• Review Article •

Systematic review of retinal toxicity after injection of cefuroxime during cataract surgery

Shan-Shan Wang[1,2], Bi-Jun Zhu[1], Jian-Nan Huang[3], Bao-Jiang Li[1], Ying-Yan Ma[1], Hai-Dong Zou[1,3]

[1]Department of Ophthalmology, Shanghai General Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200080, China
[2]Department of Ophthalmology, Shanghai Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200025, China
[3]Department of Ophthalmology, Shanghai Eye Disease Prevention and Treatment Center/Shanghai Eye Hospital, Shanghai 200040, China
Co-first Authors: Shan-Shan Wang and Bi-Jun Zhu
Correspondence to: Ying-Yan Ma and Bao-Jiang Li. Department of Ophthalmology, Shanghai General Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200080, China. mYy_29@163.com; Lee_727272@163.com
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Abstract

● This review is to elucidate the retinal toxicity following intraocular injections of cefuroxime, including possible risk factors, clinical manifestations, visual prognosis and treatment. Refereed publications were retrieved from PubMed, the Cochrane Library, and EMBASE databases, using the search terms cefuroxime, retina, macular edema, serous retinal detachment, toxic, cataract surgery. The screening was not limited by publication date, country or study type. We screened out 51 articles out of which 32 met the inclusion criteria for this systematic review. Data regarding sample size calculation reporting and trial characteristics were extracted for each trial. Retinal toxicity can be caused by both high and standard doses of cefuroxime injections in different ethnic groups, with risk factors including overdose, blood-retinal barrier disruption, anterior and posterior chamber connection. The typical clinical manifestations of retinal toxicity are cystoid macular edema and extensive serous retinal detachment, mainly involving the outer nuclear and outer plexiform layers, with a good prognosis for visual acuity in most cases, but in a small number of cases, the prognosis is not satisfactory. In conclusion, though the current use of intracameral injection antibiotics in cataract surgery is gradually increasing, the potential risks should not be ignored. Unexplained poor vision on the first day after cataract surgery can be supplemented with macular optical coherence tomography to rule out cefuroxime-related retinal toxicity.

● **KEYWORDS:** cefuroxime; retinal toxicity; cataract surgery; risk factors

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INTRODUCTION

Although the incidence of post-cataract endophthalmitis is low, when it occurs, it can be fatal to vision and therefore the prevention is important[1-3]. Of all the antibiotic prophylaxis methods for endophthalmitis currently in use, intracameral injection is supported by the most evidence. Current antibiotics commonly used for intracameral injections include cefuroxime, vancomycin, and moxifloxacin, with cefuroxime having the highest usage rate[4], which is commercially available in many European countries (Aprokam, Thea, UK). In 2007, the Society of Cataract and Refractive Surgeons (ESCRS) initiated a multicenter, multinational randomized controlled trial (RCT) study, which confirmed that intra-anterior chamber infusion of cefuroxime was effective in reducing the incidence of post-cataract endophthalmitis by approximately 5 folds, and its use has been increasing over the years[5]. Intracameral injection of cefuroxime in cataract surgery has been reported as high as 78% in Australia and up to approximately 50% in the United States, with high rates of use in the rest of the world as a currently popular means of prevention[6]. However, although intracameral injection of antibiotics has a preventive effect on the occurrence of postoperative endophthalmitis, injection of antibiotics may also be toxic to human eye, which is a double-edged sword[7]. For example, hemorrhagic occlusive retinal vasculitis is a serious side-effect of vancomycin injection[8].
Cefuroxime is a second-generation cephalosporin antibiotic that binds covalently to transpeptidases and carboxylases in bacteria through covalent bonds, thereby cleaving the bacteria

and inhibiting the synthesis of proteins in the bacterial cell wall, and is effective against most Gram-positive and negative cocci, as well as Gram-negative bacilli and anaerobes, with a broad antibacterial spectrum[9]. Among them, *Staphylococcus epidermidis* and *Staphylococcus aureus* are the most common causative agents of endophthalmitis, so cefuroxime is effective for endophthalmitis prevention and treatment which is also the most cost-effective[10]. The main routes of intraocular use of cefuroxime include intracameral and subconjunctival injections, with a standard dose of 1 mg/0.1 mL in the anterior chamber and 0.5 mL in the conjunctival sac, 62.5–125 mg/mL[4]. In one study, regression analyses showed that intracameral infections were associated with a lower risk for endophthalmitis than subconjunctival injections of cefuroxime, suggesting that intracameral injection is more effective in prevention[11].

Few studies have demonstrated intraocular toxicity of cefuroxime, and most occur at unexpectedly high doses, which can involve both anterior and posterior segments, including concomitant fibrin formation, corneal edema, increased intraocular pressure, and retinal toxicity[12]. The retinal toxicity after cefuroxime injection has been reported in recent years, causing severe visual loss after cataract surgery, and although most patients have recovered vision, some patients who have been given overdosed cefuroxime still have a poor prognosis. For example, Qureshi and Clark[13] reported a patient who was given 62.5 mg of cefuroxime in the intracameral and recovered vision to only 4/40 two months after surgery, with white sclerotic vessels observed in the macula. The current reports of retinal toxicity are all disseminated case reports or series of case reports. Therefore, the incidence of retinal toxicity, susceptibility factors and populations, and factors associated with poor prognosis are unknown. In this study, we propose to answer the above questions and to systematically summarize the clinical manifestations, prognosis, and mechanisms of cefuroxime retinal toxicity through a systematic review that summarizes previously reported cases to provide clinicians with evidence for diagnosis, prevention and treatment.

MATERIALS AND METHODS

Search Strategy and Study Selection Retrieved from PubMed, the Cochrane Library, and EMBASE databases for refereed publications, with the search terms cefuroxime, retina, macular edema, serous retinal detachment, toxic, cataract surgery, regardless of publication date, country and study type. A manual search was performed by checking the reference lists of original reports and review articles to identify studies not yet included in the computerized databases. Each article was independently reviewed by two reviewers. The titles and abstracts (if available) were screened. Full-text copies were obtained for all potentially relevant articles and reviewed for inclusion and data collection. Disagreements in selection were reconciled by a separate reviewer. Language interpreters assisted in reviewing non-English articles. References in full-text articles were screened for relevance and added if they met inclusion criteria. The final search was performed on August 18th, 2023.

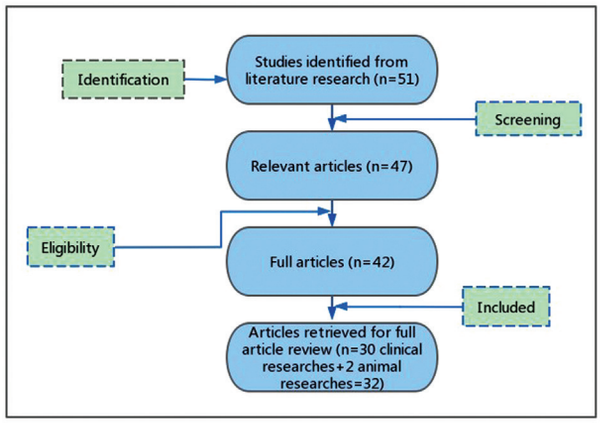

Figure 1 Flow chart of study selection Screening identified 51 articles out of which 32 met the inclusion criteria for this systematic review.

Inclusion and Exclusion Criteria An article is considered eligible for inclusion if the study meets the following inclusion criteria. 1) Case report of retinopathy after intracameral injection of cefuroxime during cataract surgery, including a commercial preparation, such as Aprokam, or a compounded solution. 2) Large retrospective, prospective or randomized study. 3) Animal studies exploring the retinal toxicity of cefuroxime.

Conference abstracts, reviews, full text without searchable raw data, duplicate publications and review articles were excluded.

Figure 1 showed the flow diagram of study selection for retinal toxicity of intracameral cefuroxime during cataract surgery. Electronic literature searches as of 1 March 2023 identified 51 potentially relevant titles and abstracts for this review. After duplicate independent abstract review, 42 records were assessed at the full text level, of which 10 were excluded in the review. There are 32 articles selected, including 30 clinical researches and 2 animal researches.

Data Extraction Data were extracted independently by two reviewers, and disagreements were resolved through discussion. Information extracted from each study included the authors of each study, country, year of reporting, follow-up period, study design information, number of subjects, epidemiology, susceptibility factors, clinical presentation, ancillary tests, treatment modalities, and prognosis.

RESULTS

Baisic Charateristics of Reported Cases Table 1 showed the studies that reported retinal toxicity after intracameral use of cefuroxime during cataract surgery and studies about macular thickness after cataract surgery with intracameral

Table 1 Studies of retinal toxicity after intracameral or sunconjunctival use of cefuroxime during cataract surgery

Study	Time	Study type	Country	Events	Total	Age	Male	Dose
Montan[14]	2002	Cohort	Switzerland	0	45	-	-	1 mg/0.1 mL
Gupta[15]	2005	RCT	UK	0	23	-	-	1 mg/0.1 mL
Cochereau[16]	2009	Cohort	France	0	256	73.3; 73.9		1 mg/0.1 mL
Lam[17]	2010	Cohort	China	0	34	73.9±7.4	-	1 mg/0.1 mL
Longo[18]	2015	Case series	Italy	5	5	60	3	1 mg/0.1 mL
Xiao[19]	2015	Case	China	2	2	68; 63	1	1 mg/0.1 mL
Aslankurt[20]	2016	Case	Türkiye	8	8	-	-	1 mg/0.1 mL
Daien[21]	2016	Cohort	France	410	46292	73.9	41.1%	1 mg/0.1 mL
Giménez-de-la-Linde[22]	2017	Cohort	Spain	0	221			1 mg/0.1 mL
Ma[23]	2017	Case series	China	0	22	76.4±4.0	8	1 mg/0.1 mL
Andreev[24]	2018	Case	Russia	1	1	-	-	1 mg/0.1 mL
Besozzi[25]	2018	Cohort	Italy	0	152	-	-	1 mg/0.1 mL
Chlasta-Twardzik[27]	2020	Case	Poland	1	1	46	1	1 mg/0.1 mL
Bryan[26]	2021	Case report	USA	1	1	63	0	1 mg/0.1 mL
Davila[28]	2021	Case report	USA	3	3	71.3	3	1 mg/0.1 mL
Spackman[30]	2022	Case	UK	1	1	80	1	1 mg/0.1 mL
Sun[29]	2023	Retrospectively	China	25	92	55.35±12.32	44	1 mg/0.1 mL
Buyukyildiz[31]	2010	Case	Türkiye	2	2	60; 56	1	2 mg/0.1 mL
Sakarya[32]	2010	Case	Japan	0	6	68.33	4	3 mg/0.1 mL
Wong[33]	2015	Cohort	USA	6	13	-	-	9 mg/0.1mL
Herrinton[34]	2016	Cohort	USA	13	63241	-	-	9 mg/0.1 mL
Faure[35]	2015	Case	France	1	1	64	1	10.0 mg/mL
Kamal-Salah[36]	2019	Case series	France	8	19	70.5	4	12.5 and 10 mg/0.1 mL
Delyfer[37]	2011	Case series	France	6	6	76	2	40.0-50.0 mg/0.1 mL
Olavi[38]	2012	Case	Greece	16	16	-	-	50 mg/0.1 mL
Qureshi[13]	2011	Case	UK	1	1	70	0	Approximately 62.5 mg
Kontos[39]	2014	Case	UK	1	1	61	0	62.5 mg/mL (subconjunctival)
Çiftçi[40]	2014	Case	Türkiye	4	4	80; 70; 60; 75	4	50-70 mg/mL
Le Dû[41]	2014	Case series	France	6	6	-	-	Suspected overdose
Zuo[42]	2018	Case series	China	20	20	64.20±9.34	7	Properly compounded

Event: Number of cases of retinal toxicity; Total: Total number of cases; Male: Number of males out of the total number; Dose: Cefuroxime injection dosage.

cefuroxime[13-42]. They were published over a 20-year period from 2002 to 2023, with a predominance of case reports and series of case reports from countries in Asia, Europe, and North America, indicating that different ethnic groups can be affected. Patients ranged in age from 43 to 80y, and both genders were affected.

Possible Risk Factors for Retinal Toxicity after Cefuroxime Injections

Dosage Retinal toxicity has been reported both in overdose and normal dose injections, with the vast majority occurring at high dose injections (approximately 2-50 times the regular dose), suggesting that overdose injection of cefuroxime is the most important risk factor of retinal toxicity. For example, in a study by Wong *et al*[33], macular edema and vision loss occurred in 6 of 13 (6/13, 46.2%) patients after intraoperative intracameral injection of cefuroxime at an excessive dose (approximately 9 mg/0.1 mL) during cataract surgery, and Delyfer *et al*[37] reported 6 cases of macular edema after intraoperative intracameral injection of cefuroxime at 40.0-50.0 mg/0.1 mL in all 6 cases (6/6, 100%). Qureshi and Clark[13] reported a case of severe visual loss after an injection of approximately 62.5 mg cefuroxime.

However, there are a few reports of normal dose injections, such as seven domestic and international studies that reported retinal toxic reactions at normal doses (1 mg/0.1 mL). This suggests that cefuroxime injection at normal doses still cannot exclude the possibility of complications. For example, Zuo *et al*[42] reported 20 cases of macular edema and serous retinal detachment after standard-dose cefuroxime injection, and incomplete posterior vitreous detachment was visible in the fundus of two patients. Xiao *et al*[19] also reported 2 cases of macular edema with serous retinal detachment after standard-

dose injection, and both recovered to 20/20 visual acuity after 1wk. In 2021, Bryan *et al*[26] reported a case of acute macular edema with serous retinal detachment in a patient after vitrectomy who received a standard-dose cefuroxime injection and recovered at 2wk of follow-up.

Other risk factors In a case series article published in *Ophthalmic Surg Lasers Imaging Retina* in 2021[28], the authors summarized cases of retinopathy that occurred after intracameral cefuroxime injection and concluded that risk factors were unstable ligaments and surgical history, including history of vitrectomy, suspensory ligament abnormalities, posterior capsule rupture, and second-stage lens implantation, *etc*., but there is a lack of relevant supporting literature and evidence. In addition to intracameral injection of cefuroxime, vancomycin has also been used to prevent endophthalmitis. The relevant literature[43-45] showed that risk factors for retinal toxicity from vancomycin include overdose, blood-retinal barrier disruption, vitreous surgery, history of previous vancomycin use, and prolonged duration of surgery, which can serve as references for subsequent studies on susceptibility factors for cefuroxime retinal toxicity.

Another three publications studied retinal toxicity of intraoperative intracameral injections of cefuroxime in cataracts in patients with a history of vitrectomy, one of which[29] reported macular edema and serous retinal detachment in 25 of 92 post-vitrectomy patients after intraoperative cefuroxime injections, suggesting that anterior and posterior chamber connection (history of vitrectomy) may be a susceptible factor for the development of retinal toxicity. Two other studies were reported in the literature, one[26] was a case report of one post-vitrectomy patient who developed macular edema and serous retinal detachment at a low dose of injection and recovered after two weeks, and the other study[27] of 152 post-vitrectomy patients in which no retinal complications were found. The injection dose was 1 mg/0.1 mL and the follow-up time was 6.26±7.78mo, although only 48 eyes (32%) in this study underwent postoperative optical coherence tomography (OCT). In the study of Daien *et al*[21], after adjustment for multiple factors, the risk of cystoid macular edema was lower in patients younger than 75 years of age than in patients 75 years of age or older. Cystoid macular edema was associated with a vitrectomy for a perioperative capsular rupture and male sex.

Clinical Manifestations and Auxiliary Examination Results of Cefuroxime Retinal Toxicity

Tables 2 and 3 presented the data on visual acuity, time to recovery (approximately 1wk) and recovered visual acuity, OCT performance. The data of interest were visual prognosis, OCT performance, electrophysiology, and fundus fluorescein angiography (FFA) performance. Since most of the retinal toxicity reported in the literature presents with typical cystoid macular edema and extensive serous retinal detachment, and a small number of the literature reports different manifestations of retinal toxicity, we have summarized the typical and atypical manifestations of retinal toxicity, respectively.

Typical retinal toxicity of cefuroxime

1) Main complaint Patients complained vison loss and central scotoma[27] on the first day after the operation. In addition, in the study of Kamal-Salah *et al*[36], one patient presented with chromatic abnormalities in the first week postoperative. Color vision abnormalities were also mentioned in the case report of Davila *et al*[28], but were not described in detail.

2) Visual prognosis In the current report of the occurrence of retinal toxicity, the visual acuity on the first postoperative day is probably between hand move (HM) and 0.5, with most visual acuity between 0.05 and 0.1. Recovery to approximately 0.1 to 1.0 is possible one week after surgery. Although most patients recover their vision at the end of the follow-up, some patients who have been given overdosed cefuroxime still have a poor prognosis. Few studies reported poor vision prognosis in patients with high-dose injections. For example, in Zuo *et al*'s[42] study, one patient had a prognosis of only 0.4 visual acuity at the one-week postoperative follow-up, despite cystoid macular edema had spontaneously improved, with a discontinuity in the ellipsoid band visible on OCT. This patient had no preoperative history of fundus lesions or surgery. Also, in Kamal-Salah *et al*'s study[36], six of the patients who were injected with 10-12.5 mg/0.1 mL in the anterior chamber, had visual acuity of only 20/40 to 20/200 at the 12-week follow-up postoperatively, with temporary or permanent impairment of the ellipsoid layer.

3) Optical Coherence Tomography The typical presentation of OCT is cystoid macular edema and extensive serous retinal detachment, mainly involving the outer nuclear and outer plexiform layers. The prognosis of OCT presentation is equally good.

In Xiao *et al*[19] reported two patients with macular thickness of 750 μm and 794 μm on the first postoperative day, respectively, with a follow-up of 3mo and a final macular thickness of 194 and 174 μm, involving mainly the outer plexiform layer, with retinal detachment pattern showing extensive and superficial serous retinal detachment surrounding the macular area and optic disc area. Delyfer *et al*[37] reported after intraoperative intracameral injection of 40.0-50.0 mg/0.1 mL in 6 patients with cataract, OCT showed a macular thickness of 843.2±212.7 μm on the first postoperative day, which recovered to 288.4±22.6 μm after 6wk. In 5 of these cases, diffuse leakage was seen in the FFA, but no retinal perfusion abnormalities were seen, and the area involved was also in the outer nuclear layer, and the detachment pattern was extensive. In Buyukyildiz *et al*[31],

Table 2 The data on visual acuity, follow-up time, time to recovery and visual prognosis

Study	Dose	Day 1 vision acuity (post-operation)	Recovery time	Follow up time	Visual prognosis
Montan[14]	1 mg/0.1 mL	-	-	3mo	20/30 or better
Gupta[15]	1 mg/0.1 mL	-	-	4 to 6wk	6/9 or better
Cochereau[16]	1 mg/0.1 mL	-	-	-	-
Lam[17]	1 mg/0.1 mL	-	-	3mo	Around 0.32
Longo[18]	1 mg/0.1 mL	1.0[a]	7d	30d	0
Xiao[19]	1 mg/0.1 mL	20/200; finger count	1wk	3mo	20/20; 20/20
Aslankurt[20]	1 mg/0.1 mL	2.5/10	1wk	-	-
Daien[21]	1 mg/0.1 mL	-	-	-	-
Giménez-de-la-Linde[22]	1 mg/0.1 mL	-	-	-	-
Ma[23]	1 mg/0.1 mL	-	-	-	0.13±0.09[a]
Andreev[24]	1 mg/0.1 mL	0.2	6d	-	20/20
Besozzi[25]	1 mg/0.1 mL	-	-	6.26±7.78mo	-
Chlasta-Twardzik[27]	1 mg/0.1 mL	0.02	10d	24mo	20/20
Bryan[26]	1 mg/0.1 mL	20/400	2wk	6wk	20/30
Davila[28]	1 mg/0.1 mL	20/200; 20/40; 20/100	-	1mo	20/30; 20/60; 20/70
Spackman[30]	1 mg/0.1 mL	-	-	3wk	Well
Sun[29]	1 mg/0.1 mL	0.91±0.39[a]	1wk	1wk	0.31±0.29[a]
Buyukyildiz[31]	2 mg/0.1 mL	20/400; 20/400	1wk; 3mo	6mo; 3mo	20/20; 20/25
Sakarya[32]	3 mg/0.1 mL	-	-	6mo	20/20
Wong[33]	9 mg/0.1mL	0.74[a]	5.2d	1mo	20/30 or better
Herrinton[34]	9 mg/0.1 mL	-	-	-	-
Faure[35]	10.0 mg/mL	20/100	1w	2mo	20/20
Kamal-Salah[36]	12.5 and 10 mg/0.1 mL	-	-	12wk	Permanent damage
Delyfer[37]	40.0-50.0 mg/0.1 mL	0.95±0.40[a]	-	1, 5d, 6wk	0.09±0.06[a]
Olavi[38]	50 mg/0.1 mL	-	-	-	Finger count/2 m to 1.0
Qureshi[13]	Approximately 62.5 mg	4/60	2mo	2mo	4/40
Kontos[39]	62.5 mg/mL (subconjunctival)	6/60+1	6d	6wk	6/9.5
Çiftçi[40]	50-70 mg/mL	Light perception; hand move; hand move; hand move	-	-	
Le Dû[41]	Suspected overdose	-	-	-	
Zuo[42]	Properly compounded	0.78±0.31[a]	1wk	1wk	0.13±0.80[a]

[a]Visual acuity expressed in logMAR.

two patients with macular thickness of 909 and 559 μm on the first postoperative day were followed up for 6mo and 3mo, respectively, with final macular thickness of 205 and 208 μm. In Sun *et al*[29], 25 patients with macular thickness of 716.00±126.97 μm, which recovered to 218.76±36.31 μm after 1wk of follow-up, with OCT morphology showing high edema in the outer nuclear layer and subretinal fluid accumulation in the macula, partially accompanied by serous retinal detachment of the neuroepithelial layer in the posterior pole. In the study of Aslankurt *et al*[20], the mean thickness change from postoperative 1d to 1wk postoperatively was 544.5 to 246.5 μm in 8 patients, and in that article, although a standard measure of cefuroxime was injected intraoperatively, this may have contributed to retinal toxicity because the operator used cefuroxime solution instead of salt solution to water-tighten the wound.

In contrast, unlike the previous study, in the study by Wong *et al*[33] it was shown that the OCT morphology showed severe thickening of the outer plexiform layer and severe and extensive subretinal thickening. In addition, it has been shown that an increase in OCT thickness can be seen after cefuroxime injection despite the absence of clinical manifestations. In the study by Lam *et al*[17] a mean increase in macular retinal thickness of 4.6% was found after intraoperative cefuroxime injection without clinical manifestations, and the level of thickening was not described in this literature. However, no statistical difference in retinal thickness between the cefuroxime injection and balanced salt solution injection groups was reported in the study by Gupta *et al*[15].

4) Electrophysiology Electrophysiological manifestations were seen in retinal photoreceptor damage. In the study of Delyfer *et al*[37], a decrease in dark adaptation electrophysiological b-wave was seen 6wk after high-dose injection, indicating reduced optic rod cell function. In the study of Olavi[38], a decrease

Table 3 The data on OCT performance, FFA, electrophysiology, as described in the literature

Study	Dose	CMT D1	Final CMT	Layer
Montan[14]	1 mg/0.1 mL			
Gupta[15]	1 mg/0.1 mL	-	249±44	
Cochereau[16]	1 mg/0.1 mL			
Lam[17]	1 mg/0.1 mL	-	178.7±51.5	
Longo[18]	1 mg/0.1 mL	857	192	OL
Xiao[19]	1 mg/0.1 mL	750; 794	194; 174	ONL
Aslankurt[20]	1 mg/0.1 mL	544.5	246.5	
Daien[21]	1 mg/0.1 mL			
Giménez-de-la-Linde[22]	1 mg/0.1 mL			
Ma[23]	1 mg/0.1 mL	249.57±22.13 (1wk)	260.86±20.48	
Andreev[24]	1 mg/0.1 mL			
Besozzi[25]	1 mg/0.1 mL			
Chlasta-Twardzik[27]	1 mg/0.1 mL	697		ONL
Bryan[26]	1 mg/0.1 mL	567	384	ONL
Davila[28]	1 mg/0.1 mL			
Spackman[30]	1 mg/0.1 mL			
Sun[29]	1 mg/0.1 mL	716.00±126.97	218.76±36.31	ONL
Buyukyildiz[31]	2 mg/0.1 mL	909; 559	205; 208	
Sakarya[32]	3 mg/0.1 mL			
Wong[33]	9 mg/0.1mL	891	252	OPL
Herrinton[34]	9 mg/0.1 mL			
Faure[35]	10.0 mg/mL			ONL
Kamal-Salah[36]	12.5 and 10 mg/0.1 mL	231.625	232.25	
Delyfer[37]	40.0-50.0 mg/0.1 mL	843.2±212.7	288.4±22.6	ONL
Olavi[38]	50 mg/0.1 mL			
Kontos[39]	62.5 mg/mL (subconjunctival)			
Le Dû[41]	Suspected overdose			
Zuo[42]	Properly compounded	240.30±68.47	167.90±29.96	ONL
Atypical retinal toxicity of cefuroxime				
Qureshi[13]	Approximately 62.5 mg		274 (6wk)	
Çiftçi[40]	50-70 mg/mL			

CMT D1: Central macular thickness on the first postoperative day; Final CMT: Central macular thickness finally; OPL: Outer plexiform layer; ONL: Outer nuclear layer; OL: Outer layer.

in dark adaptation a- and b-wave was seen after high-dose injection. In the study of Faure *et al*[35], a mild decrease in both electroretinogram a- and b-waves was seen in patients with a mild delay in the flicker signal. In rabbit experiments[46], an electrophysiological study showed no functional impairment in the low dose group (1 mg/mL) but overall retinal dysfunction in the high dose group (10 mg/0.1 mL). Electrophysiology response is characterized by an electronegative pattern. And electrophysiology improvement begins with normalization of the b/a ratio. However, there is still a lack of research evidence for the long-term prognosis of electrophysiology.

5) Fundus angiography The typical presentation of FFA is diffuse leakage without abnormal perfusion, with petal-like fluorescence accumulation seen in late stages. Kontos *et al*[39] found mild patchy choroidal filling and no evidence of underlying neovascular membrane or vasculitis. There was no early leakage from macular capillaries or late disc leakage. Another study conducted by Buyukyildiz *et al*[31] indicated that fluorescein angiograph view at 8min on postoperative day 1. No abnormal angiographic finding is seen, although there is intraretinal fluid accumulation and neurosensorial retinal elevation. Delyfer *et al*[37] found diffuse leakage without abnormal retinal perfusion in cefuroxime toxic eyes which indicated that the blood-retinal barrier at the retinal pigment epithelium (RPE) may be disrupted. No retinal or choroidal hyperpermeability was found in the study of Faure *et al*[35]. Sun *et al*[29] showed multiple fluorescein leakage in the middle stage and petal-like fluorescein accumulation in the macula in the later stage. In the study of Chlasta-Twardzik *et al*[27], on early phase a non-fluorescent zone was visible adjacent to the optic

disc. Outside it was surrounded by an irregularly fluorescent band. In late phase a diffusing fluorescein from the periphery of the non-fluorescent zone was reaching the disk. Numerous, diffuse, non-fluorescent spots corresponding to RPE formation within and in the borders of peripapillary atrophy were noted. The hyperfluorescent spot of the approximate size of 400-500 μm located parafoveally in the upper nasal region of the macula was visible from early phases and presented diffuse borders in late phases. Foveal avascular zone did not reveal noticeable changes. Indocyanine green angiography was performed in one patient. The Indocyanine green angiography angiogram with early, intermediate, and late phases did not show choroidal perfusion abnormalities[37].

Microfield data were introduced in the study of Ma *et al*[23], and no significant changes in microfield were seen.

Atypical retinal toxicity of cefuroxime Retinal toxicity of cefuroxime overdose may also manifest as retinal hemorrhage, retinal infarction, and optic nerve atrophy. In a case report published by Çiftçi *et al*[40], after an intraoperative overdose of 50-70 mg/mL of cefuroxime in four patients, one patient developed central and inferior retinal hemorrhage and optic nerve atrophy. One patient developed peripapillary and macular hemorrhage, as well as optic nerve atrophy. One patient had peripapillary and inferior retinal hemorrhage and macular folds attributable to retinal fibrovascular formation. One patient had peripapillary, macular, and inferior retinal hemorrhage. The patients complained of lack of vision, they could only perceive hand motion. The authors suggested that the greater presence of lesions in the central and inferior retina may be related to differences in drug concentration due to the patient's head position.

Also, Qureshi and Clark[13] reported in 2011 that a 70-year-old patient was injected with a dose of approximately 62.5 mg of cefuroxime, and two weeks after surgery, developed macular infarction with macular edema, and after receiving 4.0 mg of intravitreal tretinoin, visual acuity failed to improve, with a final small-aperture visual acuity of 3/60.

Treatment of Retinal Toxicity The prognosis of retinal toxic reactions caused by intracameral injection of cefuroxime is good, and observation is the mainstay of clinical practice. Other treatments include drops of prednisolone acetate 1% *quater in die* (QID), ketorolac 0.5% QID, moxifloxacin QID, dexamethasone 0.1% *quaque die* (QD), neomycin 0.35% QD, polymyxin B 6000 U/mL QD, acetazolamide 500 mg *bis in die* (BID), vitreous intravitreal tretinoin 4.0 mg/0.1 mL, *etc*., but there is no evidence that the recovery time from drug treatment is shorter than that observed clinically[13,19,24,26-28,30-31,39].

Delyfer *et al*[37] explored the need for intracameral flushing or vitrectomy to improve patient prognosis. Regarding the need for intracameral flushing, according to previous studies, the median intracameral level of cefuroxime was 2742 mg/L for 30s and 756 mg/L for 60min after drug instillation[14]. Concentrations thus declined by a factor of 4 in 1h, and thus there is no significant benefit from intracameral flushing 24h after surgery. Regarding the need for vitrectomy, an animal study[47] showed that vitrectomy increased the intraocular clearance of vancomycin, but it did not alter the threshold for retinal toxicity retinal toxicity produced by the antibiotic. The retinal toxicity produced by massive intravitreal injection of the antibiotic was primarily related to peak concentration rather than duration of tissue exposure, and the risk of immediate vitrectomy in the operated eye was greater.

DISCUSSION

The efficacy of intracameral cefuroxime as a prophylactic measure against post-cataract surgery endophthalmitis is well-established. However, concerns regarding its potential retinal toxicity and associated risks have emerged in recent years, with increasing reports of severe vision loss following cataract surgery. This review aims to summarize the possible risk factors contributing to cefuroxime-induced retinal toxicity, including overdose, blood-retinal barrier disruption, and anatomical factors such as vitreous surgery, suspensory ligament abnormalities, posterior capsule rupture, and second-stage lens implantation.

Previous studies have demonstrated that vitrectomized eyes are particularly susceptible to altered bioavailability and toxicokinetic of intracameral agents. According to Stefánsson[48], macular edema may result from changes in the hydrostatic pressure balance within the retinal vasculature and tissue. Current research generally supports the hypothesis that acute intraretinal and subretinal fluid accumulation may be attributed to alterations in vitreous cavity pressure. Furthermore, prior anterior retinectomy may compromise the structural integrity of the inner retina, rendering it more vulnerable to hydrostatic pressure changes. The adhesive traction between the vitreous and macula is thought to stimulate Müller cells, triggering the release of various mediators that promote vascular leakage, ultimately leading to macular edema and subretinal fluid accumulation[49].

While the majority of patients do not exhibit clinical signs of toxicity following routine dose administration, the potential subclinical effects remain unclear. There is insufficient evidence regarding changes in retinal thickness, and electrophysiological examinations in these patients are scarce. Animal studies have provided valuable insights into this issue. One study utilizing albino rabbits[46] demonstrated that low-dose cefuroxime (1 mg/0.1 mL) injection did not result in statistically significant changes in retinal electrophysiology or histological morphology. However, high-dose injection (10 mg/0.1 mL) caused a significant reduction

in electrophysiology amplitude (b-wave reduction), with only partial recovery observed at 4-week follow-up. Histological examination revealed substantial retinal tissue damage in the high-dose group. Notably, glial fibrillary acidic protein (GFAP) immunoreactivity was observed in both dose groups, with more extensive expression in the high-dose group. GFAP immunostaining serves as a sensitive indicator of Müller cell response to retinal stress[50-53] and can detect subtle retinal changes that may not be apparent through electrophysiology or light microscopy.

The mechanism of cefuroxime-induced retinal toxicity may involve multiple pathways. Studies suggested that cefuroxime promotes the overexpression of L-glutamate transporter protein 1 in the central nervous system[54], potentially reducing L-glutamate concentrations in outer plexiform synapses. This reduction could lead to bipolar cell depolarization and subsequent electrophysiology b-wave amplitude reduction. Additionally, cefuroxime may disrupt the blood-retinal barrier, causing damage to photoreceptor cells and RPE cells, leading to fluid accumulation[19,31,37]. Some researchers have proposed that cefuroxime-induced dysfunction of the RPE sodium-potassium pump may contribute to retinal toxicity[42].

Despite these findings, some researchers[55-59] have questioned the reliability of reports regarding cefuroxime-induced toxic retinopathy following phacoemulsification when proper dilution protocols are followed. They argue that mathematical accuracy in protocol design does not necessarily translate to clinical accuracy, particularly when using small-volume (1 mL) syringes for dilution steps, as these syringes do not permit adequate mixing. Furthermore, 1 mL syringes have been shown to have an approximate 10% margin of inaccuracy in delivering 0.1 mL volumes, a phenomenon that has been documented in insulin dosage and neonatal drug delivery. Therefore, the use of commercially available cefuroxime formulations specifically designed for intraocular injection is strongly recommended, as this approach eliminates the need for small-volume syringe dilution and reduces the potential for dosing errors.

In summary, while intracameral cefuroxime remains an effective prophylactic measure against endophthalmitis, its potential retinal toxicity warrants careful consideration. The evidence from animal studies suggests that high doses can cause significant retinal damage, and even low doses may induce subclinical changes detectable through GFAP immunostaining. The use of pre-formulated cefuroxime solutions and careful attention to dosing protocols are essential to minimize the risk of retinal toxicity in clinical practice. Further research is needed to better understand the mechanisms of cefuroxime-induced retinal toxicity and to establish safe dosing guidelines for patients with various ocular conditions.

CONCLUSION

Our review and synthesis of the literature regarding the risks of cefuroxime therapy support the following recommendations. First, high-dose injections of cefuroxime can significantly increase the incidence of retinal toxicity, suggesting the need to avoid dilution errors in clinical use, such as the use of commercial preparations. Meanwhile, patients after cataract surgery need standardized postoperative follow-up. In addition to focusing on visual acuity, intraocular pressure, and anterior segment performance, follow-up with OCT, electrophysiology, and other ancillary examinations needs to be increased to detect possible retinal toxic reactions in a timely manner. The existing studies are still lacking in long-term follow-up, especially for electrophysiological long-term follow-up studies. Unexplained poor vision on the first day after cataract surgery can be supplemented with macular OCT to rule out cefuroxime-related retinal toxicity. It is strongly recommended to use commercially available cefuroxime designed for intraocular injection, which eliminates the need for small volume syringes for dilution.

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