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Safety of undiluted intracameral moxifloxacin without postoperative topical antibiotics in cataract surgery

Andrew Xingyu Zhou · Wyatt Boyer Messenger · Steven Sargent · Balamurali Krishna Ambati

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Abstract The objective of this study is to evaluate the safety of undiluted 0.5 % intracameral moxifloxacin for postoperative endophthalmitis prophylaxis in cataract surgery patients without the use of additional postoperative topical antibiotics. All phacoemulsification cataract surgeries performed by a single surgeon (B.A.) at the John A. Moran Eye Center from June 2012 to May 2015 were reviewed retrospectively. From June 2012 to April 2014, patients were given topical 0.5 % moxifloxacin postoperatively. From May 2014 to May 2015, all patients were given moxifloxacin intracamerally with no antibiotics postoperatively. The follow-up period was 1 month after surgery. Preoperative visual acuity and postoperative visual acuity, corneal edema, and anterior chamber reaction were recorded and compared between the two groups. 384 cataract surgeries were performed during the study period. None of the 384 eyes in the study developed endophthalmitis. Of those 384 eyes, 222 were included in the study for analysis based on the inclusion and exclusion criteria. 131 were part of the topical antibiotic group and 91 were part of the intracameral group. The differences in uncorrected visual acuity at 1 day postoperatively ($p = 0.595$) and best corrected visual acuity at 1 month postoperatively ($p = 0.099$) were not statistically significant. Differences in corneal edema ($p = 0.370$) and anterior chamber reaction ($p = 0.069$) at 1 day postoperatively and corneal edema ($p = 0.512$) and anterior chamber reaction ($p = 0.512$) at 1 month postoperatively were also not statistically significant. Undiluted 0.5 % moxifloxacin can be safely injected intracamerally following cataract surgery without additional postoperative antibiotic prophylaxis to prevent endophthalmitis without adverse effects on patient outcomes.

Keywords Endophthalmitis · Intracameral · Moxifloxacin · Cataract · Phacoemulsification

Introduction

Cataract surgery is the most commonly performed surgical procedure in the United States [1]. It is usually a very successful surgery, but as with any procedure, there are risks of infection. In the eye, infection is particularly devastating and can result in blindness or loss of the eye. Thus, postoperative endophthalmitis, though rare, is an extremely feared complication of cataract surgery and much work has been done to study its prevention.

The use of intracameral antibiotics varies greatly in different parts of the world. In the United Kingdom, a

A. X. Zhou · W. B. Messenger · S. Sargent · B. K. Ambati (✉)
John A. Moran Eye Center, University of Utah School of Medicine, 65 Mario Capecchi Drive, S5668, Salt Lake City, UT 84132, USA
e-mail: bala.ambati@utah.edu

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survey in 2008 found that 55 % of ophthalmologists use intracameral antibiotics [2]. A similar survey in Australia in 2012, where a commercial preparation of intracameral cefazolin was available at that time, showed that 84.4 % used intracameral antibiotics [3]. A survey of European Society of Cataract and Refractive Surgeons (ESCRS) members in 2012 showed that 74 % always or usually used intracameral antibiotics [4]. These results are in contrast to a survey of American Society of Cataract and Refractive Surgery (ASCRS) members in 2014 which showed that 50 % were using intracameral antibiotics, with 84 % injection antibiotics directly. 65 % of the respondents were practicing in the United States. The varying degree of use is partially due to the availability of commercial preparations of intracameral antibiotics, which are currently not available in the United States [5].

Several antibiotics have been used for intracameral injection. In the ESCRS survey, 82 % used cefuroxime, while others used vancomycin, moxifloxacin, or gentamicin [4]. In Australia, cefazolin is popular due to the availability of a commercial preparation [3]. The most studied antibiotics for intracameral use are vancomycin, cefuroxime, and moxifloxacin. There are advantages and disadvantages to each. Cefuroxime has been shown to be effective in a randomized controlled trial by ESCRS and various other retrospective studies have shown benefit [6]. However, it needs to be prepared for intracameral injection, and errors in preparation have been associated with adverse effects [7]. Although vancomycin is effective against methicillin-resistant *Staphylococcus aureus* (MRSA), the United States Centers for Disease Control and American Academy of Ophthalmology have discouraged the use of vancomycin for endophthalmitis prophylaxis due to lack of supporting data for its effectiveness, possible ocular toxicity, and the emergence of antibiotic resistance [8]. Like cefuroxime, vancomycin also needs to be prepared for intracameral injection. In contrast, commercially available moxifloxacin 0.5 % ophthalmic solution, a fourth-generation fluoroquinolone with a broad spectrum of action, does not need to be prepared by compounding or dilution, thus avoiding possible risks associated with vancomycin and cefuroxime preparation [9]. Moxifloxacin is also self-preserved, hence there is less chance of adverse reaction to preservatives found in other antibiotics [10]. Several studies have also demonstrated its safety in the eye [10–14]. Thus, we believe it holds great promise to be used intracamerally for endophthalmitis prophylaxis. We, therefore, performed a retrospective review of the safety of intracameral moxifloxacin in cataract surgery patients, compared to a cohort of patients who did not receive intracameral antibiotics.

Methods

This study examined cataract surgeries that were performed by a single surgeon (B.A.) at the John A. Moran Eye Center at the University of Utah School of Medicine from June 2012 to May 2015. Patient charts were reviewed retrospectively. Institutional Review Board approval was obtained. All patients undergoing phacoemulsification cataract surgery without other ocular pathologies were included in this study. Patients were excluded if they had a diagnosis of glaucoma, a macular or retinal disorder (such as age-related macular degeneration, diabetic retinopathy, or retinal detachment), uveitis, a corneal disorder (such as Fuch's endothelial dystrophy, prior corneal transplant, or pterygium). Patients were also excluded if they had a complication during surgery or did not have examination findings recorded at 1 month postoperatively. All patients in the study underwent surgery as follows.

Preoperatively, patients received one drop of 0.5 % proparacaine, three drops each of 2.5 % phenylephrine, 1 % cyclopentolate, 0.5 % ketorolac, and 5 % povidone-iodine, and one application of 3.5 % lidocaine ophthalmic gel.

Intraoperatively, phacoemulsification cataract extraction with intraocular lens placement was performed. In the intracameral moxifloxacin treatment group, an injection of 500 μg in 0.1 mL 0.5 % preservative-free moxifloxacin was given intracamerally at the conclusion of the procedure. All patients, including those in the intracameral group, were given 1 drop each of 5 % povidone-iodine, 1 % prednisolone acetate, and 0.5 % moxifloxacin in the operating room after surgery.

Postoperatively, the intracameral patients were given 0.1 % nepafenac and 1 % prednisolone acetate drops four times a day for 2 weeks. The cohort which did not receive intracameral moxifloxacin received postoperative 0.1 % nepafenac, 1 % prednisolone

acetate, and also topical 0.5 % moxifloxacin drops four times a day for 1 week. Prednisolone was given to control postoperative inflammation and nepafenac was given for cystoid macular edema prophylaxis. Patients were examined at 1 day and 1 month after surgery. Visual acuity without correction, anterior chamber reaction, and corneal edema were measured. At the 1 month exam, patients were also refracted to obtain best corrected visual acuity (BCVA).

Statistical calculations were performed using Microsoft® Excel®. Age and visual acuity were compared with two-sample *T* tests, while gender, anterior chamber reaction, and corneal edema were compared with two-sample proportion tests. Visual acuities were averaged with the LogMAR method [15].

Results

During the course of the study, 384 cataract surgeries were performed. None of the 384 eyes in the study developed endophthalmitis. Of those 384 eyes, 222 were included in the study for analysis based on the inclusion and exclusion criteria. 131 were part of the topical antibiotic group and 91 were part of the intracameral group. Demographic information for both groups is shown in Table 1. There was no significant difference in the ages and genders of the two groups. Visual acuity results are shown in Table 2. There was no significant visual acuity difference between the two groups preoperatively, 1 day postoperatively, and 1 month postoperatively. Anterior chamber reaction and corneal edema results are shown in Table 3. There was no significant difference between the intracameral group and control group in terms of anterior cell reaction and corneal edema at 1 day postoperatively and 1 month postoperatively.

With respect to adverse events, in the control group, one patient developed cystoid macular edema in both operated eyes, one patient developed a Herpes simplex virus infection, and one patient developed iritis. In the intracameral group, one patient developed iritis in both operated eyes.

Discussion

Our results showed that there was no significant difference between topical administration of moxifloxacin postoperatively and a single injection of moxifloxacin intracamerally at the end of cataract surgery in terms of visual acuity, corneal edema, and anterior chamber reaction at 1 day postoperatively and 1 month postoperatively. Although no eyes developed endophthalmitis in this study, the number of eyes analyzed was too small to determine if there is a significant difference in endophthalmitis rates between topical and intracameral moxifloxacin administration.

The most common organisms causing postoperative endophthalmitis in the United States are gram-positive bacteria. In a 2012 study, 20 years of positive vitreous cultures at a tertiary referral center in the United States (Yale-New Haven Hospital) were analyzed. The results showed that the most common causative organisms were gram-positive bacteria (80.6 %), followed by gram-negative bacteria (12.5 %), and finally fungi (6.9 %). The most common gram-positive bacteria were coagulase-negative *Staphylococcus*, Viridans *Streptococcus*, *Streptopcoccus pneumonia*, *Propionibacterium acnes*, other *Streptococcus* species, *Staphylococcus aureus*, *Enterococcus faecalis*, and *Micrococcus* species. The most common gram-negative bacteria were *Klebsiella* species, *Moraxella* species, and *Haemophilus* species [16].

The median minimal inhibitory concentrations (MIC_{50}) of these organisms in vitro are all below 0.50 μg/ml [9]. A study on the intraocular concentration of moxifloxacin after intracameral injection in humans showed that the drug gets diluted 3.3 times with a 0.1 ml injection [17]. Thus, with an injection of 500 μg in 0.1 ml, the initial concentration in the anterior chamber is about 1515 μg/ml. This is in

Table 1 Patient demographics

	Intracameral moxifloxacin	Control	*p* value
Male/female	51/40	69/62	0.620
Age	65.07 ± 9.30	64.69 ± 10.27	0.775

Table 2 Visual acuity

	Intracameral moxifloxacin (logMAR)	Control (logMAR)	*p* Value
BCVA preoperatively	0.261 ± 0.392 (Snellen equivalent 20/36)	0.217 ± 0.265 (Snellen equivalent 20/33)	0.367
VA 1 day postoperatively	0.178 ± 0.202 (Snellen equivalent 20/30)	0.193 ± 0.210 (Snellen equivalent 20/31)	0.595
BCVA 1 month postoperatively	0.004 ± 0.082 (Snellen equivalent 20/20)	0.023 ± 0.086 (Snellen equivalent 20/21)	0.099

VA visual acuity, *BCVA* best corrected visual acuity

Table 3 Anterior chamber reaction and corneal edema

	Intracameral moxifloxacin	Control	*p* value
>1+ cell 1 day postoperatively	0.060 (5/84)	0.033 (4/120)	0.370
>1+ edema 1 day postoperatively	0.188 (14/84)	0.083 (10/120)	0.069
>0 cell 1 months postoperatively	0.011 (1/91)	0.023 (3/131)	0.512
>0 edema 1 months postoperatively	0.011 (1/91)	0.023 (3/131)	0.512

contrast to the moxifloxacin levels achieved from topical administration, which can range from 0.88 to 2.28 μg/ml in the anterior chamber depending on the dosing regimen [18, 19]. A study in rabbit eyes demonstrated that moxifloxacin has a half-life of about 1 h in the anterior chamber [17]. Based on a half-life of 1 h (assuming moxifloxacin clearance in humans correlates to that in rabbits), we calculated that the concentration after intracameral delivery remains above the MIC_{50} of 0.50 μg/ml for over 11 h.

Moxifloxacin resistance in endophthalmitis pathogens has been emerging for several years. Minimum inhibitory concentrations to inhibit the growth of 90 % of organisms (MIC_{90}) has been reported as high as 32 μg/ml for both methicillin-resistant *Staphylococcus aureus* and coagulase-negative *Staphylococcus* [20]. Fluoroquinolones are concentration-dependent antibiotics (in contrast to cefuroxime, which is time-dependent), and thus, bactericidal effect is higher with increasing concentration [21]. With topical administration, antibiotic concentration in the aqueous humor does not reach the MIC_{90} for resistant bacteria. However, with intracameral administration, antibiotic concentration peaks at about 46 times the MIC_{90} and remains above the MIC_{90} for over 5 h. Kill-curve studies have demonstrated that moxifloxacin can reduce bacterial numbers by 99.9 % in less than 2 h for *Staphylococcus epidermidis* and fluoroquinolone-susceptible *Staphylococcus aureus*, and less than 3 h for fluoroquinolone-resistant *Staphylococcus aureus* [22]. Therefore, an intracameral injection of moxifloxacin should keep the concentration above the MIC_{90} of the most resistant organism for a sufficient period of time for bacterial killing to occur.

Lower concentrations of fluoroquinolones can lead to selection of resistant organisms while higher concentrations prevent selection. One hypothesis on antibiotic resistance describes a mutant prevention concentration (MPC) that prevents growth of resistant organisms and mutant selection window (MSW) that promotes selection of resistant organisms. Maximizing time above MPC and out of MSW will prevent the development of resistance [23]. In the case of intracameral antibiotics, high levels of antibiotic are able to be achieved, which in theory, should both reduce the chance of endophthalmitis caused by resistant organisms and prevent the development of resistant organisms.

Another advantage of intracameral injection of moxifloxacin is that it is more cost-effective in comparison to topical administration when taking into account cost of the drug and the money saved by preventing endophthalmitis [24]. In terms of raw cost for endophthalmitis prophylaxis without taking into account money saved by prevented cases, a 750 mg vial of cefuroxime used for intracameral preparation is

$2.64 USD [25]. This vial will make enough for a large number of patients, making the drug cost per patient almost negligible. A 3 mL bottle of 0.5 % moxifloxacin is $153.30 USD. For a patient receiving topical moxifloxacin, one bottle will be used and thus the cost per patient will be $153.30 USD. One 3 mL bottle of moxifloxacin can be split up to 20 times for intracameral injection, resulting in a cost per patient of $7.67 USD. All prices were obtained from Lexicomp® [26]. Even though intracameral moxifloxacin is less cost-effective than intracameral cefuroxime, moxifloxacin has other clinical advantages that may justify the cost as mentioned earlier. In addition, many patients have difficulty using eye drops consistently and in the correct manner. Over 90 % of patients show an incorrect technique when administering drops, which can lead to lack of drug delivery and contamination [27].

The efficacy and safety of intracameral moxifloxacin has been studied extensively before, but no studies have used the high concentration (injecting 500 μg in 0.1 mL) that this study uses without postoperative antibiotics. Ekinci Koktekir et al., Lane et al., Arbisser, and Galvis et al. used 250 μg in 0.05 mL with postoperative topical antibiotics [12–14, 28]. Espiritu et al. used 500 μg in 0.1 mL with postoperative topical and oral antibiotics [10]. Matsuura et al. used 500 μg/mL with an aqueous humor replacement technique [11]. Rudnisky et al. did not look specifically at moxifloxacin and did not provide details on the administration of moxifloxacin [29]. Shorstein et al. used 100 μg in 0.1 mL in the setting of patients allergic to cefuroxime, with postoperative antibiotics according to surgeon preference [30]. Arshinoff et al. used 100–500 μg in 0.1–0.2 mL in the setting of sequential bilateral cataract surgery [31]. Finally, Friling et al. used 200 μg in 0.1 mL in an epidemiologic study in Sweden [32].

The results of this study suggest that undiluted 0.5 % moxifloxacin can be safely injected intracamerally following uncomplicated cataract surgery with stable, sealed wounds to prevent endophthalmitis without adverse effects on patient-oriented outcomes. However, due to the low incidence of endophthalmitis, much larger prospective studies need to be performed to determine exactly how intracameral moxifloxacin administration compares to topical application in terms of preventing endophthalmitis. In the future, such studies may demonstrate that intracameral antibiotics are sufficient for endophthalmitis prophylaxis without topical antibiotics. With such large numbers of cataract surgeries being performed in the United States and throughout the world, even minor differences in efficacy can make a difference for a large number of patients.

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Compliance with ethical standards

Conflict of interest The authors report no potential conflicts of interest. University of Utah Institutional Review Board approval was obtained.

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