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To cite this article: Wassim Ghazal, Alain Saad, Romain Courtin, Damien Gatinel & Christophe Panthier (2021) Effect of Intracameral Cefuroxime on Graft Endothelial Cells in Descemet Membrane Endothelial Keratoplasty: A Comparative Study, *Current Eye Research*, 46:7, 936-942, DOI: [10.1080/02713683.2020.1858487](https://doi.org/10.1080/02713683.2020.1858487)

To link to this article: <https://doi.org/10.1080/02713683.2020.1858487>



Published online: 16 Dec 2020.



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Effect of Intracameral Cefuroxime on Graft Endothelial Cells in Descemet Membrane Endothelial Keratoplasty: A Comparative Study

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ABSTRACT

Purpose: To evaluate the effect of intracameral cefuroxime on graft endothelial cell loss after simple Descemet Membrane Endothelial Keratoplasty (DMEK) and combined DMEK and cataract surgery.

Materials and Methods: Single-center retrospective comparative analysis. One hundred and three patients were included, 31 in the cefuroxime group and 72 in the non-cefuroxime (NC) group. Best Spectacle-Corrected Visual Acuity (BSCVA), endothelial cell density (ECD) of the graft measured by specular microscopy, and the recipient's pachymetry were recorded pre-operatively and at 1, 3, and 6 months after surgery.

Results: In the cefuroxime group, BSCVA was 0.22 ± 0.27 LogMAR, 0.15 ± 0.24 LogMAR and 0.07 ± 0.22 , respectively, at 1, 3, and 6 months after surgery with no significant differences found when compared to the NC group ($p > .05$). Anatomical outcomes were similar as mean pachymetry decreased from 599 ± 51 μ m preoperatively to 511 ± 30 μ m at 6 months after surgery in the cefuroxime group and from 607 ± 67 μ m preoperatively to 519 ± 32 μ m at 6 months in the NC group ($p = .25$). Endothelial cell loss was comparable between both groups: 33.4% versus 33.6% at 1 month ($p = .97$), 37.4% versus 34.9% at 3 months ($p = .68$) and 41.6% versus 38.3% at 6 months ($p = .42$) in the cefuroxime and NC groups, respectively. The rates of rebubbling, graft rejection, and cystoid macular edema were not significantly higher in the cefuroxime group.

Conclusion: The use of intracameral cefuroxime during simple or combined DMEK did not lead to higher graft endothelial cell loss.

ARTICLE HISTORY

Received 3 October 2020
Revised 15 November 2020
Accepted 25 November 2020

KEYWORDS

Cornea; descemet membrane endothelial keratoplasty (DMEK); graft surgery; cefuroxime intracameral injection; cataract

Introduction

Descemet Membrane Endothelial Keratoplasty (DMEK) has revolutionized corneal transplant surgery by providing rapid recovery and improved visual outcomes since it was first described by Melles et al. in 2006.¹ When combined with phacoemulsification, it provides an effective treatment for patients presenting with both cataract and endothelial cell disorders, such as Fuch's dystrophy. Compared to previous techniques, DMEK also offers the benefit of more predictable refractive outcomes, as well as lower complications such as rejection or wound dehiscence.²

Endophthalmitis is a dreaded and devastating complication of cataract surgery. Some of the well-known risk factors include advanced age (80 years or more), immunocompromised state secondary to systemic diseases, diabetes mellitus, presence of septic focus in and around the eye, posterior capsular break, and wound leak.³ Most of these risk factors can also be found in patients undergoing DMEK.

Current rates of infectious endophthalmitis secondary to phacoemulsification vary from 0.03 to 0.2% across the world⁴ and have been reduced five-fold since the widespread use of intracameral antibiotics such as cefuroxime.⁵

In a 2019 study by Borkar et al., the rate of endophthalmitis following endothelial keratoplasty was 0.2%, significantly lower than after Penetrating Keratoplasty (PK).⁶ Although these rates appear low, there is no consensus on the use of intracameral

antibiotics during simple DMEK or combined DMEK and cataract surgery.

Multiple studies regarding the toxicity of intracameral cefuroxime to corneal endothelial cells during cataract surgery have been conducted in the past.^{7–10} However, the potential adverse effect of cefuroxime on graft endothelial cells has yet to be evaluated.

The aim of this study is to investigate the effect of intracameral cefuroxime in simple DMEK or combined DMEK and cataract surgery on graft endothelial cell loss.

Patients and methods

Patient selection

This retrospective study included patients who underwent simple DMEK or combined DMEK (DMEK and phacoemulsification), between March 2016 and February 2019, at the Rothschild Foundation, Paris, France.

The data collection process was as follows: as of June 2018, all patients scheduled for simple or combined DMEK surgery in our practice received an intracameral cefuroxime injection at the end of surgery, in accordance with the guidelines recommending its use after phacoemulsification. Intracameral cefuroxime injection was not performed before this date by any corneal surgeon for DMEK procedures. Therefore, we searched for the keywords “intracameral cefuroxime” in all operative

reports from our electronic health record database prior to and after June 2018 and manually reviewed the retrieved records to separate patients into the cefuroxime group and the non-cefuroxime control group. Controls had the same surgical indications and a similar preoperative best-corrected visual acuity as patients included in the cefuroxime group. Inclusion criteria were simple or combined DMEK procedure for Fuchs' endothelial dystrophy, pseudophakic bullous keratopathy, or herpetic endotheliitis, with a follow-up period of at least 6 months. Exclusion criteria were previous corneal surgery, lack of preoperative donor information or a follow-up period shorter than 6 months.

For patients with a documented allergy to penicillin, even though the risk of cross-reactivity with cephalosporins is reported to be low, and negligible in the case of cefuroxime,^{11,12} intracameral cefuroxime was not administered during simple or combined DMEK. These patients were included in the NC group. No patient had a known allergy to cefuroxime.

The study was conducted in accordance with the tenets of the declaration of Helsinki and was approved by the local Institutional Review Board (IRB). Informed consent was obtained for all participants.

Donor tissue preparation

Graft preparation was made with a slightly modified version of the donor preparation technique NIOS,¹ as described in a previous article.¹³

DMEK surgery

Surgeries were performed with no viscoelastic except for combined procedures. We used the standardized "no touch" technique as described by Dapena et al.¹⁴ All patients were in hospital setting and kept a strict supine position throughout the first 5 hours after the surgery.

Postoperative treatment for all patients included artificial tears as well as a corticosteroid anti-inflammatory agent associated with an antibiotic (dexamethasone/tobramycin suspension, Alcon; 4 times a day for the first month, with progressive tapering over the next months).

Intracameral cefuroxime

All patients included in the cefuroxime group received an injection of 1 mg/0.1 mL of a licensed cefuroxime solution (Aprokam®) at the end of the procedure, as recommended for cataract surgery. After purging the syringe, a volume of 0.1 mL of cefuroxime solution was injected with a 30-gauge Rycroft cannula through a paracentesis performed with a 15-degree blade. This was performed after 100% air tamponade was obtained, in order to reduce the size of the air bubble. In the NC group, the same volume (0.1 mL) of BSS was injected after tamponade to flush out the air and reduce the size of the bubble.

Rebubbling

Significant graft detachment was defined by a large (more than 33% of the surface) and/or central graft detachment.¹⁵ When

such graft detachment was detected during the follow-up period by slit-lamp examination or optical coherence tomography (OCT) Optovue (RTVue®, Optovue, Fremont, CA), an intracameral air injection ("rebubbling") was performed to promote graft re-adhesion. The procedure was performed in most cases at the slit lamp.

Measurements

The following parameters were evaluated for all patients: best spectacle-corrected visual acuity (BSCVA), endothelial cell density (ECD), and the recipient's central corneal thickness, preoperatively and at 1, 3, and 6 months after surgery. The age of the donor and preoperative endothelial cell count of the graft were also recorded.

The central corneal thickness analysis was taken from OCT imaging (RTVue®, Optovue, Fremont, CA), and postoperative ECD was evaluated in vivo using a non-contact specular microscope (CEM-530; Nidek Co Ltd, Japan). After capturing 16 images, a semi-automated analysis calculated the central and paracentral ECD. In the case of an incorrect ECD measurement, the center of 15 cells was manually marked on one central image. Intraoperative and postoperative complications were noted. The previously provided ECD of the donor corneal button was evaluated in vivo with inverted light microscopy.

Statistical analysis

Categorical variables are presented as numbers and percentages. Continuous variables are presented as mean \pm standard deviation. Gaussian distribution of all variables was verified using the Shapiro–Wilk test, and a two-sided Student's *t*-test was performed for comparison between both groups. *P* values less than 0.05 were considered statistically significant ($p < .05$). All Statistical analyses were performed using Statview® software (Optima, France) and Excel® software (Microsoft, Corp. USA).

Results

Patients' characteristics

Overall 103 patients were included in our study, 31 in the cefuroxime group and 72 in the control non-cefuroxime group (2 controls for 1 patient). Table 1 summarizes the baseline demographic and clinical variables of both groups. Surgical indications were Fuchs' endothelial dystrophy, pseudophakic bullous keratopathy and secondary to herpetic endotheliitis. Preoperative BSCVA, preoperative pachymetry, donor age, and preoperative ECD were comparable between the two groups ($p > .05$).

Visual outcomes

No statistically significant ($p > .05$) differences were noted between the 2 groups regarding postoperative visual acuity. In the cefuroxime group, the mean BSCVA was 0.22 ± 0.27 LogMAR, 0.15 ± 0.24 LogMAR and 0.07 ± 0.22 , respectively, at 1, 3, and 6 months after surgery, and 0.16 ± 0.18 LogMAR, 0.10 ± 0.12 LogMAR, and 0.09 ± 0.10 LogMAR for the NC group (Figure 1). The mean BSCVA gain at 6 months was also

Table 1. Demographic and clinical data of patients in the cefuroxime and non-cefuroxime control group.

Parameters	Cefuroxime group	Non cefuroxime group	P value
Categorical variables	N = 31	N = 72	
Gender, n (%)			
Male	8 (25.8)	25 (34.7)	
Female	23 (74.2)	47 (65.3)	
Surgical indications, n (%)			
Fuch's dystrophy	27 (87)	67 (93)	
Pseudophakic bullous keratopathy	2 (6.5)	4 (5.6)	
Herpes	2 (6.5)	1 (1.4)	
Type of surgeries, n (%)			
Single DMEK	3 (9.7)	7 (9.7)	
Combined procedure (cataract and DMEK)	28 (90.3)	65 (90.3)	
Continuous variables	Mean ± Standard Deviation	Mean ± Standard Deviation	P value
Donor graft characteristics			
Age, (years)	73 ± 8	72 ± 9	.84
Endothelial cell count, (cells/mm ²)	2705 ± 106	2709 ± 146	.89
Patients			
Age, (years)	67 ± 11	72 ± 9	.02
Preoperative BSCVA, (LogMAR)	0.50 ± 0.30	0.46 ± 0.21	.49
Preoperative pachymetry (µm)	599 ± 51	607 ± 67	.56

n = number, DMEK = Descemet Membrane Endothelial Keratoplasty, BSCVA = Best Spectacle-Corrected Visual Acuity

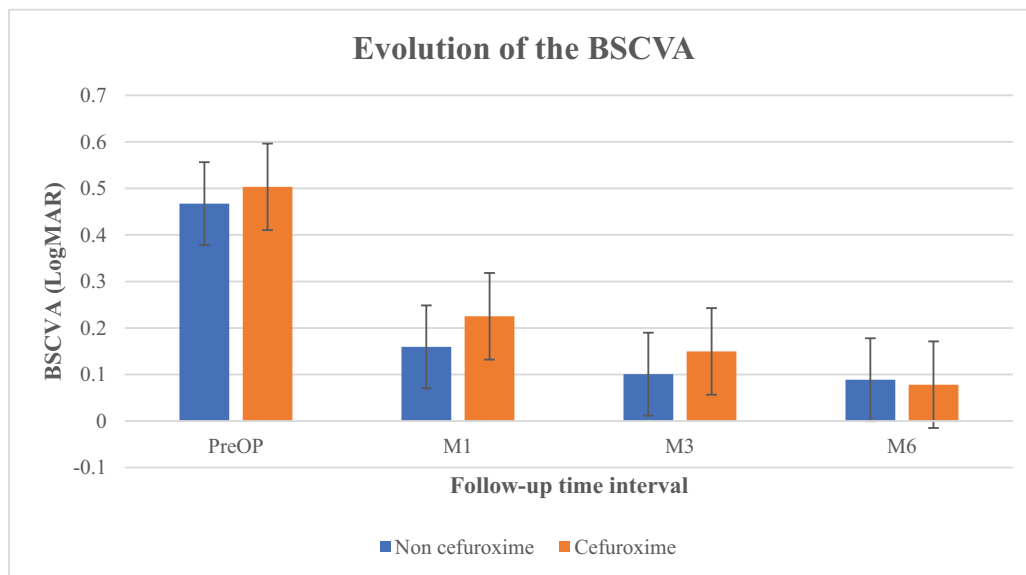


Figure 1. Evolution of the BSCVA during follow-up time interval in cefuroxime and non-cefuroxime control groups. BSCVA in LogMAR. Follow-up in months. BSCVA = Best spectacle-corrected visual acuity, PreOP = preoperative measure, M1 = one month postoperative, M3 = three months postoperative, M6 = six months postoperative.

comparable: 0.35 ± 0.32 LogMAR for the cefuroxime group, and 0.36 ± 0.18 LogMAR for the NC group ($p = .88$). At 6 months after surgery, 90% of eyes in the cefuroxime group reached $>20/25$ (>0.8) visual acuity and 61% $>20/20$ (>1.0). In the NC group, 68% of eyes reached $>20/25$ visual acuity, and 51% $>20/20$ (>1.0) at 6 months after surgery.

Pachymetry

Mean central corneal thickness decreased from 599 ± 51 µm preoperatively to 552 ± 63 µm at 1 month, 514 ± 38 µm at 3 months, and 511 ± 30 µm at 6 months in the cefuroxime group. In the NC group, mean central corneal thickness decreased from 607 ± 67 µm preoperatively to 554 ± 62 µm at 1 month, 517 ± 32 µm at 3 months, and 519 ± 32 µm at 6 months (Figure 2). No statistically significant difference was noted between the 2 groups at follow-up intervals ($p > .05$).

At 1 month after surgery, pachymetry decreased by 44.9 ± 65 µm and 55.7 ± 79 µm in the cefuroxime and NC group, respectively ($p = .51$) (Figure 3). At 3 months after DMEK, the mean central corneal thickness decrease was similar in both groups (-89 ± 51 µm in the cefuroxime group, versus -81.9 ± 56 µm in the NC group, $p = .58$) (Figure 3).

Postoperative pachymetry at 6 months did not differ between the cefuroxime and NC groups (511 ± 30 µm and 519 ± 32 µm, respectively, $p = .44$). In addition, pachymetry decreased by 84.9 ± 48 µm and 90.2 ± 63 µm in the cefuroxime and NC groups, respectively ($p = .69$) (Figure 3).

Endothelial cell density

ECD was at 1819 ± 466 cells/mm² versus 1869 ± 584 cells/mm² at 1 month postoperative ($p = .80$), 1747 ± 611 cells/mm² versus 1775 ± 525 cells/mm² at 3 months ($p = .88$) and 1587 ± 443 cells/mm²

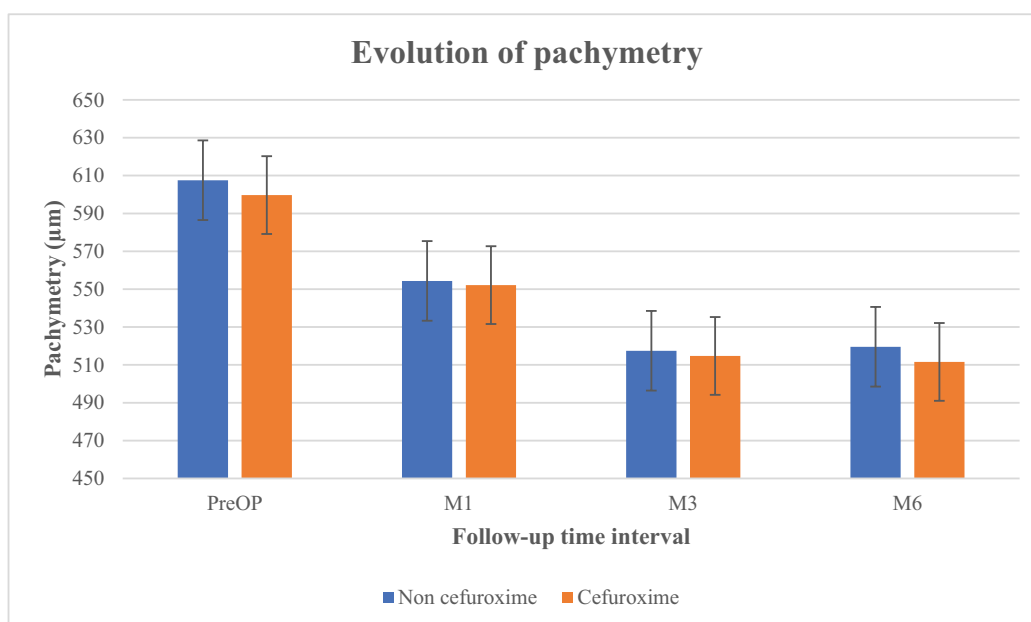


Figure 2. Evolution of pachymetry (μm) during follow-up time interval in cefuroxime and non-cefuroxime control groups. PreOP = preoperative measure, M1 = one month postoperative, M3 = three months postoperative, M6 = six months postoperative.

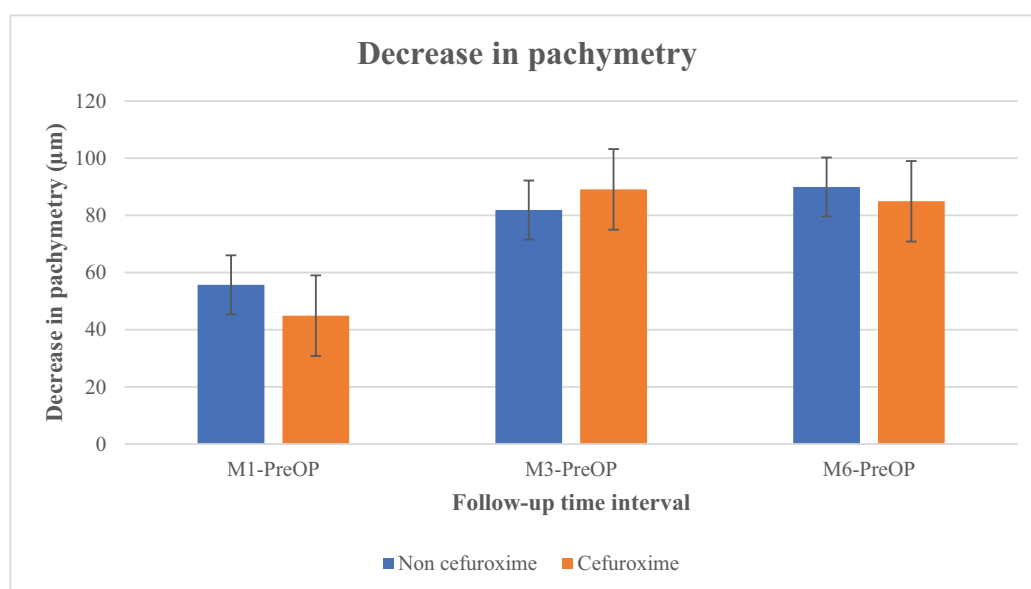


Figure 3. Decrease in pachymetry (μm) during follow-up time interval in cefuroxime and non-cefuroxime control groups. PreOP = preoperative measure, M1 = one month postoperative, M3 = three months postoperative, M6 = six months postoperative.

mm² versus 1661 ± 507 cells/mm² at 6 months ($p = .55$), in the cefuroxime and NC groups, respectively (Figure 4). Endothelial cell loss between both groups did not differ at follow-up time intervals: 33.4% versus 33.6% at 1 month ($p = .97$), 37.4% versus 34.9% at 3 months ($p = .68$) and 41.2% versus 37.3% at 6 months ($p = .42$) in the cefuroxime and control groups, respectively (Figure 5).

Complications

There was only one case of pupillary block in the NC group and none in the cefuroxime group. Rebubbling rates secondary to graft

detachment were slightly higher in the cefuroxime group (45.1%) than in the NC group (34.7%), but with no statistical relevance ($p = .31$). There was no statistically significant difference in cystoid macular edema incidence between both groups: 6.5% (2/31) in the cefuroxime group, versus 2.8% (2/72) in the NC group (odds ratio 2.39; 95% confidence interval 0.16–34.41; $p = .58$). Graft rejection occurred between the first and sixth month after surgery in 1 case in the cefuroxime group (3.2%) and 4 cases in the NC group (5.6%), with no statistically significant difference (odds ratio 0.57; 95% confidence interval 0.01–6.08; $p = 1$).

No cases of endophthalmitis were noted in either groups during follow-up.

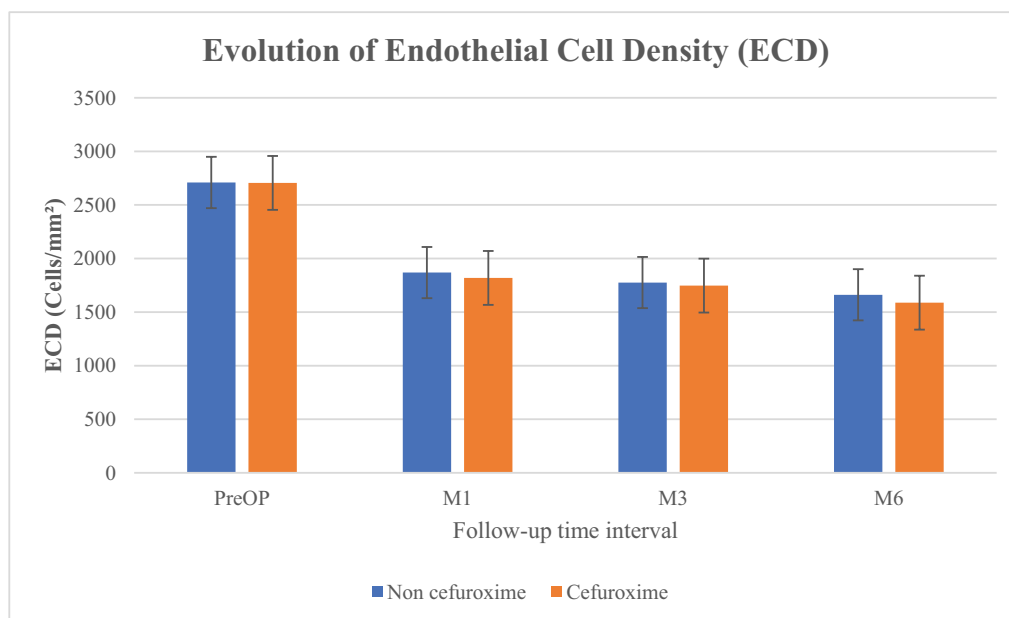


Figure 4. Evolution of endothelial cells density (ECD) (cells/mm²) during follow-up time interval in cefuroxime and non-cefuroxime control groups. PreOP = preoperative measure, M1 = one month postoperative, M3 = three months postoperative, M6 = six months postoperative.

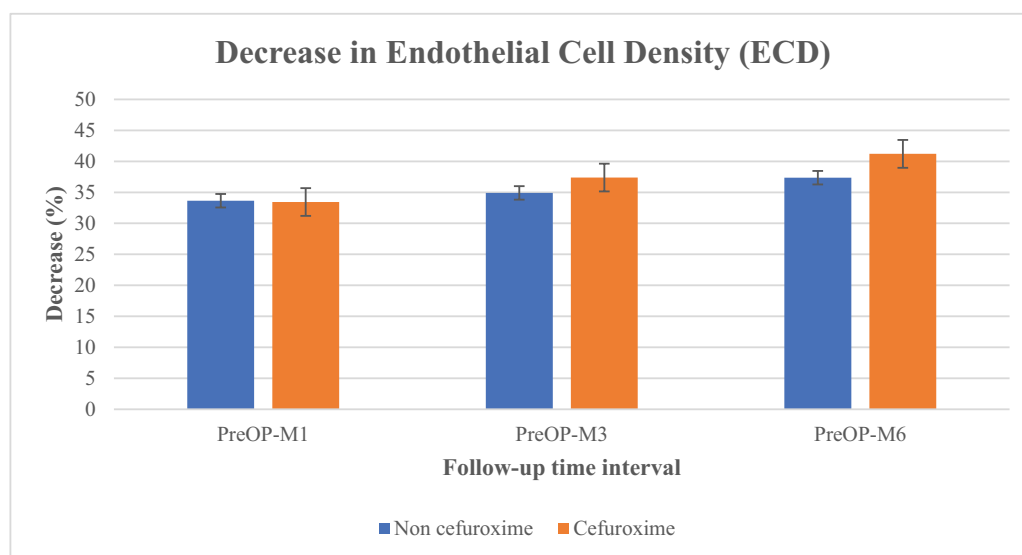


Figure 5. Decrease in the endothelial cell density (cells/mm³) during follow-up time interval in cefuroxime and non-cefuroxime control groups. PreOP = preoperative measure, M1 = one month postoperative, M3 = three months postoperative, M6 = six months postoperative.

Discussion

The main purpose of this study was to evaluate the safety of intracameral cefuroxime on graft survival after DMEK surgery, specifically its effect on endothelial cell density. In order to ensure a valid comparison between both groups, we compared patients who received an intracameral injection of cefuroxime at the end of surgery to twice as many patients who had not received intracameral cefuroxime (NC group), with the same surgical indications and a similar preoperative best-corrected visual acuity to avoid known and important confounding factors. All surgeons were highly experienced in DMEK procedure, and we did not include patients from the first 100 cases to avoid the learning curve effect for each surgeon. The same standardized “no touch” technique,

described by Dapena et al,¹⁴ was used by all surgeons and all patients received the same postoperative treatment.

Endophthalmitis is the most dreaded complication of all ocular surgeries. Surgeons strive to avoid it, especially in the case of cataract surgery. In a large meta-analysis regarding the antibiotic prevention of post-cataract endophthalmitis published in 2015, the pooled data showed that the incidence rate of endophthalmitis was 0.035% when intracameral antibiotics were used compared to 0.2% when intracameral antibiotics were not used.¹⁶ Furthermore, Daien et al. reported a decrease in the incidence of post-cataract endophthalmitis from 0.11 to 0.05% between 2010 and 2014, in a population-based study from France.¹⁷ This was attributed to an increase in the use of intracameral cefuroxime by cataract surgeons (from 11.1% in 2010 to 79.1% in 2014).

Endophthalmitis following endothelial keratoplasty may lead to poor visual outcomes as well as a higher risk of rejection or graft failure. More recently, Borkar et al. reported that endophthalmitis after keratoplasty developed at similar rates between eyes that received concurrent cataract extraction or lens manipulation procedures (0.4%) as compared to those without these procedures (0.4%) ($p > .99$).⁶ Although these rates appear low, there is limited evidence in the literature to guide the prophylaxis of endophthalmitis after simple DMEK or combined DMEK and cataract surgery.

Several studies in the past have evaluated the toxicity of intracameral cefuroxime to corneal endothelial cells after cataract surgery. According to Montan et al., intracameral cefuroxime did not have a statistically significant effect on postoperative visual acuity, induced laser flare intensity, or endothelial cell loss compared with non-administration of intracameral antibiotic prophylaxis.⁷ In another study by Delyfer et al., modifications in central corneal thickness and ECD in patients who received high doses of cefuroxime during cataract surgery were similar to those observed after uneventful phacoemulsification.⁹ However, the use of intracameral cefuroxime is not mentioned in previous studies regarding simple or combined DMEK surgery, and only one study reported the effect of intracameral ophthalmic cefuroxime solution (Aprokam)[®] in the prophylaxis of cataract surgery in patients with penetrating keratoplasty.¹⁸ To the best of our knowledge, this is the first comparative study regarding the effect of intracameral cefuroxime on graft survival, when used for endophthalmitis prophylaxis after DMEK surgery.

Visual and anatomical recovery were not negatively affected by the use of intracameral cefuroxime. In fact, visual outcomes and postoperative corneal thinning were never statistically different between the cefuroxime and NC groups during follow-up. At 6 months, mean BSCVA was comparable between both groups (Figure 1). It was also comparable to the mean BSCVA (0.11 ± 0.13 LogMAR) reported by Hamzaoglu et al. 6 months after DMEK.¹⁹ The mean BSCVA gain at 6 months was also equivalent: 0.35 ± 0.32 LogMAR for the cefuroxime group, and 0.36 ± 0.18 LogMAR for the NC group ($p = .88$). Mean postoperative pachymetry was similar between both groups at 1, 3, and 6 months after surgery ($p > .05$) (Figure 2). The decrease in corneal edema also followed the same trend in the cefuroxime and NC group at all follow-up time intervals when compared to preoperative values (Figure 3). Intracameral cefuroxime did not seem to slow visual and anatomical recovery following DMEK surgery.

The use of intracameral cefuroxime during DMEK surgery did not lead to a significantly higher endothelial cell loss. At 6 months, ECD showed a slightly higher decrease in the cefuroxime group than in the NC group, although not statistically significant (41.2% vs. 37.3%, $p = .37$) (Figure 5). Our findings are consistent with previous reports by Parker et al. (34% endothelial cell loss, $n = 186$),²⁰ and Tourtas et al. (41%, $n = 35$).²¹ The major limitation in our study, besides the retrospective fashion, is the relatively low number of subjects included in both groups, which may explain the non-significant difference in ECD decrease. ECD analyses in a larger sample would have probably yielded statistically significant results, and confirmed the similar ECD decrease between both groups. Furthermore, endophthalmitis rates may have been higher in a larger sample. In this study, there were no cases of endophthalmitis in either groups following DMEK surgery.

Therefore, it was not possible to ascertain the protective effect of intracameral cefuroxime against endophthalmitis. This was not however the main purpose of our study. We believe that future prospective, randomized comparative studies, using a proper control group injected with placebo, would further prove the efficacy of intracameral cefuroxime in preventing endophthalmitis, as well as its safety on graft survival following DMEK surgery.

Rebubbling rates were not significantly higher in the cefuroxime group than in the NC group and had no influence on postoperative ECD nor pachymetry. These rates are similar to those reported in the literature (range from 6 to 63%).^{19,22–24} In addition, there was no statistically relevant difference in graft rejection rates between both groups at 6 months after DMEK: 3.20% versus 5.55% for the cefuroxime and NC groups, respectively (odds ratio 0.57; 95% confidence interval 0.01–6.08; $p = 1$). However, these rates may be higher with a longer follow-up period.

We report a low incidence of cystoid macular edema (CME) after DMEK (6.45% in the cefuroxime group and 2.78% in the NC group). These rates are in fact lower than reported by Kocaba et al.²⁵ (13.8%, $n = 80$), Heinzelmann et al. (13%, $n = 158$),²⁶ and Hoerster et al. (12%, $n = 75$).²⁷ However, this may be due to the fact that macular Optical Coherence Tomography (OCT) was only performed when slow visual recovery did not seem to be linked to poor corneal deswelling. On the other hand, the incidence of CME did not seem to be significantly increased in the cefuroxime group compared to the NC group (odds ratio 2.39; 95% confidence interval 0.16–34.41; $p = .58$). When evaluating the safety of intracameral cefuroxime for the prevention of endophthalmitis after cataract surgery, Daien et al. reported that CME was not increased for patients receiving cefuroxime injections (odds ratio 0.86; 95% confidence interval 0.71–1.05).¹⁷ The higher incidence of CME in the cefuroxime group in our study was not statistically relevant. This may be due to the small sample size and should not be overestimated.

In conclusion, in this first comparative study regarding the effect of intracameral cefuroxime on graft survival after simple and combined DMEK, there was no evidence of higher graft endothelial cell loss in the cefuroxime group. Moreover, our findings suggest that the use of cefuroxime did not adversely affect the anatomical or visual outcomes following DMEK surgery.

Declaration of interest

The authors report no conflicts of interest.

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