Investigating the effect of intracameral cefuroxime on oxidative stress and apoptosis in the rat cornea

Investigando o efeito de cefuroxima intracameral sobre o estresse oxidativo e a apoptose na córnea de ratos

Ufuk Ozkan[1,2], Ali Akal[2,3], Kudret Ozkan[1,2], Omer Faruk Yilmaz[2,4], Fatih Mehmet Adıbelli[2]

1. Department of Ophthalmology, Sanliurfa Mehmet Akif Inan Training and Research Hospital, Sanliurfa, Turkey.
2. Department of Ophthalmology, Harran University School of Medicine, Sanliurfa, Turkey.
3. Department of Ophthalmology, Kayseri Training and Research Hospital, Kayseri, Turkey.
4. Department of Ophthalmology, Hendek State Hospital, Sakarya, Turkey.

ABSTRACT | Purpose: We examined the effect of intracameral administration of cefuroxime on oxidative stress and endothelial apoptosis in rat corneal tissue. **Methods:** In total, 30 rats were divided into 3 groups of 10 rats each (intracameral administration of cefuroxime 0.1 mg/0.01 mL (cefuroxime group); intracameral administration of balanced salt solution 0.01 mL (control group); or absence of intracameral injection (sham group). Corneal endothelial apoptosis was assessed by immunohistochemical analysis using caspase-3 and caspase-8. Total oxidant status, total antioxidant status, oxidative stress index, and paraoxonase and arylesterase levels were examined in corneal endothelial tissue and serum. **Results:** Paraoxonase levels in the serum were significantly different between the sham and cefuroxime groups (p=0.027). A significant difference was also observed in total oxidant status levels between the cefuroxime and balanced salt solution groups (p=0.023). In addition, there were significant differences in total antioxidant status levels in corneal tissue between the cefuroxime and sham groups (p<0.001) and between the cefuroxime and balanced salt solution groups (p<0.001). Furthermore, significant differences were also observed in oxidative stress index levels between the cefuroxime and balanced salt solution groups (p=0.001) and between the cefuroxime and sham groups (p=0.026). According to the immunohistochemical staining results, a significant association with caspase-3 activity existed between the cefuroxime and balanced salt solution groups (p=0.007), while no significant difference was found with caspase-8 activity (p=0.541). Caspase-3 activity exhibited a significant relationship between the sham and balanced salt solution groups (p=0.018), but no relationship was found with caspase-8 activity (p=0.623). **Conclusion:** Immunohistochemical examination revealed that intracameral cefuroxime increased apoptosis when compared to the sham and balanced salt solution groups. Moreover, intracameral cefuroxime increased oxidative stress in the cornea and simultaneously induced apoptosis.

Keywords: Apoptosis; Caspase-3; Caspase-8; Cefuroxime; Oxidative stress factors

RESUMO | Objetivo: Examinamos o efeito da administração intracameral da cefuroxima sobre o estresse oxidativo e a apoptose endotelial no tecido corneano de ratos. **Métodos:** No total, 30 ratos foram divididos em 3 grupos de 10 ratos cada (administração intracameral de cefuroxima 0,1 mg/0,01 mL (grupo cefuroxima), administração intracameral de solução salina balanceada 0,01 mL (grupo controle) ou ausência de injeção intracameral (grupo sham)). A apoptose endotelial da córnea foi avaliada por análise imuno-histoquimica usando caspase-3 e -8. O status oxidante total, o status antioxidante total, o índice de estresse oxidativo e os níveis de a paraoxonase e arilesterase foram investigados no tecido endotelial da córnea e no soro. **Resultados:** Os níveis de paraoxonase no soro foram significativamente diferentes entre os grupos sham e cefuroxima (p=0,027). Foi também observada uma diferença significativa nos níveis de estado oxidante total entre os grupos cefuroxima e solução salina balanceada (p=0,023). Além disso, houve diferenças significativas nos níveis de status antioxidante total no tecido da córnea entre os grupos cefuroxima e sham (p<0,001) e entre os grupos cefuroxima e solução salina balanceada (p<0,001). Diferenças significativas também foram observadas nos níveis do índice de estresse oxidativo entre os grupos cefuroxima e solução salina balanceada (p=0,001) e entre os grupos cefuroxima e sham (p=0,026). De acordo com os resultados

de coloração imuno-histoquímica, houve associação significativa com a atividade da caspase-3 entre os grupos cefuroxima e solução salina balanceada (p=0,007), enquanto não houve diferença significativa com a atividade da caspase-8 (p=0,541). A atividade da caspase-3 exibiu uma relação significativa entre os grupos sham e solução salina balanceada (p=0,018), mas nenhuma relação foi encontrada com a atividade da caspase-8 (p=0,623). **Conclusão:** O exame imuno-histoquímico revelou que a cefuroxima intracameral aumentou a apoptose quando comparada com os grupos sham e solução salina balanceada. Além disso, a cefuroxima intracameral aumentou o estresse oxidativo na córnea e induziu simultaneamente a apoptose.

Descritores: Apoptose; Caspase-3; Caspase-8; Cefuroxima; Fator de estresse oxidativo

INTRODUCTION

Cataract surgery is a commonly performed procedure. Endophthalmitis is an adverse complication of cataract surgery. The incidence of endophthalmitis is reported to be 0.1% for cataract surgery, 0.15% for trabeculectomy, 0.2% for keratoplasty, 0.3% for secondary intraocular lens implantation, 0.02% for decollement surgery, 0.15% for vitrectomy, and 0.03% for strabismus surgery[1]. To prevent the risk of endophthalmitis, various antibiotics are administered intravenously, intracamerally, and topically before, during, and after surgery. One antibiotic that is administered intracamerally at the end of surgery is cefuroxime[2-4].

Cefuroxime is a second-generation cephalosporin that is effective against the majority of gram-positive cocci seen in the conjunctiva and eyelashes (with the exception of enterococci and methicillin-resistant staphylococci). Cefuroxime is particularly effective against the gram-negative bacteria *Escherichia coli*, *Proteus*, and *Klebsiella* species[5].

Highly reactive metabolites, known as free radicals, damage essential cellular components, such as lipids, proteins, and DNA, as oxygen is used in the body[6]. Various defense mechanisms can eradicate these reactive metabolites and prevent injury[7]. Corneal endothelial cell damage may impair corneal endothelial cell density, cause corneal edema, and lead to vision loss. Measuring total oxidant and antioxidant status levels in the body is easier and more reliable compared to measuring large numbers of antioxidants and antioxidants individually[8]. Some ophthalmic preparations (e.g., moxifloxacin) are capable of increasing oxidative stress and causing cell damage[9,10]. Several clinical studies have been performed on intracameral injection of cefuroxime at the end of cataract surgery. In these studies, clinically used concentrations were safe and significantly decreased the incidence of endophthalmitis; conversely, higher concentrations may induce irreversible corneal endothelial cell death[11,12].

Despite its widespread use, no study in literature has investigated the effect of cefuroxime on oxidative stress and apoptosis. The purpose of the present study was to investigate the effect of cefuroxime on oxidative stress parameters and corneal endothelial cell morphology. Because we could not study human corneal tissue, we used rat corneal tissue in the present study.

METHODS

Establishment of the study groups

Thirty adult male Wistar albino rats weighing 180-240 g were used in this study. The rats were classified into 3 groups (cefuroxime, balanced salt solution [BSS], and sham) of 10 rats each. The animals were housed at room temperature in a 12 h day and 12 h night cycle in standard cages containing no more than 5 rats each. One rat from the BSS group died in its cage on the second day. Thus, the study was conducted with 10 rats in the cefuroxime group, 10 in the sham group, and 9 in the BSS group.

All experiments in the present study were performed according to the "Principles of Laboratory Animal Care" and approved by the Ethical Committee on Human and Animal Research at Dicle University, Diyarbakır, Turkey.

Surgical techniques and tissue preparation

Intracameral injection model

Sterile surgical instruments were used in the present study. A combination of ketamine and xylazine was prepared for anesthesia using a mixture of ketamine at 0.87 cc (87 mg/kg) (Ketalar, Pfizer Pharmaceuticals, Istanbul, Turkey, pH 4.4) and xylazine at 0.13 cc (13 mg/kg) (Rompun 2%, Bayer AG, Leverkusen, Germany, pH 5.5 ± 0.3). Anesthesia was induced with an intraperitoneal injection appropriately adjusted for body weight (approximately 0.33 cc).

Injections were performed under an OME-5000 Surgical Microscope (Olympus Optical Co., Ltd., Tokyo, Japan). The rats' eyes were immobilized using corneoscleral forceps, and the anterior chamber was entered tangential to the limbus using an insulin syringe (0.30 × 8 mm, 30 G × 16/5," Ayset Medical Products Industry Co., Adana, Turkey) at the 12 o'clock position. The cefuroxime group received cefuroxime (0.1 mg/0.01 mL)

(Seffur, Tüm Ekip Pharmaceuticals, Istanbul, Turkey), and the control group received BSS (0.01 mL) [Industrıa Farmaceutica Galenica Senese Materino d'Arbia (SI), Italy]. No procedure was performed on the sham group. Enucleation was performed under anesthesia 7 days after injection using corneoscleral scissors. Specimens were fixed in 10% formaldehyde for pathological examination (29 corneas), and biochemical specimens were placed into dry boxes (29 corneas). Finally, an abdominal incision was made, and blood samples (1.5 mL) were collected from the inferior vena cava. All rats were subsequently decapitated. Serum samples were separated from the cells by centrifugation for 10 minutes at 3000 rpm. Serum and tissue samples were stored at -70°C until measurement of TAS and TOS activity[9,13]. All samples were examined after 1 day; the same protocols used to evaluate the blood samples were used for tissue evaluation.

Total antioxidant status measurement

Total antioxidant status levels were measured using commercially available kits (Rel Assay Diagnostics Kit; RL0017, Mega Tip, Gaziantep, Turkey) following the Ozcan Erel method[14]. Hydroxyl radicals, the most potent biological radical, are produced using this method. In the assay, the ferrous ion solution present in Reagent 1 is mixed with hydrogen peroxide, which is present in Reagent 2. Sequentially produced radicals, including the brown-colored dianisidinyl radical cation produced by hydroxyl radicals, are also potent radicals. Using this method, the antioxidant effect in the sample is measured against these potent free radical reactions that are initiated by the hydroxyl radicals. The assay exhibited excellent precision values below 3%, and the results are expressed as nmol Trolox equiv/mg protein.

Total oxidant status measurement

Total oxidant status levels were measured using the previously described laboratory method by Ozcan Erel with commercially available kits (Rel Assay Diagnostics Kit; RL0024, Mega Tip)[15]. Briefly, oxidants in the sample oxidized the ferrous ion-o-dianisidine complex to ferric ion; this reaction was enhanced by glycerol molecules, which are abundantly present in the reaction medium. The ferric ion generated a xylenol orange-colored complex in an acidic medium. The color intensity, which was measured spectrophotometrically, correlated with the total amount of oxidant molecules in the sample. The assay was calibrated with hydrogen peroxide, and the results were expressed as micromolar hydrogen peroxide equivalent per liter (μmol H_2O_2 Eq/L).

Oxidative stress index calculation

The OSI was defined as the ratio of TOS to TAS levels[14]. For our calculations, TAS units were converted into mmol/L, and the OSI was calculated according to the following formula: OSI (arbitrary units) = TOS (μmol H_2O_2 Eq/L)/TAS (mmol Trolox Eq/L)[16]. Results were expressed in arbitrary units.

Paraoxonase enzyme activity measurement

The activity of PON, a HDL-cholesterol-associated lipophilic, hydrophobic, and antioxidant enzyme, was measured using commercially available kits (Rel Assay Diagnostics Kit; RL0031, Mega Tip). The PON enzyme paraoxon (*O,O*-diethyl-*O*-*p*-nitrophenyl phosphate) hydrolyzed the substrate, leading to the formation of a colored *p*-nitrophenol product. The absorbance of the resulting product was observed at 412 nm in kinetic mode and expressed as U/L[17].

Arylesterase activity measurement

Commercially available kits (Rel Assay Diagnostics Kit; RL0055 Mega Tip) were used to measure serum PON1 arylesterase (ARES) activity[18]. Serum ARES activity was determined by the presence of phenol following the reaction of phenyl acetate. The molar extinction coefficient of phenol was 4,000 $M^{-1}cm^{-1}$, and the results were expressed as kU/L.

Caspase-3 and caspase-8 staining

The corneal tissues were fixed with 10% formaldehyde. Next, 4-mm sections from paraffin blocks were stained with caspase-3 (cleaved; clone: N/A, catalog no. PP 229 AA, Biocare Medical) and caspase-8 (clone: C502S, catalog no. GTX59555, Gene Tex) using the traditional method. Tonsillar tissue was used as a control, and all specimens were examined under light microscopy (Olympus BX51TF Olympus Corp., Tokyo, Japan). Immunohistochemical staining was assessed semiqua ntitatively, with "0" indicating negative staining; "+," weak staining; "++," moderate staining; and "+++," intense staining[9,13].

Statistical analysis

Statistical analysis was performed using SPSS Statistics software, version 11.5 (SPSS Inc., Chicago, IL, USA). Results were expressed as median values (maximum-minimum). A non-parametric ANOVA test was conducted for statistical analysis, and inter-group comparisons were made using the Bonferroni correction. Caspase-3 and caspase-8 levels were compared between the

groups using the χ² test. P values <0.05 were considered statistically significant.

RESULTS

Findings related to oxidative stress

The TAS, TOS, OSI, PON, and ARES levels in blood samples and corneal tissues are presented in tables 1 and 2.

In serum specimens, no statistically significant difference was identified between the TAS, OSI, and ARES groups (Table 1). A significant difference was demonstrated in PON levels between the sham and cefuroxime groups (p=0.027). The difference in TOS levels between the cefuroxime and BSS groups was also significant (p=0.023).

In corneal tissue, no statistically significant difference was seen between the TOS, PON, and ARES groups (Table 2). TAS levels were significantly different between the cefuroxime and sham groups (p<0.001)

and between the cefuroxime and BSS groups (p<0.001) but not between the BSS and sham groups. OSI levels differed significantly between the cefuroxime and BSS groups (p=0.001) and between the cefuroxime and sham groups (p=0.026).

Apoptosis-related findings

According to the immunohistochemical staining results, upon examination of the corneal endothelium, the cefuroxime and BSS groups were significantly related in terms of caspase-3 levels (p=0.007), while no significant difference in caspase-8 activity was noted (p=0.541). No significant difference was found between the cefuroxime and sham groups in terms of caspase-3 (p=0.270) or caspase-8 (p=0.494) activity (Table 3, Figures 1-2). A significant relationship in terms of caspase-3 activity (p=0.018) was seen between the sham and BSS groups but there was no significant difference in terms of caspase-8 activity (p=0.623).

Table 1. Comparison of oxidative stress parameters in serum

Groups	Sham group (n=10)	BSS group (n=9)	Cefuroxime group (n=10)	*p value*
TAS (mmol Trolox equiv/L)	0.96 (0.83-1.08)	1.02 (0.86-1.17)	0.93 (0.77-1.11)	0.210
TOS (mmol H_2O_2 equiv/L)	22.24 (12.53-26.56)	25.19 (18.43-37.27)[c*]	16.94 (14.45-26.64)	0.026
OSI (arbitrary units)	2.31 (1.46-3.16)	2.53 (1.78-3.18)	2.03 (1.52-2.40)	0.070
PON (units/liter [U/L])	112.23 (70.63-144.50)[b*]	99.79 (76.46-108.22)	90.07 (76.92-110.81)	0.024
Arylesterase (ARES) [U/L]	136.50 (83.56-175.06)	120.41 (96.66-132.70)	115.45 (88.81-135.27)	0.132

TAS= Total antioxidant status; TOS= Total oxidant status; OSI= Oxidative stress index; PON= paraoxonase and arylesterase.
*P<0.050, **P<0.010, ***P<0.001.
a= significant difference between the sham and BSS groups; b= significant difference between the cefuroxime and sham groups; c= significant difference between the cefuroxime and BSS groups.

Table 2. Comparison of oxidative stress parameters in corneal tissue

Groups	Sham group (n=10)	BSS group (n=9)	Cefuroxime group (n=10)	*p value*
TAS (mmol Trolox equiv/L)	0.06 (0.05-0.10)[b***]	0.04 (0.02-0.16)[c***]	0.19 (0.12-0.47)	<0.001
TOS (mmol H_2O_2 equiv/L)	8.19 (7.05-10.25)	7.34 (5.92-10.19)	8.67 (6.56-10.86)	0.140
OSI (arbitrary units)	12.20 (7.19-15.73) [b*]	14.88(4.10-32.87) [c**]	4.13 (2.30-7.78)	0.001
PON (units/liter [U/L])	3.86 (2.01-5.61)	3.54 (0.57-6.26)	4.24 (1.86-7.76)	0.453
Arylesterase (ARES) [U/L]	5.24 (1.94-6.02)	2.81 (2.15-4.80)	3.08 (1.10-10.49)	0.397

TAS= Total antioxidant status; TOS= Total oxidant status; OSI= Oxidative stress index; PON= paraoxonase and arylesterase.
*P<0.050, **P<0.010, ***P<0.001.
a= significant difference between the sham and BSS groups; b= significant difference between the cefuroxime and sham groups; c= significant difference between the cefuroxime and BSS groups.

Table 3. Comparison of immunohistochemical results of caspase-3 and caspase-8

| Caspase-3	0	+	++	+++	Total	Caspase-8	0	+	++	+++	Total
Sham group	5	5	-	-	10		4	4	1	1	10
BSS group	6	-	3	-	9		2	3	3	1	9
Cefuroxime group	2	7	1	-	10		2	6	2	-	10

Negative staining, (+) Weak staining, (++) Moderate staining, (+++) Intense staining.

DISCUSSION

Prophylactic intracameral cefuroxime is used in intraocular surgery for endophthalmitis prophylaxis. The results of a large multicenter study performed by the European Society for Cataract and Refractive Surgery including 16,211 patients reported that the rate of endophthalmitis after cataract surgery decreased by 4.9-fold with the use of intracameral cefuroxime[19]. Another prospective study conducted in Spain involving 13,652 cataract patients indicated that intracameral cefuroxime effectively reduced the risk of postoperative endophthalmitis[20]. Reports of complications due to the use of cefuroxime led us to question its reliability. Therefore, we performed this experimental study to investigate the effects of cefuroxime on oxidative stress and apoptosis in the cornea and blood.

Postoperative intracameral antibiotic administration at the end of surgery allows high intraocular bioavailability and effective intraocular concentration[21]. Recently, cefuroxime has been used and recommended as an antibiotic[22]. Cefuroxime not only provides less gram positivity compared to vancomycin but also establishes gram-negative bacterial effectiveness. Cefuroxime is a time dependent, slow acting, and bactericidal antibiotic that is not effective against methicillin-resistant *Staphylococcus aureus*, *Pseudomonas*, and *Enterococcus*[5]. A study found that cefuroxime sodium (1 mg/0.1 mL) appeared to be effective in preventing endophthalmitis[21]. Another study reported a significant decrease in postoperative endophthalmitis using intracameral cefuroxime in addition to hemorrhagic retinal infarction due to an overdose of cefuroxime after complicated cataract surgery[23]. A study investigating corneal endothelial cell numbers, anterior chamber cell density, and the development of cystoid macular edema in 45 patients who were administered intracameral cefuroxime concluded that cefuroxime is a safe agent[24]. Other studies have reported no statistically significant difference in macular thickness and cystoid macular edema between groups that were administered intracameral cefuroxime after cataract surgery and control groups[25,26]. Another study reported that no histological changes were observed using electron microscopy in rabbit corneas after administering intracameral cefuroxime[27]. One study
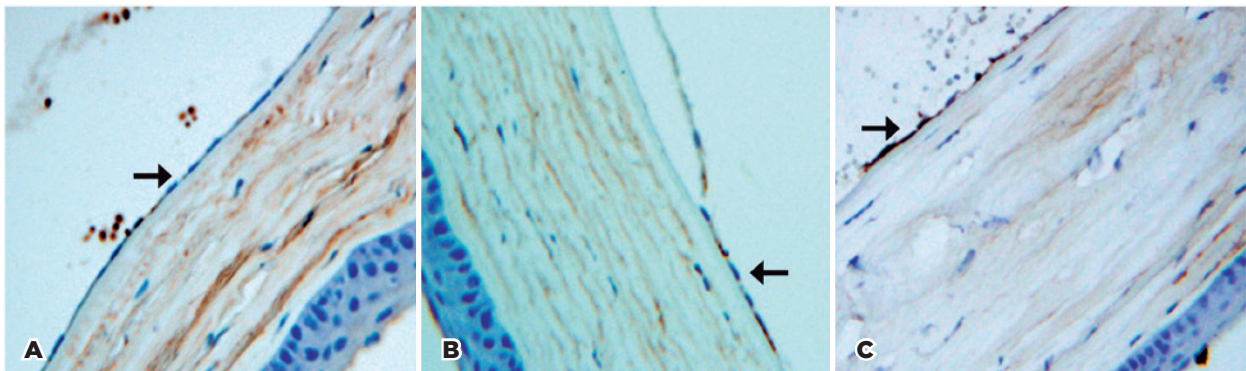
Figure 1. Immunohistochemical staining of corneal endothelial cells for caspase-3 (400×); negative (A), weak (B), moderate (C).
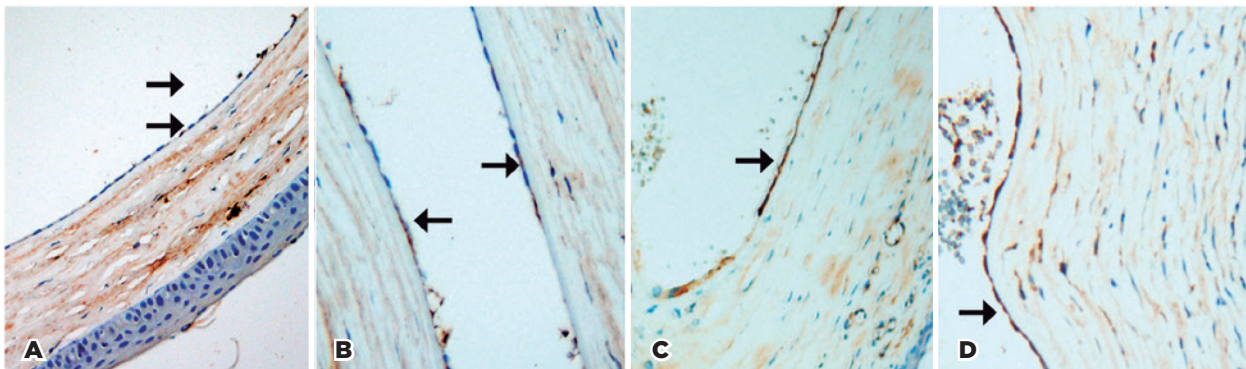
Figure 2. Immunohistochemical staining of corneal endothelial cells for caspase-8 (400×); negative (A), weak (B), moderate (C), intense (D).

found that intracameral injection of cefuroxime sodium (9 mg/0.1 mL) resulted in transient macular edema and diminished visual acuity in approximately 19% to 75% of exposed eyes, resolving largely within 1 week. The safe therapeutic concentration window is currently between 1 and 3 mg/0.1 mL[28].

In the present study, cefuroxime dosage was prepared with a sensitivity of 0.1 mg/0.01 mL. The dosage administered in the present study is the recommended concentration for endophthalmitis prophylaxis. High dosages may cause adverse effects. The dosage we used caused changes in the rat cornea but could not induce any changes in the human cornea because human and rat corneas are not the same. We believe that larger studies including more animals will be useful.

To the best of our knowledge, no previous study has investigated the effects of cefuroxime on corneal endothelial cells and oxidative stress in serum. One study reported that sunlight and atmospheric oxygen exposure to the cornea, due to its location and function, may increase oxidative stress levels, and oxidative stress may play a key role in the pathogenesis of keratoconus and Fuchs endothelial dystrophy[29]. They postulated that the use of intracameral cefuroxime during anterior segment surgery may be more toxic for corneal tissue in patients with corneal pathology and recommended the use of intracameral cefuroxime in such cases. In our study, intracameral cefuroxime in rats did not affect oxidative stress levels in serum but did increase oxidative stress in the cornea and induce apoptosis through caspase-3, suggesting that care must be used when administering cefuroxime.

Apoptosis is one of the primary types of programmed cell death. A study reported that L-carnitine can regulate the volume of human corneal cells under hyperosmotic stress and reduce hyperosmotic stress-associated apoptosis[30]. One study of porcine corneal endothelial cell cultures showed that mitomycin-induced cellular apoptosis is mediated by caspase-8 and caspase-9, emphasizing that this may occur through mitochondrial regulation and p53- and p21-dependent signal transduction pathways[31]. Another study using an *in vitro* model to test the direct effect of vitamin supplementation on lipid peroxidation and apoptosis in endothelial cells revealed a significant decrease in free radical injury in corneal endothelial cells with the use of antioxidant vitamins, which prevented lipid peroxidation and associated apoptosis[32]. One study compared the cytotoxic and apoptotic characteristics of cefuroxime and vancomycin in a human corneal endothelial culture[12]. The authors demonstrated dose-dependent toxicity and narrow safety margins, reporting that their use in higher concentrations led to irreversible cell death. They performed the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) test for cytotoxicity, and Annexin V binding combined with propidium iodide co-staining was used to identify viable, early, and late apoptotic cells. In the present study, we performed immunohistochemical staining of caspase-3 and caspase-8 and measured oxidative stress using the Ozcan Erel method. Another study reported that intracameral moxifloxacin administration in rats increased oxidative stress in the corneal endothelium and serum and induced apoptosis[9].

Although a significant difference in TOS was seen between the BSS and cefuroxime groups, the absence of a significant difference in terms of OSI suggests that TAS neutralizes the negative effects of TOS, implying that these drugs do not affect oxidative stress markers in serum.

A significant difference in TAS levels in the corneal tissue was found between the cefuroxime and sham groups, manifesting as increased oxidative stress in the cefuroxime group. A comparison of TAS levels between the cefuroxime and sham groups demonstrated an increase in oxidative stress with cefuroxime. A comparison of OSI values between the cefuroxime and sham groups showed that cefuroxime plays a role in enhancing oxidative stress.

While caspase-8 was relatively inactive in the cefuroxime and BSS groups, caspase-3 was activated and apoptosis was induced. Comparatively, no difference was seen in the BSS and sham groups in terms of caspase-8 activity, and no significant difference was noted in caspase-3 or caspase-8 levels between the cefuroxime and sham groups.

Though we were unable to fully explain the difference between caspase-3 and caspase-8, we believe this difference may be due to dosage error or injection technique. Larger studies exploring these differences will be useful.

In our study, intracameral administration of cefuroxime as a bactericidal increased oxidative stress in the cornea and induced apoptosis. However, we plan to use intracameral administration of cefuroxime for its protective effect against endophthalmitis in patients without corneal pathology by adjusting the dose appropriately.

Our work has some limitations. We should have used the Western blot with a higher specificity instead of immunohistochemical staining but this was not possible due to cost and lack of experience.

Other limitations of the present study include that this study was performed on a small number of experimental animals. The paracentesis procedure used to

inject BSS or cefuroxime into the anterior chamber induces uveitis in animals, including rabbits and rats, which is closely associated with oxidative stress. Using a control group of patients with paracentesis would have been more effective. Additionally, studies comparing cefuroxime and other preparations may also be useful in identifying molecules that are less toxic to the eye.

In the present study, we detected the oxidative stress-enhancing effect of intracameral cefuroxime in the corneal tissue and apoptosis induction in the corneal endothelium. No difference was demonstrated in terms of OSI in the sera of the experimental animals. Cefuroxime administered intracamerally for bactericidal purposes increases oxidative stress in the cornea and induces apoptosis.

Further studies are needed on the use of this drug in the eye involving larger numbers of animals and comparing this drug with other drugs.

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