Evaluation of Intracameral Moxifloxacin in Trabeculectomy Surgery on Corneal Endothelial Cells

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Abstract

Objective: The purpose of the current study is to assess the safety of intracameral (IC) injection of moxifloxacin 500 µg/0.1 ml on corneal endothelial function after trabeculectomy. **Subjects and methods:** The participants in this interventional cross-sectional trial were those who had been recommended for trabeculectomy surgery from the Outpatient Ophthalmology Clinics at Research Institute of Ophthalmology and Al-Zahraa University Hospital Cairo, Egypt. in the period from April 2020 to October 2020. In this study, 30 patients with 30 eyes each got standard postoperative systemic and topical ocular treatment in addition to injection with IC moxifloxacin at the end of trabeculectomy. The age range of participants was 33-69 years. All subjects underwent a comprehensive ophthalmologic examination including best corrected visual acuity (BCVA), examination was conducted using a slit lamp and indirect ophthalmoscope. Intraocular a noncontact specular microscope (CEM-350 NIDEK co.) was done in the preoperative day as well as 1 month and 3 months and recording of the endothelial cell density (ECD), the coefficient of variation (CV), and the percentage of hexagonal cells (HEX) was done. **Results:** No statistically significant difference was found in the endothelial cell density in the cases within 1 and 3 months of surgery. The P-value and the T-test were calculated at 95% confidence level. It showed that for ECD, P-Value were 0.011, 0.012, 0.006 respectively, this suggested that the ECD after 1 and 3 months was noninferior at 0.05%. Both CV and HEX were greater than or equal to 5% (ie, 0.518% ≥ 5%). **Conclusion:** Corneal endothelial cell safety is acceptable for 500 µg intracameral moxifloxacin, well tolerated, recommending its application for enhancing antibacterial coverage for the prevention of postoperative endophthalmitis.

Key Words: Intracameral, moxifloxacin, trabeculectomy, corneal endothelial cells.

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Introduction:

The topical fourth generation fluoroquinolone moxifloxacin hydrochloride has been used widely because it offers broad-spectrum defense against both Gram-positive and Gram-negative bacteria [1]. This potent impact promoted its intracameral use as a means of preventing postoperative endophthalmitis [2-4]. Numerous investigations revealed that its intracameral injection was safe [5-7].

A range of 0.25–2.5 µg/ml5 was reported as the lowest level at which the majority of the likely endophthalmitis-causing bacteria are inhibited. Vigamox (Alcon, Fort Worth, Texas), is the intracameral moxifloxacin used most frequently in cataract surgery in the US. due to the lack of preservatives [8]. Vigamox injection of (moxifloxacin, 250 µg in 0.05 ml or 150 µg in 0.03 ml) is the widely utilized procedure that begins with a concentration of 0.5 mg/ml. in the anterior chamber, which is greater than the necessary amount to prevent postoperative endophthalmitis [9].

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Comparing topical drops to intracameral dosages, antibiotic penetration into the anterior chamber is quite limited. Antibiotics administered directly intracameral provide a number of advantages versus topical drop regimens. By using this injection technique, the anterior chamber receives very high concentrations dose in the immediate postoperative period and at the end of surgery with the intention of removing bacteria before wound closure [10].

Even though multiple in vitro studies found that increasing moxifloxacin dosages resulted in increased corneal endothelial cell damage [11], Different dosages of intracameral moxifloxacin were reported to be used in vivo (50 to 500 µg, 100 µg, 250 µg, and 500 µg) after cataract surgery, there are no negative side effects [12-14]. Using doses between 100 and 500 µg, a meta-analysis of research came to the same results.

IC moxifloxacin use on a regular basis has not been the subject of any studies that we are aware of. Our study's goal was to assess the safety of prophylactic intracameral moxifloxacin injection after trabeculectomy surgery.

Methodolgy

This interventional cross-sectional study included patients who had been recommended for trabeculectomy surgery (April 2020 – the last follow up at October 2020)from the Outpatient Ophthalmology Clinics at Research Institute of Ophthalmology and Al-Zahraa University Hospital Cairo, Egypt. This study involved thirty eyeballs from thirty patients. 33 to 69 years old was the average age of the participants 56 years. A written informed consent was obtained from each participant after an explanation of the study protocol was provided. The Local Ethics Committee approved the study. The procedure is in accordance with the declaration of Helsinki. A thorough ocular examination was performed on each subject, including a review of medical history, Best-corrected visual acuity was assessed using Snellen acuity charts, a slit lamp examination, gonioscopy, a 90 diopter lens, intraocular pressure measurement using Goldmann applanation tonometry, and visual field testing on automated perimetry using a 24-2 Swedish Interactive Threshold Algorithm (Humphrey; Carl Zeiss Meditec Inc., Dublin, California, USA). Primary glaucoma cases with central ECD was required to be more than 2000 cells/ mm2 in each eye at baseline with a difference between eyes of less than 200 cells as assessed by a noncontact specular microscope (CEM-350 NIDEK co.) were included. Participants were excluded if they had secondary glaucoma, blunt or penetrating trauma, any previous ocular surgery.

Surgical Technique:

The periorbital region and conjunctival cul de sac was sterilized before to the surgery using topical povidone iodine. In the superior limbus, an 8/0 vicryl traction suture was placed, and a fornix-based conjunctival flap was performed. A 3x4 mm scleral flap was made after cauterization to achieve hemostasis, and a sponge soaked with 0.2 mg/mL MMC was then put beneath the conjunctiva posterior to the flap for 2 minutes before being removed with at least 50 mL of saline solution. The procedure involved performing a side port paracentesis, removing a 1x2 mm corneoscleral block, and performing a peripheral iridectomy. Using two 10/0 nylon sutures, the scleral flap was attached to the sclera. The conjunctiva was stitched to the limbus with 10/0 nylon sutures, and any leaks were examined after the aqueous drainage was examined. The patient was randomized to receive intracameral moxifloxacin ophthalmic solution 500 µg/0.1 ml. At the end of the procedure, a 30-gauge cannula-equipped tuberculin syringe is inserted through the side port into the anterior chamber. In the preoperative day and the day of the operation, topical moxifloxacin 0.5% was used six times each. The study stayed away from surgical procedures like phacoemulsification, which had a significant impact on endothelial cells.

Postoperatively, topical prednisolone acetate 1% 6 times per day tapered over 6 weeks and moxifloxacin 0.5% 6 times per day for 2 weeks were prescribed for all patients, postoperative Slit lamp examination will be done in the first day, 1 week, 1 month, and 3 months. A noncontact specular microscope (CEM-350 NIDEK co.) was used to capture 3 images of the central corneal endothelium preoperatively and at 1 month and 3 months on both eyes of each patient for the determination of the ECD, coefficient of variation, and percentage of hexagonal cells.

RESULTS

Descriptive characteristics of the studied participants: **Table 1** shows the statistical summary for all the participants included in our analysis. It shows that the age ranges from a

minimum of 33 to a maximum of 69 years old, with an average of 56. The sample contains 13 females and 17 males aged between 33 and 69 years old. We found that the ECD baseline ranges from a minimum of 1155 to a maximum of 3083, with a mean of 2458 and a standard deviation of 414; this result suggests a wide variation of ECD baseline among the sampled participant. The CV has a mean of 28.8 and ranged from 20 to 53. Our results also showed that HEX has a mean of 68 with a minimum on 33 and maximum of 96. Across the sample, the ECD, CV and HEX after 1 and 3 months have either improved or remained the same.

Table (1): Eye-level data summarized by doses (N = 30 paired study eyes):

Variable	Obs	Mean	Std. Dev.	Min	Max
Age	30	55.833	14.193	6	75
ECDbaseline	30	2457.833	413.943	1155	3083
CV	30	28.8	5.933	20	53
HEX	30	68.267	11.132	33	96
ECD 1	30	2486.433	392.352	1253	3082
CV 1	30	28.6	6.173	21	53
HEX 1	30	68.933	6.731	48	79
ECD 3	30	2420.967	435.953	1188	2940
CV 3	30	27.933	4.705	21	43
HEX 3	30	70.4	4.19	62	78
gender	30	1.433	.504	1	2

CV = coefficient of variation; ECD = endothelial cell density; HEX = % of hexagonal cells.

Table 2 shows the Pearson pairwise correlation analysis for all the participants in our sample. We found no association between the variables, indicating no significant multicollinearity issue exists. We further confirmed this by calculating variance inflation factors (VIF), and the results (for brevity not reported) revealed no evidence of multicollinearity, as all VIFs values do not exceed 2.

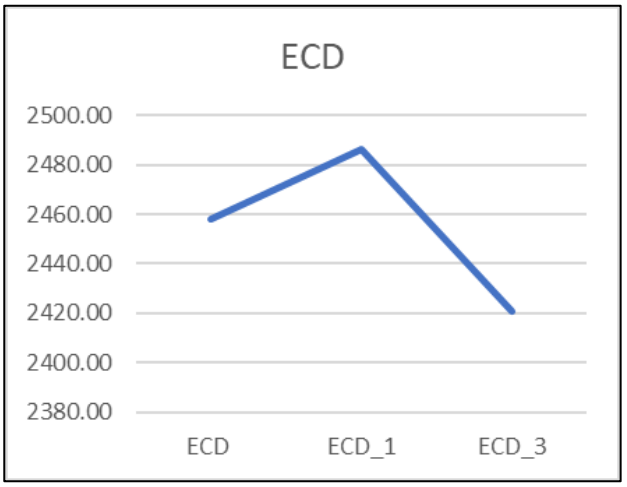
Table (2): Pairwise correlations:

Variables	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
(1) ECD baseline	1.000								
(2) CV	0.208 (0.270)	1.000							
(3) HEX	-0.176 (0.351)	-0.654 (0.000)	1.000						
(4) ECD_1	0.891 (0.000)	0.245 (0.192)	-0.169 (0.371)	1.000					
(5) CV_1	0.061 (0.751)	0.367 (0.046)	-0.359 (0.052)	-0.054 (0.778)	1.000				
(6) HEX_1	-0.286 (0.125)	-0.436 (0.016)	0.347 (0.060)	-0.305 (0.101)	-0.777 (0.000)	1.000			
(7) ECD_3	0.855 (0.000)	0.207 (0.273)	-0.161 (0.396)	0.864 (0.000)	0.009 (0.962)	-0.210 (0.265)	1.000		
(8) CV_3	0.087 (0.648)	0.460 (0.010)	-0.376 (0.040)	-0.021 (0.913)	0.648 (0.000)	-0.576 (0.001)	-0.002 (0.992)	1.000	
(9) HEX_3	-0.060 (0.754)	-0.122 (0.522)	0.043 (0.823)	-0.077 (0.687)	-0.027 (0.888)	0.040 (0.833)	-0.099 (0.603)	-0.294 (0.115)	1.000

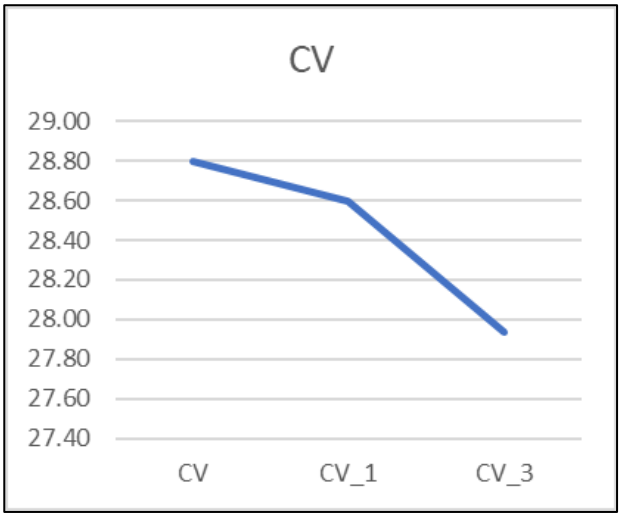
Table 3 shows the P-value and the T-test at 95% confidence level. It showed that for ECD P-Value are 0.011, 0.012, 0.006 respectively, this suggested that the ECD after 1 and 3 months was noninferior at 0.05%. Both CV and HEX were greater than or equal to 5% (ie, 0.518% ≥ 5%), we were not able to conclude that the CV and HEX were noninferior (within 5%).

Table 3: Two-sample t test with unequal variances by Gender

	Male	Female	Mean1	Mean2	diff	St Err	t value	p value
ECD baseline	17	13	2305.588	2656.923	-351.335	126.011	-2.8	.011
CV	17	13	28.117	29.692	-1.575	2.386	-.65	.518
HEX	17	13	68.412	68.077	.335	3.891	.1	.932
ECD 1	17	13	2343.353	2673.539	-330.185	121.535	-2.7	.012
CV 1	17	13	30.353	26.308	4.045	2.011	2	.056
HEX 1	17	13	68.236	69.846	-1.611	2.317	-.7	.493
ECD 3	17	13	2248.706	2646.231	-397.525	131.554	-3	.006
CV 3	17	13	28.353	27.384	.969	1.689	.55	.571



a)



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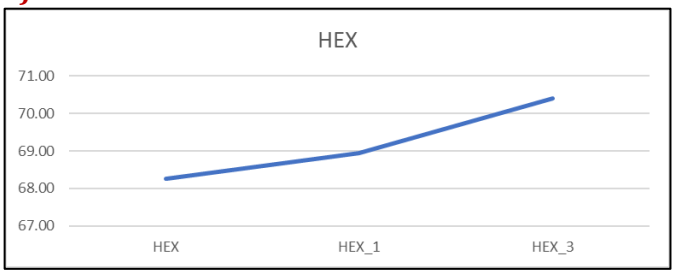

c)

Fig. 1: a. Analysis of endothelial cell density, **b.** coefficient of variation and **c.** hexagonal cells at the preoperative day, one month and 3 months.

Figure 1 showed: **a.)** correlations endothelial cell density **b.)** coefficient of variation, and **c.)** hexagonal cells at the preoperative day, one month and 3 months. In Table 4: we assessed the internal consistency of the sample scores using Cronbach's alpha test. The test revealed a Cronbach's coefficient alpha of 0.82, which provided an acceptable level of internal consistency among the items used in the sample. We also run a paired Pooled T-Test, t value and p-value indicated that the groups were different.

Table 4: The internal consistency of the sample scores.

	obs	Mean1	Mean2	dif	St Err	t value	p-value
CV - CV 1	30	28.8	28.600	.2	1.244	.15	.874
CV 1 - CV 3	30	28.6	27.934	.667	.868	.75	.449
CV - CV 3	30	28.8	27.934	.867	1.027	.85	.406
HEX - HEX 1	30	68.267	68.933	-.667	1.977	-.35	.739
HEX 1 - HEX 3	30	68.933	70.400	-1.467	1.421	-1.05	.31
HEX - HEX 3	30	68.267	70.400	-2.133	2.141	-1	.328
ECD - ECD 1	30	2457.834	2486.434	-28.6	34.515	-.85	.414
ECD 1 - ECD 3	30	2486.434	2420.966	65.467	40.151	1.65	.114
ECD - ECD 1	30	2457.834	2420.966	36.867	41.99	.9	.387

DISCUSSION

A fluoroquinolone of the fourth generation with broad spectrum action is moxifloxacin against Gram-positive and Gram-negative bacteria, atypical microorganisms, and anaerobes. Intracameral moxifloxacin has been used worldwide in the off-label prevention of postoperative cataract endophthalmitis. Vigamox (Alcon, Fort Worth, Texas) is commonly used in the US as an off label intracameral injection during cataract surgery. **Haripryia et al.** [4] assessed a retrospective cohort of more than 600,000 cataract operations in India and discovered that patients who received a single IC dosage of moxifloxacin saw a reduction in the incidence of endophthalmitis of about 4-fold. These findings significantly strengthen the ESCRS study on the use of IC medications for the prevention of endophthalmitis following cataract surgery. Thirty eyes from thirty trabeculectomy patients were included in this interventional cross-sectional investigation. At the end of surgery, the cases received an intracameral injection of moxifloxacin. Our findings showed that no association between the variables, indicating no significant multicollinearity issue exists. We further confirm this by calculating variance inflation factors (VIF), and the results (for brevity not reported) revealed no evidence of multicollinearity, as all VIFs values do not exceed 2.

The effectiveness of moxifloxacin, cefuroxime, and vancomycin against 18 distinct endophthalmitis isolates was examined by Libre and Mathews using an in vitro model [5]. The only single antibiotic eliminating all colony forming units per milliliter against all isolates, except the methicillin-resistant Staphylococcus aureus and methicillin resistant Staphylococcus epidermidis, was the 500 µg dose of moxifloxacin. These in vitro findings on treatment efficacy need to be weighed against another in vitro study that suggests moxifloxacin doses more than 500 µg/ml may be harmful to corneal endothelial cells. Due to this, a clinical evaluation of 500 µg of intracameral moxifloxacin was conducted to determine any potential variations in corneal endothelial cell toxicity and endothelial cell loss [6].

Our findings revealed that the endothelial cell density (ECD) P-Values were 0.011, 0.012, 0.006 preoperatively, after 1 and 3 months respectively, this suggested that the ECD at the follow up times was noninferior at 0.05%. The P-values of CV and HEX were greater than or equal to 5% (i.e., 0.518% ≥ 5%), we were not able to conclude that the CV and HEX were noninferior (within 5%). **Melega et al.** [1] examined 3640 eyes from 3640 patients and discovered no appreciable variations in CV and ECD. No systemic or ocular side effects from the research were experienced. Additionally, IC moxifloxacin was introduced, and its safety was evaluated by Cavalcanti **Lira et al.** [7] who contrasted the last 150 procedures with the first 150 surgeries performed following that time. Between baseline and two years after surgery, they discovered no statistically significant differences in the mean change in CV and ECD between the groups. **Melega et al.** [1] discovered that patients who did not receive IC moxifloxacin had a considerably greater incidence of endophthalmitis. Between the Control and IC groups, there were no appreciable variations in CV and ECD. Numerous studies have suggested that using IC moxifloxacin to prevent endophthalmitis would be a secure alternative [8, 9]. Additionally, numerous research [10, 11] have employed undiluted solutions up to 0.5% with no adverse findings. In a retrospective review of 18 000 operations with dosages ranging from 50 to 500 µg/mL, **Matsuura et al.** [12] discovered that moxifloxacin produced a 3-fold reduction in the risk for endophthalmitis. Following a review of 600,000 operations. According to **Haripriya et al.** [4] IC moxifloxacin significantly decreased the overall rate of endophthalmitis (3-fold in the case of manual small incision cataract

surgery and nearly 6-fold in the case of phacoemulsification). Because of its isotonicity, close to neutral pH, and lack of preservatives, IC moxifloxacin is safe. The use of a buffer, boric acid, did not appear to affect the safety of moxifloxacin (Vigamox), despite the absence of benzalkonium chloride as a preservative in the commercially available solution. Because of the quick medication turnover following intravenous administration, cefuroxime, which is time dependent, may not be as effective as IC moxifloxacin, which is concentration dependent [13].

In this study, there was no statistically significant difference in the number of ECD in cases with first month and 3 months as compared to the preoperative values (p 0.114). The mean endothelial cell density was 2486.434 cells/mm3 then three months post-operatively altered to 2420.966 cells/mm3. In contrast, the study by **Amer et al.** [14] found that the average endothelial cell density in the moxifloxacin group was 2533.21 cells/mm3 and then changed to 2006.29 cells/mm3 one month after surgery, whereas the average endothelial cell density in the controls was 2366.75 cells/mm3 and changed to 2083.75 cells/mm3. In comparison to the 526.93 cells/mm3 decline in the eyes treated with moxifloxacin, there was a reduction of 283 cells/mm3 in the controls [14].

In this study, there was no statistically significant difference in the of CV in cases with first month and 3 months as compared to the preoperative values (p 0.449). The mean CV was 28.600 then three months post-operatively altered to 27.934. Also, there was no statistically significant difference in the of HEX in cases with first month and 3 months as compared to the preoperative values (p 0.31). The mean HEX was 68.933 then three months post-operatively altered to 70.400. This is consistent with a 2007 study that examined 65 eyes and found that prophylactic intracameral injections of moxifloxacin 500 µg/0.1 ml were safe up to one month following surgery. The medicine also appeared to be safe in terms of visual recovery, anterior chamber reactivity, and ECD [15].

Our study strongly states the fact that intracameral injection of moxifloxacin is a safe drug to be used intracameral after trabeculectomy surgery with not a single case of TASS and with no toxicity on corneal endothelium. Preservation of normal ECD, CV and HEX of corneal endothelial cells are important indicators of safety for any intracameral drug and all the corneal parameters were maintained clinically in our study.

Still, there are certain problems with IC moxifloxacin, such as the potential for bacterial resistance and allergic reactions [16,17]. The goal of the present study, however, was not to assess these issues. We found no evidence of allergic reactions or endophthalmitis in the current study.

Limitations: Our study has some limitations as it was conducted in a single center with a relatively small sample size. Further studies are required to assess safety and complications of IC moxifloxacin with different doses.

Conclusion:

Corneal endothelial cell safety is acceptable for 500 µg intracameral moxifloxacin, well tolerated, which supports the usage of this concentration for an improved antimicrobial coverage that prevents postoperative endophthalmitis.

Conflict of Interest:

The authors declare that they have no competing interest.

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