Original Article

Intravitreal moxifloxacin injections in acute post-cataract surgery endophthalmitis: Efficacy and safety

Abhishek Agarwal, Manisha Nagpal

Purpose: The aim of this study was to evaluate the efficacy and safety of intravitreal moxifloxacin injections in the treatment of acute post-cataract surgery endophthalmitis with visual acuity equal to or greater than hand movements. **Methods:** Fifty two patients with post-cataract surgery endophthalmitis who presented within 6 weeks with visual acuity equal to or greater than hand movements received two intravitreal moxifloxacin injections 48 h apart. Patients with prior history of ocular disease or treatment were excluded. Patients were followed up to 3 months either for resolution of endophthalmitis or worsening of disease. Number of patients who achieved visual acuity equal to or better than 20/40 and 20/200 at the third-month follow-up visit were compared with the number of patients at presentation, using Chi-square test. In addition, pretreatment LogMAR visual acuity at the time of presentation was compared with posttreatment visual acuity at end of third month using paired *t* test. **Results:** Fifty (96.15%) patients showed complete resolution of endophthalmitis while three patients required vitrectomy. Forty-one (78.85%) and 49 (94.23%) patients achieved visual acuity equal to or better than 20/40 and 20/200, respectively, at the third-month follow-up visit as compared to eight (15.38%) and 13 (25%) patients, respectively, at presentation ($P < 0.05$). In addition, mean LogMAR visual acuity at the time of presentation was 0.755 which improved to 0.307 at the third-month follow-up visit ($P < 0.05$). None of the patients developed hypersensitivity reactions to intravitreal moxifloxacin. **Conclusion:** Intravitreal moxifloxacin injections showed promising results in acute post-cataract surgery endophthalmitis.

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Endophthalmitis is one of the most dreaded complications of the cataract surgery which may lead to severe vision loss. Its prevalence is estimated to be 0.128%.[1] Risk factors for acute post-cataract surgery endophthalmitis include clear corneal incision, extracapsular or intracapsular cataract extraction, posterior capsular rupture, silicone intraocular lenses, intraoperative complications, male gender, and old age.[2]

Intravitreal antibiotics with or without vitrectomy is the mainstay treatment of endophthalmitis. The Endophthalmitis Vitrectomy Study (EVS) compared outcomes of immediate vitrectomy versus vitreous tap in patients suffering from acute post-cataract surgery endophthalmitis and found that in patients whose initial visual acuity was hand motions or better, there was no difference in visual outcome whether or not an immediate vitrectomy was performed. However, in patients with initial light perception-only vision, immediate vitrectomy produced a threefold increase in the frequency of achieving 20/40 or better acuity and a 50% decrease in the frequency of severe visual loss as compared with a vitreous tap.[3]

Currently, intravitreal ceftazidime 2.25 mg/0.1 mL and vancomycin 1 mg/0.1 mL are used to manage post-cataract surgery endophthalmitis.[4] Intraocular vancomycin use is associated with hemorrhagic occlusive retinal vasculitis, a devastating vision-threatening complication, which portends poor prognosis.[5] There are also growing concerns regarding postoperative endophthalmitis cases caused by Gram-positive organisms with decreased vancomycin sensitivity or vancomycin resistance.[6]

Intracameral moxifloxacin prophylaxis for post-cataract surgery endophthalmitis has been studied in a meta-analysis by Bowen *et al*.[7] They had found that intracameral moxifloxacin reduced endophthalmitis rates with minimal or no toxicity at standard doses. Similarly, Haripriya *et al*.[8] and Rathi *et al*.[9] documented the efficacy of intracameral moxifloxacin in post-cataract surgery endophthalmitis prophylaxis.

Furthermore, Fisher *et al*.[10] had shown that transzonular injection of moxifloxacin in combination with corticosteroid and vancomycin into the vitreous cavity was safe and effective in reducing inflammation after cataract surgery.

Moreover, intraocular moxifloxacin intravitreal injection had been successfully used in the treatment of posttraumatic endophthalmitis due to metallic intraocular foreign body caused by multidrug-resistant Gram-negative bacillus Ochrobactrum

Department of Ophthalmology, Shri Jagdamba Charitable Eye Hospital, Andh Vidhalaya Campus, Sri Ganganagar, Rajasthan, India

Correspondence to: Dr. Abhishek Agarwal, Shri Jagdamba Charitable Eye Hospital, Andh Vidhalaya Campus, Sri Ganganagar - 335 001, Rajasthan, India. E-mail: abhishekretina@gmail.com

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intermedium.[11] Similarly, intravitreal moxifloxacin has also been proved to be effective in the treatment of posttraumatic endophthalmitis after penetrating injury with metallic wire.[12]

But safety and efficacy of intravitreal moxifloxacin in the treatment of post-cataract surgery endophthalmitis is not widely studied.

Methods

Approval for this study was obtained from the institutional review board. All research and data collection adhered to the tenets of the Declaration of Helsinki and Good Clinical practice guidelines. This was a prospective, interventional study. The study population consisted of 52 patients who presented with post-cataract surgery endophthalmitis between September 2017 and September 2019 at our institute. All patients suffering from post-cataract surgery endophthalmitis presenting within 6 weeks of surgery, with visual acuity equal to or greater than hand movement and no prior history of other ocular diseases like glaucoma, retinopathy or any other ocular surgery except cataract surgery were recruited for the study. Patients who had received prior intravitreal injections or had undergone vitrectomy for endophthalmitis and presenting vision worse than HM were excluded. Patients who had not given consent were also excluded from the study.

Detailed ophthalmic and systemic history, especially the history of diabetes, was taken followed by an ophthalmic examination which included visual acuity, intraocular pressure (IOP), slit-lamp examination, fundus examination by indirect ophthalmoscopy (if possible) and ultrasonography (USG).

All patients were given a detailed explanation of potential risks and benefits of the intravitreal moxifloxacin injections. Written informed consent was obtained from every patient. All patients received two intravitreal moxifloxacin injections 48 h apart. The intravitreal moxifloxacin injections were given in the operation theatre under sterile conditions. Pupils were dilated using 1% tropicamide and 10% phenylephrine eye drop before taking the patient to the operation theatre. Before injection, the conjunctiva bulbi, fornices, eyelid margins, and lashes were rinsed repeatedly with povidone-iodine and topical anesthesia was induced by applying 0.5% proparacaine at least three times at 5–10 min intervals. Sterile drape and eyelid speculum were used to avoid contamination of the needle with eyelashes or eyelid margin.

Vitreous tap was performed by inserting 25 G needle attached with 5 mL syringe, 3.5 mm from the limbus, and approximately 0.1 mL of vitreous fluid is aspirated. 500 μg/0.1 mL of moxifloxacin is withdrawn directly from 0.5% moxifloxacin preservative-free eye drop (Vigamox, Alcon Laboratories, Inc) with the help of 1 mL syringe and injected intravitreally with 30G needle through the par plana route at a distance of 3.5 mm from the limbus. The needle was removed carefully using a sterile cotton applicator to prevent reflux. Indirect ophthalmoscopy was used to confirm uneventful intravitreal placement of the drug and perfusion status if the fundus was visible. Patients were prescribed anti-glaucoma drugs if IOP was high postoperatively.

To determine the effective dose of moxifloxacin for intravitreal injection, the half-life and toxicity of moxifloxacin, vitreous volume, and minimum inhibitory concentration (MIC) of the causative organisms causing endophthalmitis should be considered. The vitreous volume of an adult emmetropic human eye is approximately 4 mL, giving an empiric concentration of 125 μg/mL when 500 μg moxifloxacin is injected intravitreally. As per published literature, MIC of moxifloxacin is 0.06–32 μg/mL for Staph. aureus, 0.032–32 μg/mL for *Staph. epidermidis*, 0.125–64 μg/mL for *Enterococcus*, 0.008–2 μg/mL for *Streptococcus* spp., 0.008–128 μg/mL for *Escherichia coli*, 0.032–128 μg/mL for *Klebsiella pneumoniae* and 0.25–128 μg/mL for *Pseudomonas aeruginosa*.[13] Prior studies with intravitreal moxifloxacin have established 150 μg/mL as a safe concentration for the rabbit eye and human retinal pigment epithelial cells.[11,14]

Although in noninflamed eyes, intravitreal moxifloxacin has shown an exponential decay, with a half-life of 1.72 h, but the half-life of fluoroquinolones is prolonged in inflamed eyes. This is because fluoroquinolones are eliminated from the vitreous through active transport by the retinal pigment layer pump.[15] In endophthalmitis, drug clearance of fluoroquinolones is retarded due to compromise of the active transport by retinal pigment epithelial pump. Oztürk *et al.* had shown in animal models that therapeutic drug levels of other fluoroquinolones like ofloxacin[16] and ciprofloxacin[17] were maintained up to 24–48 h in inflamed eyes after intravitreal injection. Hence, second injection was injected after 48 h.

Vitreous tap samples were sent to laboratory for bacterial and fungal microbiological staining and culture. In the microbiological laboratory, Gram and KOH staining was done from vitreous tap samples for identifying bacterial and fungal pathogens, respectively. Vitreous tap samples were then inoculated on blood agar and MacConkey agar for bacterial culture and on Sabouraud Dextrose Agar for fungal culture. Antimicrobial susceptibility testing was performed by the disc diffusion technique.

These patients were examined regularly at follow-up visits after one day, three days, five days, seven days, 4 weeks, 2 months and 3 months of second intravitreal injection or as required.

Patients were examined for signs of resolution of endophthalmitis which included complete resolution of anterior chamber and vitreous inflammation. Percentage of patients who had shown complete resolution or had required vitrectomy was calculated.

In addition, visual acuity was examined in all the patients at each follow-up visit and proportion of patients achieving visual acuity equal to or better than 20/40 and 20/200 at third-month follow-up visit was computed and compared with the proportion of patients at presentation using Chi-square test. Moreover, pretreatment LogMAR visual acuity at the time of presentation was compared with posttreatment visual acuity at end of third month was compared with paired *t* test. Results were considered statistically significant if the *P* value was less than 0.05. Statistical analysis was done with the help of InStat 3.10 software (GraphPad Software Inc.).

Furthermore, patients were also specifically observed for signs suggestive of hypersensitivity reaction to intravitreal moxifloxacin, like new onset of retinal vasculitis or worsening of anterior chamber or vitreous inflammation after the injections.

Results

Fifty two eyes of 52 patients were enrolled in this study. The mean age (SD) of enrolled patients was 56.2 (8.64) years. Male–female ratio was 1.48. The mean (SD) time of presentation of endophthalmitis was 10.7 (7.52) days [Table 1]. Table 2 shows the clinical findings of patients at presentation.

The most common risk factor associated with endophthalmitis in our study was diabetes [Table 3]. Twenty-three of 52 (44.23%) of patients had a history of diabetes and were on treatment. All the patients had normal fasting blood sugar on the day of cataract surgery. But eight out of 23 (34.8%) diabetic patients had high blood sugar at the time of endophthalmitis presentation; endocrinologist consultation was sought in all these cases to review treatment and to control blood sugar.

Patients were followed up to 3 months after intravitreal moxifloxacin injections and 50 of 52 (96.15%) patients showed signs of complete resolution of endophthalmitis but three patients required vitrectomy, two for persistent infection and one for residual vitreous opacities. In the first patient who required vitrectomy for persistent infection, *Pseudomonas aeruginosa* was isolated from vitreous tap and although the organism was sensitive to moxifloxacin in-vitro but since the clinical response was suboptimal, intravitreal vancomycin and ceftazidime were injected at the time of vitrectomy. In the second patient, who required vitrectomy for persistent infection, no organism was isolated from vitreous tap and from the sample obtained at the time of vitrectomy, and intravitreal vancomycin and ceftazidime were injected during vitrectomy. Third patient who required vitrectomy for persistent vitreous opacities was not given any intravitreal antibiotic injection.

Table 1: Demographic profile

Demographic parameters	Values
Number of patients	52
Mean (SD) Age	56.2 (8.64) years
Males	31 (59.62%)
Females	21 (40.38%)
Mean (SD) Time of presentation	10.7 (7.52) days
Mean (SD) LogMAR visual acuity at presentation	0.755 (0.417)

Table 2: Clinical findings at presentation

Clinical Findings at presentation	Number of patients (%)
Hypopyon	18 (34.62%)
Retinal visibility up to second order retinal vessels	11 (21.15%)
Retinal visibility up to first order retinal vessels	37 (71.15%)
Absent red reflex	12 (23.08%)
Retinal detachment	0 (0%)

Table 3: Risk factors for endophthalmitis

Risk Factors	Number of patients (%)
Diabetes	23 (44.23%)
Posterior Capsule Rent	9 (17.31%)
Other intraoperative complications	5 (9.62%)
Wound leakage	3 (5.77%)
Blepharitis	2 (3.85%)

At the time of presentation, eight (15.38%) patients had visual acuity equal to or better than 20/40, as compared to 41 (78.85%) patients at the third-month follow-up visit ($P < 0.05$). Similarly, 13 (25%) patients had visual acuity equal to or better than 20/200 at the time of presentation, as compared to which increased to 49 (94.23%) patients at third-month follow-up visit ($P < 0.05$). Fig. 1 compares the number of patients at the time of presentation (pretreatment) with third-month follow-up visit (posttreatment) at different levels of visual acuity. In addition, mean (SD) LogMAR visual acuity at the time of presentation was 0.755 (0.417) which improved to 0.307 (0.332) at the third-month follow-up visit ($P < 0.05$).

None of the patients developed hypersensitivity reactions like new onset of retinal vasculitis or worsening anterior chamber or vitreous inflammation after receiving intravitreal moxifloxacin injections.

Vitreous tap report was positive in 36 of 52 (69.23%) patients [Table 4]. The most commonly isolated organisms were Gram-positive bacteria, most commonly, coagulase-negative staphylococci. Antibiotic sensitivity testing showed that 100% of bacterial isolates were sensitive to moxifloxacin.

Discussion

Endophthalmitis is a serious complication associated with cataract surgery, which may result in severe visual impairment.[18] Incidence of acute endophthalmitis after cataract surgery is reported to be 0.265% in the 2000-2003 period, 0.087% in the 1990s, 0.158% in the 1980s, and 0.327% during the 1970s.[1] Clear corneal incision, no prophylactic intracameral antibiotic use, extracapsular or intracapsular cataract extraction, posterior capsular rupture, silicone intraocular lenses, intraoperative complications were found to be strongly associated with acute endophthalmitis.[2] Endophthalmitis is treated by intravitreal antibiotics along with vitreous tap or vitrectomy.

Although EVS used intravitreal vancomycin 1 mg and amikacin 0.4 mg, but today intravitreal ceftazidime 2.25 mg/0.1 mL along with vancomycin 1 mg/0.1 mL is most commonly used in cases of acute post-cataract surgery

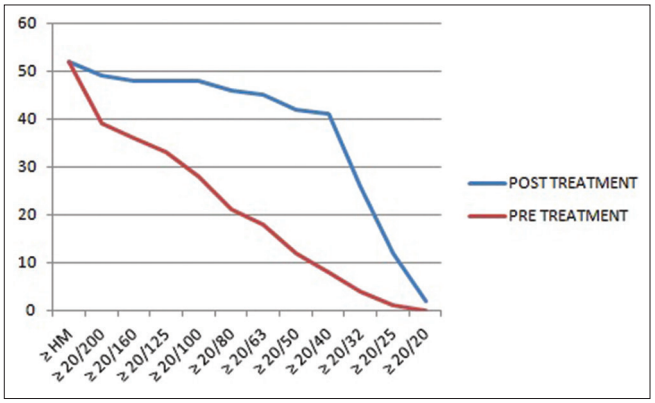

Figure 1: [Original]: Comparison between the numbers of patients at the time of presentation (pretreatment) with third-month follow-up visit (post-treatment) at different levels of visual acuity

Table 4: Results of microbiological culture and antibiotic sensitivity testing of vitreous tap samples

	Number of samples	Antibiotic Sensitivity (Number of samples)			
		Moxifloxacin	Vancomycin	Ceftazidime	Amikacin
Gram Positive					
Coagulase Negative *Staphylococcus*	26	26	25	9	NT
Streptococcus Spp	5	5	3	1	NT
Staphylococcus aureus	3	3	2	1	NT
Gram Negative					
Pseudomonas	2	2	NT	2	2
No Growth	16	NA	NA	NA	NA

NT=Not tested, NA=Not applicable

endophthalmitis.[3,4] However, intraocular vancomycin is associated with hemorrhagic occlusive retinal vasculitis (HORV), which is characterized by inflammation in anterior chamber, vitritis, sectoral retinal hemorrhages, retinal ischemia, and peripheral retinal vasculitis. HORV is a severe delayed hypersensitivity reaction to vancomycin with poor visual outcomes, as more than 60% eyes had 20/200 or worse visual acuity and 22% had no light perception (NLP). Neovascular glaucoma developed in more than 50% of the eyes.[5] Gram-positive organisms are the most common cause of postoperative endophthalmitis.[19] Vancomycin is currently used for management of endophthalmitis caused by Gram-positive organisms. However, Gram-positive organisms with decreased vancomycin sensitivity or vancomycin resistance are increasingly isolated in endophthalmitis patients and are associated with poor visual outcomes.[6]

Intravitreal moxifloxacin is found to be safe in rabbit eyes with no changes in ERG or on retinal histology.[14] Clinical trials in humans have also demonstrated the safety and efficacy of intravitreal moxifloxacin, especially in posttraumatic endophthalmitis.[11,12]

Our study showed the efficacy of intravitreal moxifloxacin in patients with post-cataract surgery endophthalmitis presenting within 6 weeks of surgery and with visual acuity equal to or greater than hand movement. 96.15% of patients showed signs of complete resolution of endophthalmitis with two intravitreal injections of moxifloxacin. Consistent with other studies, the safety profile of intravitreal moxifloxacin was excellent as we have not encountered a single case with hypersensitivity to the drug.

Various studies have shown that major pathogens causing endophthalmitis are Gram-positive cocci and coagulase-negative *Staphylococci* was found as the most common single pathogen responsible for endophthalmitis, which is consistent with our study.[3] Satpathy *et al*.[20] have shown that pathogens responsible for post-cataract surgery endophthalmitis are highly sensitive to moxifloxacin, which is also consistent with our study.

The major limitations of our study were small sample size, short follow-up of 3 months, and only selected patients who present with acute post-cataract surgery endophthalmitis with visual acuity greater than or equal to hand movements were recruited. Furthermore, our study was conducted at a single location. In future, larger studies using larger sample size, with multicenter trials involving different geographical areas, more widespread indications and longer follow-up are required to determine the safety and efficacy of this practice. It will also be interesting to note the efficacy of combination of intravitreal moxifloxacin with vitrectomy in cases of endophthalmitis in different settings. Moreover, further studies are needed to establish the optimum moxifloxacin dose, dosing frequency, and number of injections needed for resolution of post-cataract surgery endophthalmitis.

Conclusion

Our study showed that intravitreal moxifloxacin injections have promising results in acute post-cataract surgery endophthalmitis.

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Conflicts of interest

There are no conflicts of interest.

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