commercially available cefuroxime. Mesnard *et al.*[25] reported five cases of post–cataract surgery endophthalmitis (four were culture positive) after intracameral cefuroxime prophylaxis. In their series, three gram-positive and one gram-negative microorganisms were isolated, and two isolates were resistant to cefuroxime.

Moxifloxacin is a fourth-generation fluoroquinolone with action against gram-positive and selective gram-negative microorganisms; Cefuroxime is a second-generation cephalosporin with activity predominantly against gram-positive microorganisms. Intracameral cefuroxime has a time-dependent action (aqueous concentration above the MIC for 4–5 hours). Moxifloxacin has a dose-dependent action (aqueous concentration up to 300 times greater than the MIC).[26-28] Thus, intracameral moxifloxacin might have an advantage over the intracameral cefuroxime in the Indian context due to the higher incidence of gram-negative endophthalmitis.[29] But the current study showed that intracameral moxifloxacin does not necessarily prevent gram-negative infection. However, when it occurs, we noticed that the symptoms and signs could be relatively milder than the classical description.[30] Our study also showed that three microorganisms were resistant to moxifloxacin, and four organisms were resistant to cefuroxime. Incidentally, one gram-positive coccus, *Staphylococcus haemolyticus*, was resistant to both moxifloxacin and cefuroxime. Based on these findings, the preference of Indian ophthalmologists for moxifloxacin[13] may not be illogical.

The current study is not without limitations. The foremost one is that it is a retrospective study, although all the data were collected prospectively. This study did not examine the difference between intracameral cefuroxime and moxifloxacin

Table 3: Antibiotic susceptibility pattern to commonly used intracameral antibiotics of bacterial isolates from vitreous sample of patients in N-ICM and ICM groups

Group	Class	Number	Organisms	Antibiotic	
				Moxifloxacin	Cefuroxime
ICM (n=7)	GPC (n=3)	1	*Staphylococcus epidermidis*	S	S
		2	*Staphylococcus haemolyticus*	R	R
		3	*Granulicatella adiacens*	S	S
	GNB (n=4)	4	*Pseudomonas stutzeri*	R	R
		5	*Pseudomonas stutzeri*	R	R
		6	*Acinetobacter lwoffii*	S	R
		7	*Acinetobacter lwoffii*	R	R
NICM (n=11)	GPC (n=9)	8	*Streptococcus pneumoniae*	S	S
		9	*Streptococcus pneumoniae*	S	S
		10	*Staphylococcus epidermidis*	S	S
		11	*Staphylococcus warneri*	S	S
		12	*Streptococcus anginosus*	S	S
		13	*Streptococcus pneumoniae*	S	S
		14	*Staphylococcus lugdunensis*	S	S
		15	*Streptococcus pneumoniae*	S	S
		16	*Staphylococcus epidermidis*	S	S
	GNB (n=2)	17	*Haemophilus influenzae*	S	S
		18	*Haemophilus influenzae*	S	S

GNB=gram-negative bacilli; GPC=gram-positive cocci; ICM=intracameral moxifloxacin; NICM=no intracameral moxifloxacin; R=resistant; S=sensitive

prophylaxis post–cataract surgery acute endophthalmitis. The decision to use IC moxifloxacin was left to the decision of the operating surgeon. The strengths are the use of uniform clinical and microbiological protocol and documentation. All cases were in-house patients, and all surgical protocols and procedures were uniform.

Conclusion

Based on the current and earlier published studies in India, we suggest that IC antibiotic should be included as a part of the standard operating protocol for cataract surgery. This will marginally increase the cost of surgery, but the cost–benefit ratio is much higher in the event of endophthalmitis without its use. While waiting for such a policy decision, one should consider IC antibiotic during cataract surgery in the elderly (≥ 70 years), in immunodeficient people including those with diabetes, in people with one seeing eye, in events of longer duration (>30 minutes) surgery, and in events of posterior capsule rent. Should intracameral moxifloxacin be considered as the standard recommendation in cataract surgery, we will suggest that the manufacturers make available single-use intracameral antibiotic instead of current multiple-use vials. We acknowledge that the current study has not used IC cefuroxime and does not discount the similar beneficial effects in reducing post–cataract surgery endophthalmitis.

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Conflicts of interest

There are no conflicts of interest.

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