Follow-up Study on the Safety of Prophylactic Intracameral Administration of Moxifloxacin 0.5% Ophthalmic Solution in Cataract Surgery

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Disclosure: The authors have no proprietary or financial interest in any product used or cited in this study.

ABSTRACT

Objective: To determine the safety of intracameral moxifloxacin 0.5% ophthalmic solution in cataract surgery given at a dose of 500 mg/0.1 mL.

Methods: Medical records of uncomplicated phacoemulsification performed between January 2009 and December 2010 were reviewed. Each eye received 0.1 mL intracameral moxifloxacin (0.5% ophthalmic solution containing 500 mg of moxifloxacin) prophylactically. Outcome measures included anterior chamber cells and flare (Hogan System), corneal thickness, endothelial cell density, visual acuity, and intraocular pressure.

Results: 353 eyes of 244 patients, mean age of 67.51 ± 9.22 years, were included into the study. All patients completed follow-up to 3 weeks, with 79 patients (103 eyes) followed up to 3 months. All eyes had 20/40 or better vision at 3 weeks and 3 months postoperatively. Trace to +2 anterior chamber cells and flares were observed in 96% of eyes on day 1 postsurgery. All had quiet anterior chambers at subsequent follow-up examinations. Intraocular pressures recorded postoperatively were not significantly different. Mean endothelial cell count (ECC) postoperatively were 2473.25 cells/mm² at 3 weeks and 2468.42 cells/mm² at 3 months and were not significantly different from baseline (2586.57 cells/mm²) (p = 0.07 and 0.12 respectively). The mean central corneal thickness postoperatively at 3 weeks (551.92 μm) and at 3 months (542.67 μm) were not different from baseline (546.48 μm) (p = 0.47). Those with diabetes mellitus showed similar results.

Conclusion: Intracameral moxifloxacin 0.5% appears to be safe for prophylactic use in cataract surgery. At a dose of 500 mg/0.1 mL, there was minimal anterior chamber reaction, and the corneal thickness and endothelial cell density were not significantly different from preoperative.

Keywords: Intracameral moxifloxacin, Phacoemulsification, Endophthalmitis prophylaxis, Endothelial cell count, Pachymetry

Infectious postoperative endophthalmitis remains one of the most dreaded complications. Prevention of endophthalmitis is of utmost importance, as this severe intraocular infection can lead to permanent vision loss. Prophylactic measures and improvements in surgical techniques have been beneficial in combating postoperative infections, thus lessening the incidence of postoperative endophthalmitis in the last two decades [1-3].

In postoperative infectious endophthalmitis, the most common organisms are coagulase-negative *Staphylococcus*, *Staphylococcus aureus,* and gram-negative bacilli.[4] The infection can cause widespread damage to intraocular structures, resulting to permanent visual loss due to the direct invasion of the organism into the intraocular structures and the strong inflammatory response that follows. It is thought to occur when organisms are introduced into the eye during intraocular surgery. There is some evidence to suggest that the bacteria can influx into the eye after surgery, due to a pressure differential and changes in the flow through the surgical wound[5]. Once in the eye, these organisms replicate and cause widespread infection.

Techniques for infection prophylaxis are aimed at reducing organisms on the ocular surface prior to surgery, lowering exposure to organisms during the surgery, and eliminating bacteria entering the eye after completion of the cataract surgery. Many surgeons have routinely administered antibiotics intracamerally during cataract surgery; cefuroxime and vancomycin were the antibiotics used intracamerally with many published studies to support its efficacy. Cefuroxime and vancomycin still remain as the mainstay of intravitreal endophthalmitis treatment[6] but are generally reserved for this indication and not for prophylaxis.

The use of vancomycin for intracameral administration has been recognized to decrease the risk of endophthalmitis[7] but has also been reported to increase the risk of cystoid macular edema after cataract surgery[8,9] and the emergence of resistant strains to many bacteria.[10] Hence it has limited use as prophylaxis in cataract surgery.

The use of intracameral cefuroxime injected into the anterior chamber at the end of surgery has been shown to reduce the occurrence of endophthalmitis.[11] This practice has not been used widely due to concerns for the need to reconstitute this medication, the risk

of severe systemic allergic responses, and the narrow spectrum of activity of this class of antibiotics. Cefuroxime, as well as vancomycin, are available as systemic preparations and have to be reconstituted before delivery into the eye. Reconstitution of these antibiotics consequently increases the risk of toxic anterior segment syndrome (TASS).[12] Incorrect osmolality and pH can also cause TASS. Another setback with vancomycin and cephalosporin is that their efficacy is time-dependent; the concentration of the drug in the anterior chamber decreases four times in the first hour.

Taking into consideration these concerns related with vancomycin and cephalosporin, there has been an emerging interest using moxifloxacin intracamerally in recent years. It has a wide spectrum of activity and carries a lower risk of resistance developing against various microorganisms.[13,14] Moxifloxacin is available as a self-preserved ophthalmic solution, which has led to its use as prophylactic intracameral with ease. Earlier reports have indicated that the fourth-generation fluoroquinolones, moxifloxacin and gatifloxacin, are more effective than earlier generations of fluoroquinolones based on minimum inhibitory concentrations (MICs) and susceptibility results.[14,15] Several in-vivo studies using rabbit eyes have shown the potency of these antibiotics in preventing infections by common pathogens.[15,16]

This study re-evaluated the safety and efficacy of intracameral moxifloxacin 0.5% ophthalmic solution in eyes that underwent cataract surgery.

METHODOLOGY

Medical records of patients that underwent uncomplicated phacoemulsification with posterior chamber intraocular lens (IOL) implantation done by a single surgeon at a private eye center from January 2009 to December 2010 were included in the study. Eyes with other ocular pathologies other than cataract, such as corneal or vitreous opacities, glaucoma, retinopathy, maculopathy, and visual pathway problems were excluded. Other exclusions were: intraoperative complications or difficult and prolonged surgeries; nuclear sclerosis more than 4 (LOCS III classification of NO4/NC4) that needed more manipulation, fluid volume use, and phacoemulsification energy; use of intraoperative intracameral injections other than moxifloxacin (e.g., epinephrine, miotics); specular endothelial cell density less than 2,000 or moderate

polymegathism; previous ocular surgery; failure to complete postoperative study period (at least 3 weeks); and postoperative persistent increase in IOP of more than 40 mmHg for more than 1 week.

All data consisting of general information (age, sex, date of cataract surgery, medical history of diabetes) and outcome parameters (best-corrected visual acuity, intraocular pressure, endothelial cell counts, corneal thickness, anterior chamber cells and flare) were recorded. These parameters were obtained within 1 week preoperatively, day 1, 1 week, 3-4 weeks, and 3-6 months postoperatively.

Surgical Technique

All included eyes underwent standard phaco-emulsification cataract extraction with posterior chamber lens implantation performed by a single surgeon (RCE).

The pupil was dilated with tropicamide 1% and phenylephrine 10% preoperatively. Topical anesthesia consisting of proparacaine 0.5% (Alcaine, Alcon-Couvreur, Belgium) and intracameral lidocaine hydrochloride 1% (Xylocaine) 0.30 mL were given. Uneventful phacoemulsification was performed using the Infiniti System (Alcon Laboratories, Texas, USA) through a 2.2 to 2.75 mm clear corneal incision. Sodium hyaluronate 3.0%, chondroitin sulfate 4.0% (Viscoat), and sodium hyaluronate 1.0% (Provisc) were used during the surgery. Acrysoft lens was implanted.

Prophylactic Regimen

Patients received 1 drop of topical moxifloxacin every 15 minutes for 4 doses preoperatively. Povidone-iodine 0.5% was instilled into the cul de sac.

At the start of the operating day, the contents of a newly opened bottle of moxifloxacin was aspirated by a scrub nurse into a sterile 10 cc syringe and set aside. With a tuberculin syringe, a volume slightly in excess of 0.1 mL (0.3 to 0.5 mL) of the pure moxifloxacin 0.5% ophthalmic solution was aspirated from the 10 cc syringe. No solution, including saline, was added to dilute the commercial preparation. The excess amount was discarded, leaving 0.1 mL in the tuberculin syringe ready for injection into the anterior chamber. The volume contained 0.5 mg of the nonpreserved moxifloxacin. The solution prepared in the syringe was injected using a 27-gauge cannula through the side port into the capsular bag as the last step of cataract extraction and IOL implantation.

Postoperative antibiotics included topical moxifloxacin every 2 hours while awake on the day of the surgery and subsequently reduced to 4 times a day until the bottle was consumed. Topical prednisolone acetate 1% (Pred Forte) was also given postoperatively using the same dosage schedule as moxifloxacin

Patient Examinations

The patients were followed up 1 day, 1 week, 3-4 weeks, and 3 months after surgery. Best-corrected visual acuity (BCVA), endothelial cell counts, central corneal thickness, anterior chamber cells and flare, and intraocular pressures were recorded on every postoperative follow up. Specular endothelial microscopy of the central cornea was performed with a noncontact specular microscope (Noncon Robo, Konan Medical, Japan). Quantitative corneal endothelial cell analysis was done using the variable-frame analysis method and at least 50 well-defined endothelial cells were marked for analysis. Central corneal thickness was measured using the Noncon Robo. Three observers graded the anterior chamber reaction, expressed as cells and flare intensity with the Hogan system. All observations were done using a biomicroscope (Topcon or Haag-Streit slitlamp) 1 day, 1 week, 3-4 weeks, and 3 months after surgery.

Statistical Analysis

Data were recorded and analyzed using the Student paired t - test for the outcome measures. A p value less than 0.05 was considered significant.

RESULTS

Out of the 353 eyes of 244 patients, 151 were females and 93 males. Mean age was 67.51 ± 9.22 years (range 45 to 83). Majority of the patients were Asians and 4 were Caucasians. All patients completed the follow-up to 3 weeks, with 79 patients (103 eyes) followed up to 3 months.

Postoperatively, BCVA of 20/40 or better was observed in 92% of eyes and of 20/50 to 20/160 in 8% at day 1. All eyes were 20/40 or better at 3 weeks and 3 months.

At 3 weeks and 3 months postoperatively, all eyes had no corneal edema. Trace to +2 anterior chamber cells and flares were observed in 96% of eyes and +3 reaction in 4% at day 1 postsurgery. All had quiet anterior chambers at subsequent follow-up examinations.

The mean IOP on day 1 was 20.75 mmHg and at 3 weeks to 3 months were 12 mmHg. The mean difference from day 1 to 1 week and 3-4 weeks postoperatively was 1.22 mmHg ($p < 0.05$). The mean difference at 3 week to 3 months postoperatively was not significant ($p = 0.97$).

The mean endothelial cell count (ECC) preoperatively was 2586.57 cells/mm^2 and at 3-4 weeks postoperatively 2473.25 cells/mm^2, with a mean difference of 113.32 cells/mm^2 ($p = 0.07$). At 3 months postoperatively, it was 2468.42 cells/mm^2 ($p = 0.12$). The mean central corneal thickness preoperatively was 546.48 μm and at 3 weeks postoperatively was 551.92 μm, with a mean difference of 544 μm ($p = 0.47$). The difference in mean thickness preoperatively and at 3 months postsurgery was 542.67 μm ($p = 0.47$).

Fifty-eight eyes of 41 patients with a history of diabetes mellitus were also evaluated separately. Preoperative BCVA was at least 20/60 or better, with 81% having BCVA of 20/30 or better. At 3-4 weeks postoperatively, all eyes had BCVA of 20/25 or better. The mean ECC preoperatively was 2580.36 cells/mm^2 and at 3 weeks postsurgery was 2372.01 cells/mm^2, with a mean difference of 208.28 cells/mm^2 ($p > 0.05$). Preoperative central corneal thickness was 550.71 μm and postoperatively 572.28 μm ($p = 0.33$).

DISCUSSION

Incidence of postoperative endophthalmitis decreased in recent reports in different institutions.[1-3] Wykoff reported that the 8-year frequency of acute postoperative endophthalmitis was 0.025% (14 of 56672 intraocular surgeries). The percentage of postoperative endophthalmitis in cataract surgery, however, remained higher with a rate of 0.028% (8 of 28,568 cataract surgeries).[2] With sutureless clear corneal phacoemulsification as standard in cataract surgery, prevention of postoperative infectious endophthalmitis becomes extremely important to avoid devastating complications.

Contamination during surgery from the patient's own conjunctival flora and faulty wound construction intraoperatively pose a risk that an inoculum of bacteria enough to cause infection may enter the eye shortly after cataract surgery. Miyajima and colleagues noted a 10% reduction of positive cultures taken preoperatively in eyes treated with topical antibiotics. However, ocular fluid samples taken during surgery had a higher rate of positive cultures, indicating that intraoperative contamination from the lids cannot be ruled out during routine cataract surgery. The study also reported that *Propionibacterium acnes*, frequently associated in late-onset endophthalmitis, was the most frequently isolated microorganism in the intraoperative samples, further supporting the need of intracameral antibiotic injection at the end of cataract surgery.

Antibiotic penetration into the anterior chamber after topical drops is relatively low compared with intracameral doses, and is limited by an intact corneal epithelium and dilution from tears. Prophylactic intracameral antibiotic injection was recognized initially in 2002 when Montan reported a decreased rate of postoperative endophthalmitis with intracameral injection of 1 mg cefuroxime.[11] This route of injection delivers high concentration of the antibiotic agent to the anterior chamber at the end of the surgery with the presumed effect of eliminating bacteria before wound closure and in the immediate postoperative period. The European Society of Cataract and Refractive Surgery validated the use of intracameral antibiotics for postcataract surgery endophthalmitis prophylaxis, showing that intracameral cefuroxime reduced the risk of endophthalmitis by five-fold.[18]

Cefuroxime and vancomycin were injected intracamerally in earlier studies; however, untoward side effects limited their use. Vancomycin has been shown to increase the risk of cystoid macular edema after cataract surgery.[8] Cefuroxime and vancomycin are commercially available as systemic preparation and have to be reconstituted before injecting intracamerally. Reconstitution of the drug increases the risk of toxic anterior segment syndrome (TASS).[12]

Fluoroquinolones as topical antibiotics gained popularity in the last few years for infection prophylaxis after cataract surgery. The fluoroquinolones offer better broad-spectrum coverage and mode of action. Moxifloxacin is a promising candidate for endophthalmitis prophylaxis. A fouth-generation fluoroquinolone, moxifloxacin acts by inhibiting

2 bacterial enzymes involved in bacterial DNA replication. It also has superior coverage against both gram-negative and gram-positive bacteria, including the most common isolates found in endophthalmitis. Moxifloxacin is rapidly bactericidal against ocular isolates resistant to older generations of fluoroquinolones.[13,15,20] Kowalski reported that *Staphylococcus aureus* isolated from endophthalmitis in rabbit models were sensitive to the fourth-generation fluoroquinolones.[15]

Moxifloxacin 0.5% (Vigamox, Alcon Laboratories, Forth Worth, Texas, USA) ophthalmic solution has a formulation that is self-sterilizing; thus, preservatives like benzalkonium chloride that may damage ocular tissues are unnecessary.[21] It is available in a 0.5% self-preserved solution that is isoosmotic with an almost neutral pH of 6.8. These properties are compatible with the human anterior chamber fluid (pH 7.4; osmolality 305 mOsm/kg). Hence, moxifloxacin was further assessed for its safety for intracameral use.

Moxifloxacin's potency is exhibited by its minimum inhibitory concentration, ranging from 0.06 mg/mL to 0.19 mg/mL.[13] Furthermore, as the most potent available antibiotic, it would have the least chance of developing resistance because its concentration in the ocular tissues would less likely be sublethal. Addressing problems with resistant strains, the mutation prevention concentration (MPC) is another parameter for evaluating potency and defines a concentration that prevents the emergence of resistant mutants to the antibiotic. Frequent and suboptimal use of an antibiotic increases the risk of development of resistant strains. The MPC of fluoroquinolones is 8-10 times their MIC.[20] With topical use, the aqueous concentration of moxifloxacin levels slightly exceeds its MPC, whereas with intracameral injection it achieves and ensures much higher concentration than its MPC (0.38 - 2.16 mg/mL).[22]

Given all these desirable pharmacologic properties of moxifloxacin, recent studies emerged addressing the issue on the dosaging and amount of concentration injected into the anterior chamber. At doses of 100 mg/0.1 mL or 250 mg/0.05 mL of moxifloxacin 0.5% ophthalmic solution given intracamerally at the conclusion of the cataract surgery, no untoward effects were found.[23, 24]

Our study examined the safety of moxifloxacin 0.5% ophthalmic solution given intracamerally with a dose of 500 mg/0.1 mL. Eyes included in our review

were injected with 0.1 mL of pure moxifloxacin 0.5% ophthalmic solution without dilution in the anterior chamber at the end of the surgery. This was equivalent to 0.5 mg of moxifloxacin. The calculated concentration of moxifloxacin in the anterior chamber was 952 mg/mL, which was 300 times its MIC and at least 30 times its MPC.[22] This study focused on the safety parameters: corneal pachymetry and endothelial cell count, anterior chamber inflammation, and intraocular pressure.

We reviewed quantitatively the effects of intracameral moxifloxacin on the cornea through pachymetry and endothelial cell count. Eyes with present and previous ocular pathology or corneal problems were excluded. The included eyes were followed for 3-4 weeks and there were no evidence of reduced endothelial cells or increased corneal thickness, even at 3 months postoperatively.

This study also reviewed the effects of moxifloxacin on blood aqueous barrier and anterior chamber inflammation postoperatively. Eyes were examined for aqueous flare and cells on the first post operative day and on scheduled visits. We found no evidence that moxifloxacin causes raised aqueous flare or cell levels. All eyes had zero to trace cells or flare at 3-4 weeks postoperatively and 79 eyes with 3-month follow-ups had zero cell or flare.

Fifty-eight eyes of 41 patients with a history of diabetes mellitus also showed no significant difference in corneal endothelium and pachymetry at 3-4 weeks postoperatively.

In summary, intracameral moxifloxacin 0.5% at a dose of 500 mg/0.1 mL is safe for prophylactic use in cataract surgery.

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