Nepafenac 0.1% versus fluorometholone 0.1% for preventing cystoid macular edema after cataract surgery

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PURPOSE: To compare a topical nonsteroidal antiinflammatory drug (nepafenac 0.1%) and a topical steroidal antiinflammatory drug (fluorometholone 0.1%) in preventing cystoid macular edema (CME) and blood–aqueous barrier (BAB) disruption after small-incision cataract extraction with foldable intraocular lens (IOL) implantation.

SETTING: Shohzankai Medical Foundation, Miyake Eye Hospital, Nagoya, Japan.

DESIGN: Randomized double-masked single-center clinical trial.

METHODS: Patients were randomized to receive nepafenac 0.1% eyedrops or fluorometholone 0.1% eyedrops for 5 weeks after phacoemulsification with foldable IOL implantation. The incidence and severity of CME were evaluated by fluorescein angiography, retinal foveal thickness on optical coherence tomography, and BAB disruption on laser flare–cell photometry.

RESULTS: Thirty patients received nepafenac and 29 patients, fluorometholone. Five weeks postoperatively, the incidence of fluorescein angiographic CME was significantly lower in the nepafenac group (14.3%) than in the fluorometholone group (81.5%) ($P<.0001$). The fovea was thinner in the nepafenac group than in the fluorometholone group at 2 weeks ($P=.0266$) and 5 weeks ($P=.0055$). At 1, 2, and 5 weeks, anterior chamber flare was significantly less in the nepafenac group than in the fluorometholone group ($P<.0001$, $P<.0001$, and $P=.0304$, respectively). The visual acuity recovery from baseline was significantly greater in the nepafenac group (80.0%) than in the fluorometholone group (55.2%) ($P=.0395$). There were no serious side effects in either group.

CONCLUSION: Nepafenac was more effective than fluorometholone in preventing angiographic CME and BAB disruption, and results indicate nepafenac leads to more rapid visual recovery.

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Cataract extraction and intraocular lens (IOL) implantation continues to undergo significant advancement, allowing recovery of vision immediately after surgery. Contributing factors include effective prevention of postoperative inflammatory reaction and cystoid macular edema (CME).

Although studies of the pathogenesis of postoperative inflammation, including CME, are ongoing, the role of prostaglandin, an inflammatory mediator, has recently received much attention.[1,2] The effect of nonsteroidal antiinflammatory drugs (NSAIDs), a biosynthesis inhibitor of prostaglandins, applied locally during surgery to prevent miosis,[3] CME,[4–7] and inflammation[8] was first reported in Japan. Since then, more than 50 peer-reviewed papers have been published on this subject; a few recent metaanalyses and reviews[9–11] confirmed that topical NSAIDs are effective in preventing and treating postoperative inflammation, including CME. These reports, however, simultaneously indicate the need for further research on the safety, side effects, and efficacy of visual recovery with the use of NSAIDs as well as for comparative studies of steroidal drops and the refinement of pharmacokinetics and formulation of NSAIDs.[9–11]

One NSAID recently developed to meet these demands is nepafenac.[12] Nepafenac is a prodrug that is metabolized, after topical application, into amfenac, which is an active metabolite.[13] Having a high corneal permeability rate, the drug rapidly penetrates intraocular tissues, where it is hydrolyzed into amfenac to

exert an antiinflammatory effect.[12,14] Similar to other NSAIDs, amfenac works to control synthesis of prostaglandins by inhibiting cyclooxygenase (COX).[12] A study using a rabbit inflammation model induced by a paracentesis[13] found amfenac blocked activities of COX-1 and COX-2; the 50% inhibitory concentrations were 0.25 μM and 0.15 μM, respectively. Furthermore, the amount of prostaglandin E_2 in the aqueous humor and the extravasation of proteins depended on the concentration of the nepafenac. The same experimental model found that the effect of nepafenac 0.1% after 1 topical application lasted 8 hours. These findings suggest that nepafenac has promise in preventing postoperative inflammation.

To date, there have been preliminary clinical evaluations of the efficacy of nepafenac in preventing clinically significant CME and postoperative inflammation.[15–18] However, to our knowledge, there have been no prospective randomized clinical trials of nepafenac to quantitatively analyze postoperative inflammation, including CME, using fluorescein fundus angiography, laser flare–cell photometry, or optical coherence tomography (OCT) or to evaluate its effect on postoperative visual outcome and safety.

Thus, this prospective randomized double-masked clinical trial compared nepafenac and fluorometholone, a steroidal agent, given for 5 weeks after cataract and IOL surgery performed through a small incision.

PATIENTS AND METHODS

This study was approved by the Institutional Review Board, Shohzankai Medical Foundation, Miyake Eye Hospital, Nagoya, Japan, and was performed in accordance with the Helsinki Declaration. All patients provided written informed consent after they were given full explanations of the nature of the study and of fluorescein fundus angiography.

Included in the study were patients older than 20 years who had phacoemulsification cataract extraction and IOL implantation between October 2007 and April 2008 at Shohzankai Medical Foundation, Miyake Eye Hospital. Patients were excluded if they (1) had taken systemic, topical, or ointment steroidal agents within 14 days of surgery; (2) had had an intraocular or periocular injection of steroidal agents within 90 days of surgery; (3) had taken systemic or topical NSAIDs within 7 days of surgery; (4) had a history of ophthalmic surgery (including laser surgery) or of ocular trauma that could affect the study results; (5) had pseudoexfoliation syndrome; (6) had a history of chronic or recurring ocular inflammation (eg, uveitis or scleritis); (7) had diabetic retinopathy; (8) had an ocular anomaly (eg, aniridia, congenital cataract); (9) had iris atrophy; (10) had disorders that would preclude improvement in visual function; (11) had macular edema; (12) had severe corneal epithelial disorder (eg, corneal ulcer); (13) had no visual function in the contralateral eye; (14) were scheduled to have other ocular surgery from baseline to 5 weeks after cataract surgery; (15) had secondary IOL implantation, (16) were allergic to or might have been sensitive to NSAIDs, amfenac, or fluorometholone; (17) had a positive skin reaction to fluorescein; (18) had a tendency to bleed or were currently on anticoagulants; (19) had had prostaglandin-type treatment for glaucoma within 4 days of surgery; (20) had been included in a previous study of prostaglandin type antiglaucoma drugs; (21) had joined another clinical study within 30 days of the study; (22) had ocular infection, (23) had uncontrollable diabetes mellitus; (24) had severe liver, kidney, or heart disorder; (25) might have been pregnant or were currently breast feeding; (26) had other factors determined to be unsuitable for the study.

Table 1. Trial schedule.

Test Item	Baseline	Postoperative 1 D	1 Wk	2 Wk	5 Wk
Patient background	Yes				
Visual acuity	Yes	Yes	Yes	Yes	Yes
Intraocular pressure	Yes	Yes	Yes	Yes	Yes
Fundus examination	Yes		Yes	Yes	Yes
Slitlamp examination	Yes	Yes	Yes	Yes	Yes
Ocular coherence tomography	Yes	—	Yes	Yes	Yes
Fluorescein angiography	—	—	—	—	Yes
Laser flare-cell meter		Yes	Yes	Yes	Yes
Drug administration*	Yes	Yes	Yes	Yes	Yes

*One day preoperatively to 5 weeks postoperatively

Trial Drugs and Method of Application

Drugs tested in the trial were nepafenac 0.1% (Nevanac), an ophthalmic suspension containing 1 mg of nepafenac in 1 mL of suspension, and fluorometholone 0.1% (Flucon), an ophthalmic suspension containing 1 mg of fluorometholone in 1 mL of suspension. The latter drug served as a control. Both drugs were applied topically to assigned patients.

The 2 drugs had identical outer appearances and could not be differentiated. The same physician (J.N.) served as the medical monitor and assigned 1 of the drugs to each patient.

One drop of the test drug or the control drug was given to patients 3 times a day starting the day before surgery until 5 weeks postoperatively. An additional 1 drop was given on the day of surgery.

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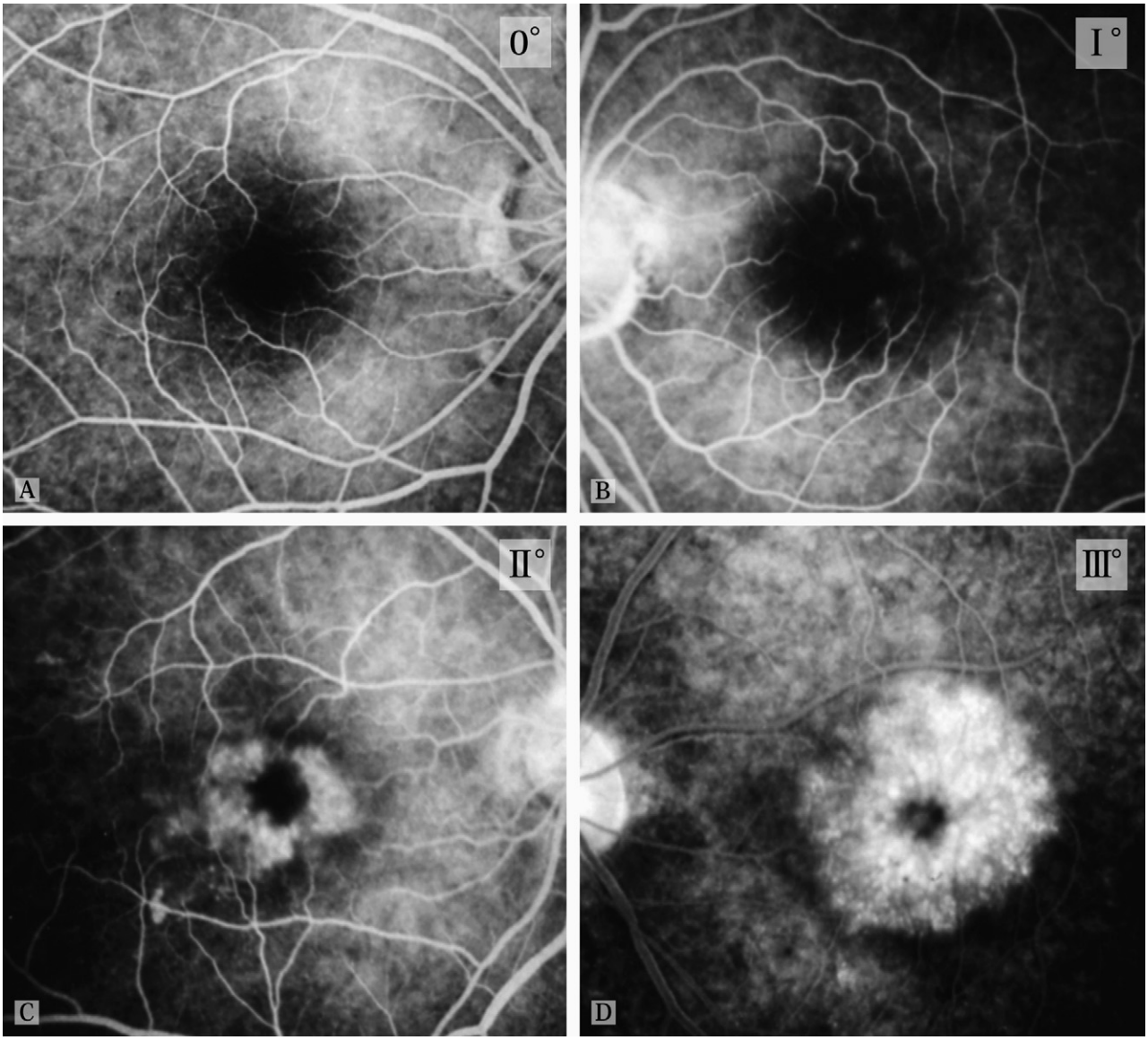

Figure 1. Representative example of each grade of CME using the Miyake classification at the late phase of fluorescein angiography (ie, 15 minutes after intravenous injection of sodium fluorescein 10%). *A*: In grade 0, there is no sign of fluorescein leakage. *B*: In grade 1, there is slight fluorescein leakage into the cystic space, but not enough to enclose the entire fovea centralis. *C*: In grade II, there is complete circular accumulation of the fluorescein in the cystic space, but the diameter of the accumulation is smaller than 2.0 mm. *D*: In grade III, the fluorescein leakage surrounds the fovea and is larger than 2.0 mm in diameter (reprinted with permission of *Archives of Ophthalmology*[19]).

In addition to the 2 drugs, levofloxacin ophthalmic solution 0.5% (Cravit) was applied to each eye 5 times before surgery and 3 times a day after surgery for 2 weeks.

Surgical Technique

Through a small incision requiring no or 1 suture, 1 of 2 surgeons (I.O., G.M.) performed continuous curvilinear capsulorhexis and phacoemulsification. This was followed by implantation of an acrylic foldable IOL (Acrysof SN60WF, Alcon Laboratories, Inc.) in the capsular bag.

Outcome Measures

Table 1 shows timing and types of evaluations performed and recorded. The amount of anterior flare was measured with laser flare–cell photometry (FC-1000, Kowa Co., Ltd.) and foveal thickness with OCT (Cirrus HD-OCT, Carl Zeiss Meditec AG). Approximately 30 minutes after intravenous injection of fluorescein sodium, fluorescein angiography was used to confirm the presence of CME and the same physician (K.M.) determined and graded the severity using the Miyake classification[4] in a double-masked manner. Figure 1 shows details of the classification.[19]

Statistical Analysis

The following statistical analyses were used to evaluate the results: chi-square test, Fisher test, Student *t* test, and Welch *t* test for patient and surgical background; chi-square test and Wilcoxon rank sum test for incidence of

Table 2. Patient characteristics.

Parameter	Patients, n (%)			*P* Value
	Total	Nepafenac Group	Fluorometholone Group	
Patients	59 (100.0)	30 (50.8)	29 (49.2)	
Sex				
Male	32 (54.2)	16 (53.3)	16 (55.2)	.8873*
Female	27 (45.8)	14 (46.7)	13 (44.8)	
Type of cataract				
Age related	58 (98.3)	30 (100.0)	28 (96.6)	.4915†
Other	1 (1.7)	0	1 (3.4)	
Emery-Little classification				
Grade 1	4 (6.8)	2 (6.7)	2 (6.9)	.694†
Grade 2	46 (78.0)	25 (83.3)	21 (72.4)	
Grade 3	6 (10.2)	2 (6.7)	4 (13.8)	
Grade 4	3 (5.1)	1 (3.3)	2 (6.9)	
Age classification 1				
18-64 years	28 (47.5)	16 (53.3)	12 (41.4)	.3580*
≥65 years	31 (52.5)	14 (46.7)	17 (58.6)	
Age classification 2				
65–74 years	21 (67.7)	11 (78.6)	10 (58.8)	.280†
75–84 years	10 (32.3)	3 (21.4)	7 (41.2)	
85–94 years	0	0	0	

*Chi-square test
†Fisher test

CME; Student *t* test and repeated-measures analysis of variance for retinal foveal thickness and aqueous flare amount; and Wilcoxon rank-sum test for visual acuity. A *P* value less than 0.05 was considered statistically significant.

RESULTS

Patient Demographics and Surgical Parameters

Of the 60 patients enrolled in the study, 30 were in the nepafenac group and 30 in the fluorometholone group. These patients were included in the safety evaluation. One patient in the fluorometholone group was excluded because the patient wanted a bilateral procedure immediately after signing up for the study. Therefore, 59 patients (30 nepafenac group, 29 fluorometholone group) were included in the efficacy evaluation. Regarding the incidence of CME, 1 patient in the nepafenac group had macular degeneration that precluded fluorescein fundus angiography and dropped

Table 3. Surgical parameters.

Parameter	Total (N = 59)	Nepafenac Group (n = 30)	Fluorometholone Group (n = 29)	*P* Value
Surgery time (min)				
Mean ± SD	10.3 ± 2.2	10.2 ± 2.4	10.5 ± 2.1	.5896*
Range	7, 15	7, 15	8, 15	
US time (sec)				
Mean ± SD	46.7 ± 26.2	49.1 ± 26.7	44.2 ± 25.8	.4703*
Range	4.0, 114.0	4.0, 114.0	4.0, 109.9	
Irrigation amount (mL)				
Mean ± SD	52.4 ± 22.9	54.7 ± 24.0	50.0 ± 21.9	.439•
Range	20, 120	20, 120	20, 110	
Age (y)				
Mean ± SD	65.0 ± 10.1	64.3 ± 7.8	65.7 ± 12.2	.6139†
Range	37, 83	48, 82	37, 83	

US = ultrasound
*Student *t* test
†Welch *t* test

Table 4. Distribution of CME severity based on the Miyake classification.

Group	CME Severity, n (%)			
	Grade 0	Grade I	Grade II	Grade III
Nepafenac (n = 28)	24 (85.7)	0	4 (14.3)	0
Fluorometholone (n = 27)	5 (18.5)	6 (22.2)	11 (40.7)	5 (18.5)

CME = cystoid macular edema; n = patients

out of the study and another patient was dropped for an unwillingness to attend the examination. Two patients in the fluorometholone group dropped out of the trial, 1 because a humeral fracture prevented fluorescein fundus angiography and another because of posterior lens capsule rupture during surgery. Of the patients who had fluorescein fundus angiography, 2 (7.1%) of 28 in the nepafenac group and 3 (10.1%) of 27 in the fluorometholone group had diabetes without diabetic retinopathy. One patient in the nepafenac group and 4 patients in the fluorometholone group were excluded from baseline central foveal thickness analysis because lens opacities hindered foveal thickness measurement. Finally, the patient with the posterior lens capsule rupture in the fluorometholone group was excluded from the laser flare–cell meter analysis because the test had to be performed 1 day after surgery.

Tables 2 and 3 show patient characteristics and surgical parameters. There was no statistically significant difference in any parameter between the 2 groups.

Efficacy

The incidence of CME up to 5 weeks after surgery was 14.3% (4 of 28 cases) in the nepafenac group and 81.5% (22 of 27 cases) in the fluorometholone group; the difference between the 2 groups was statistically significant ($P<.0001$, χ^2 test). The difference in severity of CME, determined using the Miyake classification, was also statistically significant between the 2 groups ($P<.0001$, Wilcoxon rank-sum test). The CME was classified as III (severe according to Miyake classification) in 5 eyes in the fluorometholone group and in no eye in the nepafenac group (Table 4).

Table 5 shows the central foveal thickness measured with OCT. Postoperatively, the central fovea was thinner in the nepafenac group than in the fluorometholone group. The difference between the 2 groups became statistically significant starting the second week after surgery (week 2, $P=.0266$; week 5 week, $P=.0055$).

Table 6 shows the amount of postoperative flare measured with the laser flare–cell meter. At 1, 2, and 5 weeks, the amount of aqueous flare was statistically significantly lower in the nepafenac group than in the fluorometholone group (1 week, $P<.0001$; 2 weeks, $P<.0001$; 5 weeks, $P=.0304$).

Table 7 shows the change in logMAR CDVA. There was a statistically significant difference between the 2 groups in change in CDVA from baseline to the last examination logMAR ($P=.0395$, Wilcoxon rank-sum test). Significantly more eyes in the nepafenac group than in the fluorometholone group had improved CDVA after surgery; 24 eyes (80.0%) and 16 eyes (55.2%), respectively, had an improvement of 3 or more lines of CDVA. No eye in either group lost lines of CDVA.

Safety

Table 8 shows the adverse events. No patient in either group had a severe adverse event. There was no correlation between the test drug and the rate of adverse events in either group.

In the nepafenac group, the adverse events were mild; therefore, some patients had no treatment and

Table 5. Between-group comparison of central foveal thickness measured with OCT.

Group/Parameter	Baseline	Postoperative		
		1 Wk	2 Wk	5 Wk
Nepafenac				
Mean thickness (μm) ± SD	188.0 ± 21.0	190.4 ± 18.3	191.2 ± 18.4	194.3 ± 20.7
Patients (n)	29	30	30	30
Fluorometholone				
Mean thickness (μm) ± SD	190.6 ± 16.0	193.0 ± 16.0	211.7 ± 51.9	220.1 ± 58.2
Patients (n)	25	29	29	29
P value*	.6216*	.7788†	.0266†	.0055†

*Student *t* test
†Repeated-measures analysis of variance comparing the least square means of treatments by visit (main effect of treatment, $P=.0447$; treatment by visit interaction, $P=.0081$)

Table 6. Between-group comparison of amount of flare measured with the laser flare–cell meter.

	Postoperative			
Group/Parameter	1 D	1 Wk	2 Wk	5 Wk
Nepafenac				
Mean flare (photons/msec) ± SD	16.7 ± 14.4	12.9 ± 6.3	12.9 ± 5.9	12.0 ± 5.5
Patients (n)	30	30	30	30
Fluorometholone				
Mean flare (photons/msec) ± SD	21.4 ± 14.1	48.3 ± 23.3	29.0 ± 12.9	19.3 ± 10.7
Patients (n)	28	29	29	29
P value*	.1479	.0001	.0001	.0304

*Repeated-measures analysis of variance comparing the least square means of treatments by visit (main effect of treatment, $P = .0001$; treatment by visit interaction, $P = .0001$)

those who did achieved full recovery. In the fluorometholone group, the 2 patients with moderate adverse events received treatment and achieved full recovery; some patients with mild adverse events had no treatment and those who did achieved full recovery.

DISCUSSION

Our comparative study analyzed the effect of topical application of nepafenac 0.1% in preventing CME and the safety of its use after cataract surgery with IOL implantation. We compared the results with those of fluorometholone 0.1%. The incidence of CME was determined using fluorescein angiography. We also performed a comprehensive analysis including retinal foveal thickness with OCT, blood–aqueous barrier (BAB) function with the laser flare–cell meter, and visual acuity. Although numerous studies have reported the effect of NSAIDs on postoperative inflammation, including CME, there are few studies like ours that have comprehensively analyzed the problem physiologically, morphologically, and functionally.[9–11]

The incidence of CME determined with fluorescein fundus angiography was significantly lower in the nepafenac group than in the fluorometholone group. In addition to the incidence, there was a between-group difference in severity of CME evaluated using the Miyake classification,[4] and more eyes in the fluorometholone group had severe CME. Specifically, grade III CME, which indicates that the edema may persist, occurred in 5 eyes (18.5%) in the fluorometholone group and in no eye in the nepafenac group. These quantitative findings suggest nepafenac is more effective than fluorometholone in preventing CME. This finding is in accordance with the retinal foveal thickness measured with OCT, which 2 and 5 weeks after surgery was significantly thicker in the fluorometholone group than in the nepafenac group.

Table 7. Change in logMAR CDVA.

	Patients, n (%)			
Group	≥3-Line Increase	2-Line Increase	1-Line Increase	No Change
Nepafenac (n = 30)	24 (80.0)	4 (13.3)	0	2 (6.7)
Fluorometholone (n = 29)	16 (55.2)	7 (24.1)	1 (3.4)	5 (17.2)

Suggested factors in CME after cataract and IOL surgery include hypotony,[20] vitreous traction,[21] inflammation,[22] and the prostaglandin theory.[2,4–7] The prostaglandin theory explains the incidence as follows[4]: Inflammatory mediators such as prostaglandins, which are biosynthesized by the anterior uvea and lens epithelial cells, are triggered by surgical trauma, leading to disruption of the BAB. As a result, various inflammatory mediators accumulate in the aqueous humor; the accumulation also relates to diminished active transport of prostaglandins existing at the iris and ciliary body.[23] The mediators are dispersed throughout the vitreous and increase permeability of retinal vessels; in other words, the blood–retinal barrier (BRB) becomes disrupted, inducing CME over time. Predispositions to BAB and BRB disruption include aging, hypertension, diabetic mellitus, and other diseases that risk inducing CME.

According to this hypothesis, disruption of the BAB is a dominating factor in CME, which Miyake suggested in 1978.[5] Since then, the natural course and biochemical aspect of BAB disruption have been explained as resulting from the traumatic effect to the uvea and lens epithelial cells (LECs) and is thought to be responsible for synthesis of inflammatory mediators such as prostaglandins.[24–27] In addition, recent studies[26,27] suggest that this synthesis occurs while LECs undergo the wound-healing process. In a study of IOL implantation in baboon eyes, Miyake et al.[26] quantified the amount of prostaglandin E_2 in the aqueous humor and found that the amount significantly increased in the operated eye

Table 8. Adverse events.

	Adverse Events, n (%)			
	Nepafenac Group (n = 30)		Fluorometholone Group (n = 30)	
Event	Mild	Moderate	Mild	Moderate
Ocular				
Decreased lacrimation	1 (3.3)	0	1 (3.3)	0
Conjunctivitis allergic	1 (3.3)	0	1 (3.3)	0
Abnormal sensation in eye	1 (3.3)	0	0	0
Retinal hemorrhage	0	0	1 (3.3)	0
Keratoconjunctivitis sicca	0	0	1 (3.3)	0
Chorioretinopathy	0	0	1 (3.3)	0
Systemic				
Influenza	0	0	0	1 (3.3)
Insomnia	0	0	1 (3.3)	0
Vomiting	2 (6.7)	0	0	0
Constipation	1 (3.3)	0	0	0
Diarrhea	0	0	1 (3.3)	0
Humeral fracture	0	0	0	1 (3.3)

and that this was more apparent 8 days after surgery than 1 day after surgery. Furthermore, Nishi et al.,[27] after culturing LECs, confirmed that the amount of prostaglandin E_2 and interleukin-1 increased in the culture medium, where cells were undergoing metaplasia. These data suggest that the inflammatory mediators increase in the aqueous for 1 to 2 weeks after cataract and IOL surgery. This finding explains the so-called spike-like increase in flare 1 to 2 weeks after surgery in eyes receiving steroidal agents. In contrast, NSAIDs prevented the spike-like increase of flare, implying that NSAIDs are more effective than steroidal agents in preventing postoperative inflammation. In the present study, the spike-like increase in flare occurred in the fluorometholone group 1 to 2 weeks after surgery, whereas nepafenac effectively prevented that phenomenon.

At the time of final examination (5 weeks after surgery), there was a significant difference in CDVA from baseline between the 2 groups ($P = .0395$). Twenty-four of 30 eyes in the nepafenac group had an improvement in logMAR CDVA of 3 or more lines, while only 16 of 29 eyes in the fluorometholone group had this level of improvement. As stated, the use of angiographic CME, foveal thickness, and aqueous flare as parameters confirmed that nepafenac is more effective than fluorometholone in preventing inflammation and in improving postoperative vision. The latter finding is significant because previous studies were not able to clearly define the effect of NSAIDs in improving vision after surgery.[9] Nepafenac's contribution to early recovery of vision may be the result of its high corneal permeability and effective and prolonged prevention of COX-1 and COX-2; the improvement in basic cataract and IOL surgical technique also plays a role.[12–14] Rapid recovery of the level of vision needed for early return to society is a common and significant interest of all patients having cataract and IOL surgery.

Side effects of topical NSAIDs have been reported to include mild ones, such as transient burning, stinging, and conjunctival hyperemia, as well as severe ones, such as toxic keratitis and corneal melting.[28,29] There are reports that nepafenac can also cause increased corneal haze after corneal surface ablation and delayed wound healing[30]; however, such events have not been confirmed to date.[31] In general, it is not clear which NSAID causes more side effects or whether there is a correlation between NSAIDs and any of the side effects.[11] In the present study, we found no significant difference in severe side effects between nepafenac and fluorometholone.

In conclusion, nepafenac was more effective than fluorometholone in preventing CME and BAB disruption and in providing early recovery of vision. Because NSAIDs are more costly than steroidal agents, especially in the United States, medico-economic review is necessary. Even so, we believe that the NSAID nepafenac can be recommended for routine use in patients having cataract and IOL surgery.

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