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Research Article

Safety of Prophylactic Intracameral Gatifloxacin Injection in Cataract Surgery

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Abstract

Purpose: To evaluate the safety of intracameral injection of gatifloxacin as prophylaxis for endophthalmitis in routine cataract surgery.

Methods: In this prospective study, 41 eyes of 41 patients were included. In the first group, 23 eyes received an intracameral injection of gatifloxacin (0.3 mg/0.1 mL), while 18 eyes were received an intracameral injection of cefuroxime (1 mg/0.1 mL) in the second group, at the end of surgery. The best corrected visual acuity, endothelial cell density (ECD), coefficient of variation (CoV) and central foveal thickness (CFT) were evaluated at baseline and 1, 3 and 6 months after surgery.

Results: All the patients have better visual acuity postoperatively and these were comparable between groups at months 6 ($P = 0.228$). The ECD significantly decreased at postoperative months 6 in both groups and these were comparable between groups ($P = 0.839$). The CoV increased postoperatively in both groups however the differences were not significant between groups during follow up period ($P > 0.05$). There was an increase trend in the CFT postoperatively and these also did not show any significant difference between groups during follow up period ($P > 0.05$).

Conclusions: The results indicate that intracameral gatifloxacin is as safe as cefuroxime in cataract surgery in terms of visual acuity, endothelial cell changes and foveal thickness.

Keywords: *Antibiotics; Cataract Surgery; Cefuroxime; Endophthalmitis; Gatifloxacin*

Introduction

Postoperative endophthalmitis is a serious complication that may cause blinding after cataract surgery. Studies report an incidence rate after cataract surgery from 0.06% to 0.49% in the United States and Europe [1,2]. The most common reasons of the disorder are the ocular flora or microorganisms that colonized the surface of eye structures [3].

To prevent its devastating effects, the use of prophylactic measures in cataract surgery has been significantly expanded. Several preoperative, intraoperative, and postoperative strategies have been developed over the years, although there is still no consensus on the best method and regimen of administration. Preoperative antiseptics and antibiotics are usually administered to decrease bacterial colonization of the ocular surface. To that end, the use of preoperative povidone-iodine 5.0% in the conjunctival sac remains the most accepted method and is now considered the standard of care in cataract surgery [3]. In contrast, the role of preoperative topical antibiotics is controversial, with some studies showing no significant effect on anterior chamber contamination [4].

Intraoperatively, subconjunctival injections of antibiotics have been progressively replaced by intracameral injections, mainly as a result of that as it has been shown that subconjunctival injections do not attain sufficiently high intraocular drug concentrations. European

Society of Cataract and Refractive Surgeons (ESCRS) Endophthalmitis Study Group showed that intracameral cefuroxime application during the cataract surgery significantly decreases the risk of postoperative endophthalmitis [2].

Despite the ESCRS[2] revealed the favorable effects of cefuroxime, other antibiotics are probably effective due to the variability in the antibacterial activity spectrum. Ophthalmologists in the United States prefer to use moxifloxacin for postoperative endophthalmitis prophylaxis [5,6]. Gatifloxacin is a fourth-generation fluoroquinolone agent as well as moxifloxacin. Depending on the wide activity spectrum, they are currently the best favorable topical antibiotics [7,8]. Moxifloxacin is self-preserved with a reasonably extensive literature built up about its safety [9,10]. In a previous study intracameral gatifloxacin 0.3% and moxifloxacin 0.5% was reported to be nontoxic to the rabbit corneal endothelium [11]. However, there is limited data concerning about the possible effect of the intracameral use of gatifloxacin that contains benzalkonium chloride as preserving agent [12]. Hence, we aimed to assess the safety of intracameral gatifloxacin injection as a prophylactic measure for postoperative endophthalmitis in cataract surgery with comparing to intracameral use of cefuroxime. Because there are many studies comparing moxifloxacin to cefuroxime therefore we decided to compare gatifloxacin to cefuroxime.

Methods

In this prospective comparative study we evaluated 41 eyes of 41 patients who underwent phacoemulsification cataract surgery and IOL implantation from February of 2012 to January of 2013. Patients were divided into two groups: 23 patients have received intracameral gatifloxacin (gatifloxacin group) and 18 age-sex matched patients have received intracameral cefuroxime (cefuroxime group). Exclusion criteria included a history of ocular surgery or trauma, corneal disease, glaucoma, uveitis, vitreous opacities, retinopathy, and visual pathway defects. Other exclusion criteria were current treatment with systemic steroids, immune-suppressants, anticoagulants, or prostaglandin analogue eye drops. Patients with intraoperative complications and Lens Opacities Classification System III (LOCS III) [13] P-scale value greater than 3.5 were also excluded.

The antibiotic dilutions were performed by the operating room nursing staff. The gatifloxacin injection was prepared from a commercially available gatifloxacin 0.3% solution (Zymar, Abdi İbrahim) and 0.3 - 0.4 mL was taken to a tuberculin syringe in sterile conditions. This solution had a pH of 6.0 and an osmolality of 260 - 330 mOsm/kg. The drug was not diluted and 0.1 mL (0.3 mg/0.1 mL) was administrated to anterior chamber at the end of the surgery. Cefuroxime was prepared from a 15 mL solution containing 1500 mg of cefuroxime. Then 0.1 mL of the solution was aspirated into a 1.0 mL syringe. The solution was diluted 10.0% with a balanced salt solution, and 0.1 mL or 1.0 mg of cefuroxime was injected intracamerally. This solution had a pH of 7.28 and an osmolality of 366 mOsm/kg.

Pupils were dilated with repeated doses of tropicamide 1.0% and phenylephrine 10.0%. Preoperatively, povidone–iodine 10.0% (Betadine) was applied to the periocular skin and then povidone–iodine 5.0% was administrated into the conjunctival sac at the operating site at least 5 minutes before surgery. All patients received topical anesthesia with proparacaine. Uneventful cataract surgeries were performed by the same surgeon with 3.2 superotemporal clear corneal incisions using a phaco-chop technique. We did not use trypan blue for anterior lens capsule staining in any patients. The combination of sodium hyaluronate 3% and chondroitin sulfate 4% (Viscoat, Alcon Laboratories, Inc.) was applied to protect the corneal endothelium, and sodium hyaluronate 1% (Provisc, Alcon Laboratories, Inc.) was used for the implantation of intraocular lens (IOL). A hydrophobic acrylic IOL (Activa^{UD} UD 613, VSYBio, Turkey) was implanted in all cases. After the ophthalmic viscosurgical device was removed and the surgeon ensured that the corneal incisions were adequately sealed, the antibiotic agent was injected via the side port into the capsular bag using a 27-gauge cannula. At the end of the surgery, 1 or 2 drops of 5% povidine-iodine was instilled on cul-de-sac in all eyes. The postoperative regimen included topical lomefloxacin 4 times daily for 2 weeks and topical dexamethasone 0.1% 4 times per day for 4 weeks.

Postoperative examinations were performed at 1, 3 and 6 months after surgery. These following preoperative and postoperative examinations were performed: best corrected visual acuity (BCVA, LogMAR), intraocular pressure (IOP) (Goldmann applanation tonometry), endothelial specular microscopy (endothelial cell density [ECD] and coefficient of variation [CoV] in cell size). Corneal endothelial

specular microscopy was recorded with a noncontact specular microscope (SP 2000P; Topcon, Tokyo, Japan). CFT was assessed by spectralOCT/scanning laser ophthalmoscopy (SLO) (OPKO/OTI, Miami, FL). The data obtained before surgery were compared with those obtained after surgery within the two groups. Preoperative and postoperative data were also compared between groups. The postoperative examiner was masked to the group assignment. The study was conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki. The study was approved by the Local Ethics Committee of the participating center. All patients were informed about the purpose of the study and provided their consent.

Data were encoded and analyzed using the SPSS software (version 21.0, SPSS, Inc.). The data were normally distributed, met by the Kolmogorov–Smirnov test ($P > 0.05$). Comparisons were performed using an independent t test. A P value less than 0.05 was determined to be significant. The results are given as the mean ± standard deviation (SD).

Results

Table 1 shows the patients' demographics. There were no significant differences in the preoperative mean age, sex and BCVA between groups (Table 1).

Parameter	Gatifloxacin	Cefuroxime	P value
Sex			
Male	15	11	0.076
Female	8	7	0.876
Age			
Mean ± SD	70.23 ± 8.80	66.58 ± 10.90	0.277
Range	43 - 78	45 - 80	
BCVA (logMAR)			
Mean ± SD	1.22 ± 0.45	1.26 ± 0.40	
Range	0.50 - 2.00	0.70 - 2.00	0.703

Table 1: *Between-group comparison of preoperative patient parameters and demographics.*

BCVA: Best Corrected Visual Acuity; SD: Standard Deviation

P < 0.05 indicates statistically significance different.

Visual Acuity

Statistically significant improvements from baseline were observed in BCVA at 1, 3 and 6 months for both groups ($P < 0.001$). Preoperative BCVA values were comparable between groups ($P = 0.855$). Postoperative BCVA values were significantly higher in the gatifloxacin group compared to cefuroxime group at month 1 ($P = 0.009$) and months 3 ($P = 0.036$). However the differences between groups were not significant at months 6 ($P = 0.228$) (Figure 1).

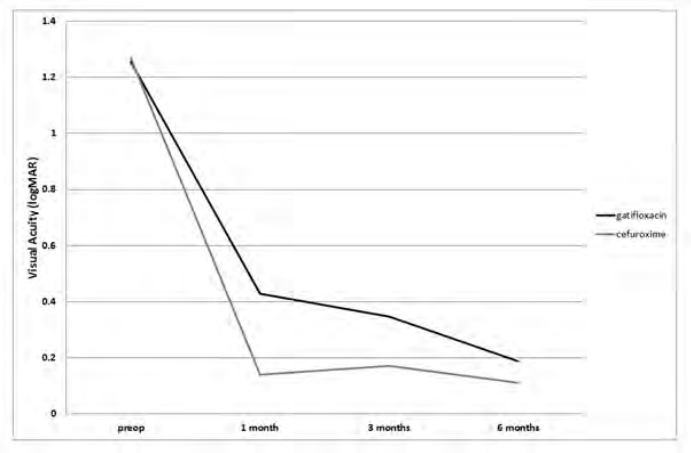

Figure 1: *Changes in visual acuity during follow up.*

Endothelial Cell Density

Table 2 shows the mean ECD and CoV in both groups. In the gatifloxacin group, the ECD showed a significant decrease at postoperative months 3 (P = 0.010) and months 6 (P = 0.002). However, the differences between the 1 and 3 month mean values and between the 3 and 6 month mean values were not statistically significant (P = 0.342 and P = 0.627, respectively).

	Endothelial Cell Density (Cells/mm^2)		Coefficient of Variation	
Group	**Mean ± SD**	**P value**	**Mean ± SD**	**P value**
All eyes (n = 41)				
Preoperative	1789.67 ± 509.36	-	22.40 ± 6.17	-
Postoperative				
1 month	1568.87 ± 532.07	0.007	29.40 ± 7.53	< 0.001
3 months	1517.64 ± 436.08	0.001	27.47 ± 8.03	< 0.001
6 months	1436.48 ± 399.55	0.000	32.28 ± 23.84	< 0.001
Gatifloxacin (n = 23)				
Preoperative	1716.56 ± 370.02	-	21.95 ± 6.23	-
Postoperative				
1 month	1629.90 ± 619.80	0.273	28.52 ± 7.61	< 0.001
3 months	1498.35 ± 438.32	0.010	28.50 ± 6.88	< 0.001
6 months	1449.90 ± 412.03	0.002	36.66 ± 6.90	< 0.001
Cefuroxime (n = 18)				
Preoperative	1878.66 ± 669.16	-	22.81 ± 6.44	-
Postoperative				
1 month	1570.88 ± 351.76	0.068	31.31 ± 7.70	0.001
3 months	1577.70 ± 450.18	0.073	26.40 ± 9.56	0.095
6 months	1474.94 ± 353.25	0.020	26.81 ± 5.90	0.067

Table 2: *Endothelial changes over time by groups.*

SD: Standard Deviation; n: Number

P < 0.05 indicates statistically significance different.

Similarly, the ECD decreased in the cefuroxime group postoperatively however the only statistically significant difference was observed at 6 months (P = 0.020). The differences between the 1 and 3 month mean values and between the 3 and 6 month mean values were not statistically significant (P = 0.937 and P = 0.361, respectively).

The preoperative mean ECD was similar in the two groups (P = 0.365). Postoperatively, the ECD remained similar between groups (P = 0.714 at 1 month, P = 0.592 at 3 months, and P = 0.839 at 6 months) (Figure 2, A). Furthermore, the change in ECD (in percentages) compared to baseline was not significantly different between the two groups during follow up (Table 3).

	Change in ECD (mean% ± SD)			Change in CFT (mean% ± SD)		
Postoperative	**Gatifloxacin**	**Cefuroxime**	**P value**	**Gatifloxacin**	**Cefuroxime**	**P value**
1 month	34.5 ± 30.8	22.5 ± 18.1	> 0.05	12.2 ± 11.9	9.2 ±7.5	> 0.05
3 months	27.3 ± 15.5	25.6 ± 19.6	> 0.05	9.9 ± 10.9	14.3 ±15.1	> 0.05
6 months	26.8 ± 17.1	21.3 ± 20.1	> 0.05	9.1 ± 11.9	11.9 ±10.7	> 0.05

Table 3: *Comparison of the change in ECD and CFT between two groups during follow-up period.*

ECD: Endothelial Cell Density, CFT: Central Foveal Thickness; SD: Standard Deviation

P < 0.05 indicates statistically significance different.

Coefficient of Variation

In the gatifloxacin group, there was a significant increase in the CoV during follow up (all comparisons P < 0.001). The difference between month 1 and months 3 was not statistically significant (P = 0.988) however it was significantly higher at months 6 compared to months 3 (P < 0.001).

In the cefuroxime group, the CoV values were not significantly different at months 3 or months 6 after surgery (P = 0.095 and P = 0.067, respectively). However, there was a statistically significant increase at postoperative month 1 (P = 0.001). The CoV values were significantly higher at month 1 than months 3 (P = 0.022) whereas the difference was not significant between months 3 and months 6 (P = 0.870).

The preoperative mean CoV was similar in the two groups (P = 0.720). Postoperatively, the CoV remained similar between groups (P = 0.292 at 1 month, P = 0.484 at 3 months, and P = 0.230 at 6 months) (Figure 2, B).

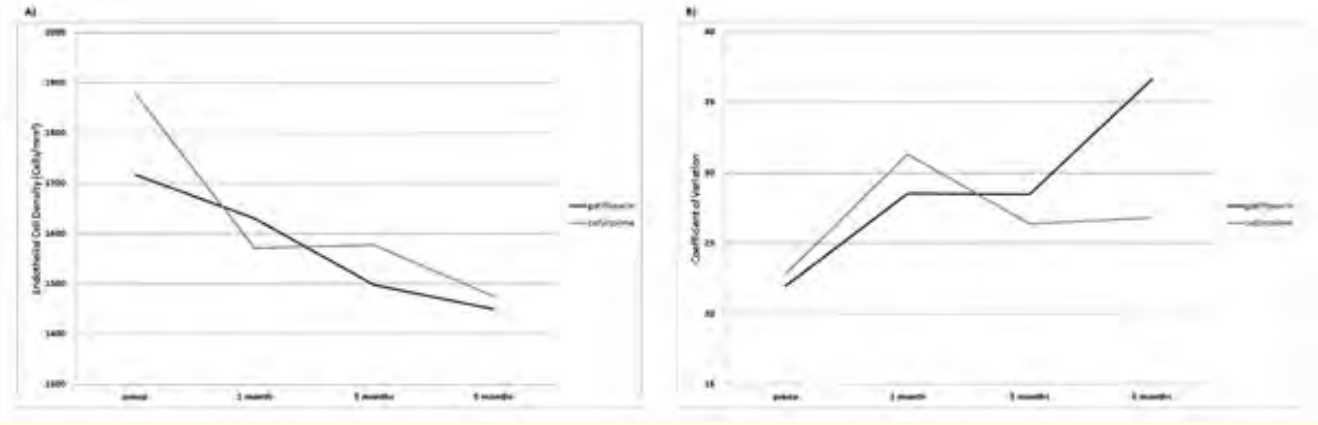

Figure 2: *Changes in (A) ECD and (B) CoV during follow up.*

Central Foveal Thickness

In the gatifloxacin group, there was a significant increase in the CFT from preoperatively to postoperatively (all comparisons P < 0.001). However, the differences between the 1 and 3 month mean values and between the 3 and 6 month mean values were not statistically significant (P = 0.580 and P = 0.564, respectively).

In the cefuroxime group, there was an increase trend in the CFT from preoperatively to postoperatively however; the differences were not statistically significant (P > 0.05). Similarly, these differences between the 1 and 3 month and between the 3 and 6 month were not statistically significant (P = 0.866 and P = 0.670, respectively).

The mean preoperative CFT was similar in the two groups (P = 0.874). Postoperatively, these were not significantly different between groups (P = 0.132 at 1 month, P = 0.240 at 3 months, and P = 0.597 at 6 months) (Figure 3). The change in ECD (in percentages) compared to baseline was not significantly different between the two groups during follow up (Table 3).

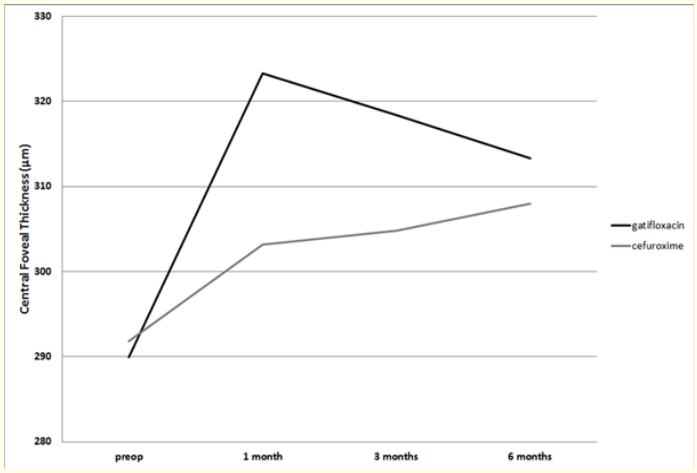

Figure 3: *Changes in CFT during follow up.*

Discussion

Postoperative bacterial endophthalmitis is still a serious complication that may cause severe visual impairment against the precise preoperative surgical preparations and the usage of prophylactic antiseptics and antibiotics. Several factors are proposed to be involved in this process; these include the surgical technique, intraoperative contamination of the anterior chamber, and increasing age of patients having phacoemulsification.

Intraocular contamination is known to occur during cataract extraction or within the first hours after surgery. Anterior chamber aspirates obtained during phacoemulsification show contamination rates ranging from 2% to 43% [14,15]. Coagulase-negative *Staphylococcus, Propionibacterium acnes*, and other conjunctival flora are the most commonly isolated microorganisms [16].

Preoperative povidine iodine usage is currently one of the most effective methods to decrease the proportion of the pathogen microorganism [17]. Since the ESCRS study evaluated the effectiveness of intracameral cefuroxime and established the clinical benefits of a dose of 1 mg after cataract extraction, the use of intracameral antibiotics has gained worldwide acceptance [2].

Numerous studies have assessed the safety of intracameral injections of cefuroxime in terms of endothelial toxicity and ocular inflammation. Montan., *et al*. did not find any significant difference in endothelial cell loss between 45 patients receiving 1 mg intracameral

cefuroxime and 45 patients who did not receive intracameral prophylaxis [18]. Even higher doses of cefuroxime did not significantly damage the corneal endothelium, although injections of 40 mg to 50 mg, instead of the recommended 1 mg, were associated with transient macular edema and serous retinal detachment [19].

Because of the resistance progress to previously administrated antibiotics, new agents are suggested for the endophthalmitis prophylaxis, such as fourth-generation fluoroquinolones [20,21]. Considering the safety, moxifloxacin and gatifloxacin may be the most appropriate fourth-generation fluoroquinolone agents, due to the ready-to use concentrations preventing the dilution errors damages. To best of our literature knowledge, it has not been definitively determined whether cefuroxime or gatifloxacin is better than the other or more toxic to corneal endothelial cells.

Our primary objective was to evaluate corneal endothelial changes after intracameral injections of cefuroxime and gatifloxacin in preventing postoperative endophthalmitis. In physiologic conditions, the ECD decreases with age at an average rate of approximately 0.3% to 0.6% per year because *in vivo* proliferative potential of human endothelial cells is almost absent [22]. However, the corneal endothelium might be exposed to additional damage from corneal disorders, systemic diseases such as diabetes, and toxic exposure. Cataract surgery is also a common iatrogenic cause of endothelial damage, especially in patients with a low preoperative ECD.

Unlike other tissues, the corneal endothelium wound-healing process is achieved through mechanisms of cell–cell interaction. Peripheral cells interact with each other and promote cell enlargement and migration, restoring a similar pattern when possible. This process induces irreversible cell loss and alters the uniformity of endothelial cell population. Therefore, the ECD tends to decrease after significant endothelial trauma and is considered a reliable indicator of endothelium injury. However, endothelial cell morphometric analysis combined with an endothelial cell count is a more sensible index of endothelial damage and functional reserve than ECD alone [23]. The CoV is an estimation of the variance in cell area across a region of the corneal endothelium. A traumatized endothelium will be expected to have a high CoV as an early sign of endothelial cell loss.

Specular microscopy is based on the emission of a magnified reflection of light on the endothelium and is the most reliable method available in clinical practice and medical trials for endothelium evaluation. However, a small cell-counting error can have a large effect on the final ECD or CoV. To minimize sampling errors in our study, 3 measurements were taken and at least 150 cells were analyzed at the preoperative and postoperative examinations.

There was a significant decrease in ECD at postoperative 6 months in both groups in our study. However, CoV at postoperative 6 months were only significant for the gatifloxacin group. According to previous studies, the mean endothelial cell loss after modern phacoemulsification can vary from 9% to 14% depending on factors such as age and hardness of the cataract. In our study, there was no evidence of cell density recovery month 1 after surgery in both groups. Although no significant differences were found in ECD or CoV between groups at any time postoperatively, the small differences may become significant in larger population. Therefore, the comparable corneal endothelial changes between cefuroxime and gatifloxacin should be confirmed in future prospective studies in larger populations.

The potential risk for endothelial toxicity has also been associated with the chemical composition, osmolality, pH, and concentration of the drug solution in the anterior chamber [24]. The ocular surface toxicities of newer generation fluoroquinolones (gatifloxacin, moxifloxacin) have been evaluated in previous studies and have come to conflicting conclusions [25,26]. However, no study has still evaluated their toxicities in intracameral use. In the current study we have not found any significant toxicity for gatifloxacin compared to cefuroxime based on the confocal microscopy and CFT measurement obtained by OCT.

We have not found any significant toxicity for gatifloxacin compared to cefuroxime based on the confocal microscopy and CFT measurement obtained by OCT. However, these should be evaluated with additional toxicity examinations in future prospective studies including a larger study population. Furthermore, cefuroxime and gatifloxacin dilutions exhibited pH and osmolality values within safe ranges for humans in our study.

We have also analyzed the effects of the drug on visual acuity and CFT when used intracamerally. Postoperatively, all the patients have better visual acuity and these were comparable between groups. There was an increase trend in the CFT from preoperatively to postoperatively in both groups. In addition, the differences in CFT were not significant between groups. It has been shown that some drugs may lead to macular edema when used intracamerally [27]. Any well performed or uncomplicated phacoemulsification surgery may be associated with macular edema postoperatively however; the surgeries were performed by the same surgeon using the same surgical techniques. In addition, we did not include patients with intraoperative complications and Lens Opacities Classification System III (LOCS III) [13] P-scale value greater than 3.5 which may cause surgery related macular edema.

The major limitations of this study are that we did not compare the dissipated cumulative energy and the effective phaco time which may affect the endothelial cells of cornea. However, only cataract eyes with P-scale value less than 3.5 were included in both groups. Another limitation is the small sample size. Finally we did not include the corneal pachymetric changes as well as the percentage of hexagonality which might reflect cell pleomorphism.

Intracameral gatifloxacin seems to be a safe alternative to cefuroxime based on visual acuity, corneal endothelial toxicity or foveal thickness but these results should be confirmed with future studies with larger study populations including other factors which may affect the endothelial cells during surgery such as the dissipated cumulative energy and the effective phaco time.

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