The Effect of Topical Diclofenac on Choroidal Blood Flow in Early Postoperative Pseudophakias with Regard to Cystoid Macular Edema Formation

Kensaku Miyake,[1] *Kazuo Nishimura,*[1] *Seiyo Harino,*[2] *Ichiro Ota,*[1] *Sayaka Asano,*[1] *Nagako Kondo,*[1] *and Sampei Miyake*[1]

Purpose. To study the chronological change in choroidal blood flow (ChBFlow), disruption of the blood–aqueous barrier, and incidence of cystoid macular edema (CME) in early postoperative pseudophakic eyes, as well as the effect of nonsteroidal anti-inflammatory drug (NSAID) eye drops on these phenomena.

Methods. Fifty patients who underwent phacoemulsification and foldable intraocular lens (IOL) implantation were randomized to receive either topical diclofenac or fluorometholone for 5 postoperative weeks. An additional 20 subjects, with long-standing pseudophakia served as the control. The blood–aqueous barrier was examined by laser flarimetry and choroidal blood velocity (ChBVel), volume (ChBVol), and ChBFlow by laser Doppler flowmetry (LDF) at 2 days and 1, 2, and 5 weeks after surgery. The incidence and severity of CME were evaluated by fluorescein angiography at 2 and 5 weeks after surgery.

Results. Compared with patients taking diclofenac, those receiving fluorometholone showed significantly reduced ChBVol at 2 weeks (0.38 ± 0.08 vs. 0.32 ± 0.07, $P = 0.022$) and ChBFlow at 1 (11.01 ± 1.74 vs. 9.35 ± 1.51, $P = 0.003$) and 2 (11.15 ± 1.43 vs. 8.47 ± 1.27, $P = 0.000$) weeks after surgery, as well as a significantly elevated amount of anterior flare at 1 (8.9 ± 2.2 vs. 24.4 ± 18.9, $P = 0.001$) and 2 (9.2 ± 3.5 vs. 16.7 ± 12.3, $P = 0.025$) weeks after surgery. The ChBVol and ChBFlow in the fluorometholone group, however, returned to normal and was not different from the diclofenac group at 5 weeks after surgery. The incidence of fluorescein angiographic CME trended to be higher ($P = 0.08$) at 2 weeks and was significantly higher ($P = 0.001$) at 5 weeks after surgery in eyes with fluorometholone than with diclofenac.

Conclusions. Reduction of ChBFlow, disruption of the blood–aqueous barrier, and incidence of CME in early postsurgical pseudophakic eyes were more effectively prevented chronologically in eyes treated with diclofenac than in those treated with fluorometholone. (*Invest Ophthalmol Vis Sci.* 2007;48: 5647–5652) DOI:10.1167/iovs.07-0262

Causative factors of aphakic/pseudophakic cystoid macular edema (CME) remain to be identified although ocular hypotension,[1,2] vitreous traction,[3–6] inflammation,[6] and other factors[6–11] have been suggested. The inflammatory theory hypothesizes that prostaglandins (PGs), which are soluble inflammatory chemical mediators biosynthesized intraocularly, relate to the incidence of CME[12,13] and that topical application of nonsteroidal anti-inflammatory drugs (NSAIDs), which are inhibitors of PGs biosynthesis, effectively prevents CME.[14–17] These studies also report that the incidence of CME corresponds to disruption of the blood–aqueous barrier (BAB).[12,13,18] Further, recent full-field ERG findings have shown reduced oscillatory potential in eyes with CME.[19] These phenomena indicate that diseases caused by soluble mediators such as PGs are scattered throughout the eye; in other words, it can be surmised that dysfunction of the BAB and of the inner blood–retinal barrier (BRB) is widespread in eyes with CME.[20] To date, however, there are no clinical reports reporting changes of the outer BRB or of the choroid in such eyes.

On the other hand, physiological dysfunction of the retinal pigment epithelium (RPE), such as dysfunction of transporting water from the retina to the choroid, has been suggested as a possible causative factor of macular edema or CME in eyes with ischemic retinopathy, including diabetic retinopathy.[21,22] In an experiment using monkey eyes with aphakic CME, breakdown of both the inner and outer BRB was demonstrated.[23] Studies of eyes with aphakic CME revealed that there is a delay in active transport of fluorescein from the vitreous cavity.[24] All these findings indicate that CME accompanies dysfunction of the outer BRB that exists in the RPE.

In this study, we divided eyes that underwent cataract/intraocular lens (IOL) implantation surgery into two groups: one receiving steroidal eye drops and the other NSAID eye drops. We then compared between the two groups the incidence of BAB disruption and of CME as well as choroidal blood flow (ChBFlow) during the early postoperative period. We used fluctuation of the ChBFlow as one of the physiological changes in the choroid that can be clinically detected. The mechanism of pseudophakic CME was studied by observing the chronological change in the BAB function, the incidence of CME, and ChBFlow during the early period after cataract/IOL surgery.

Subjects and Methods

The study was conducted in a prospective, double-masked, randomized manner, and the drugs compared were 0.1% diclofenac eye drops (Diclod; Wakamoto, Tokyo, Japan) and 0.1% fluorometholone eye drops (Flumethrone; Santen, Osaka, Japan).

Sixty-two consecutive eyes with senile cataract were considered for the study based on the following inclusion and exclusion criteria. The inclusion criteria required the age of the patient to be between 50 and 70 years of age, subjected for unilateral surgery or to have 6 months' span between surgeries in patients with bilateral cataract. The following were excluded from the study: (1) eyes encountering acute ocular infection or inflammation during the first month of the study; (2) eyes showing sensitivity to diclofenac or fluorometholone; (3) eyes showing sensitivity to fluorescein sodium; (4) eyes with insufficient dilation,

From the [1]Shohzankai Medical Foundation, Miyake Eye Hospital, Nagoya, Japan; and the [2]Yodogawa Christian Hospital, Osaka, Japan.

Submitted for publication March 2, 2007; revised July 11 and August 21, 2007; accepted October 16, 2007.

Disclosure: **K. Miyake**, None; **K. Nishimura**, None; **S. Harino**, None; **I. Ota**, None; **S. Asano**, None; **N. Kondo**, None; **S. Miyake**, None

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Corresponding author: Kensaku Miyake, Shohzankai Medical Foundation, Miyake Eye Hospital, 3-15-68, Ozone, Kita-ku, Nagoya 462-0825, Japan; miyake@spice.or.jp.

TABLE 1. Parameter Evaluation Schedules

	Before Surgery	After Surgery			
		2 Days	1 Week	2 Weeks	5 Weeks
Visual acuity	○	○	○	○	○
Intraocular pressure	○	○	○	○	○
Blood pressure	○	○	○	○	○
LDF		○	○	○	○
Flare	○	○	○	○	○
FA				○	○

FA, fluorescein fundus angiography; (○), evaluation performed.

(pupil diameter <4 mm) and with hazy media affecting laser Doppler flowmetry (LDF); (5) eyes with history of other ocular surgeries; (6) eyes with pseudoexfoliation syndrome; (7) eyes with a history of trauma; (8) eyes with uveitis, glaucoma or other disorders; (9) eyes with complication of diabetes and kidney disorders; (10) subjects with heart failure, cardiac infarction, and cerebrovascular disease; (11) subjects with uncontrollable hypertension; and (12) eyes encountering rupture of the posterior capsule, vitreous loss, and other complications during a cataract/IOL implantation procedure. Besides these subjects, 20 normal pseudophakic eyes that have been operated on >3 months before LDF were included as control subjects.

The Institutional Review Board of the Shohzankai Medical Foundation approved the study in accordance with the Declaration of Helsinki. The nature of the study was explained to all patients, and their informed consent was obtained.

Surgery was conducted through a small incision requiring no suturing or one suture. After continuous curvilinear capsulorrhexis and phacoemulsification, an acrylic foldable IOL (Acrysof; Alcon, Fort Worth, TX) was implanted into the lens capsule. All surgeries were performed by one of two authors (SM or IO). Hardness of the lens was graded according to the Emery-Little classification.[25] Balanced salt solution was used for intraocular irrigation.

Each patient was randomly assigned to one of the two groups by one of the authors (SA), using the envelope method, and, accordingly, diclofenac or fluorometholone eye drops were given four times before surgery (3 hours, 2 hours, and 1 hour and 30 minutes) and three times a day for 5 weeks after surgery. Other topical drugs used before and after surgery included mydriatics and antibiotics only. No other drug that may have affected the ChBFlow was used concurrently.

Patient background, surgical detail, visual acuity, ocular pressure, blood pressure, CME detected using fluorescein angiography, the amount of anterior flare measured using laser cell flarimetry, and ChBFlow determined by LDF have been recorded as summarized in Table 1.

CME, captured by fluorescein angiography at 2 and 5 weeks after surgery, was analyzed by one of the authors (NK) in a masked fashion and graded with a method explained previously.[14] Briefly, 0 indicates no dye leakage or dye accumulation; 1, slight dye accumulation in the cystic space and incompletely surrounding the fovea; 2, dye accumulation surrounding the fovea with a diameter of less than 2 mm; and 3, dye accumulation surrounding the fovea with a diameter greater than 2 mm.

Laser flarimetry was conducted to measure the amount of aqueous flare by one of the authors (SA) in a masked fashion.

Relative foveal choroidal blood velocity (ChBVel), volume (ChBVol), and ChBFlow were obtained by the LDF technique (Oculix Sarl, Arbaz, Switzerland), which has been described previously.[26,27] ChBVel, which is proportional to the mean velocity of the red blood cells within the volume sampled by the laser light, and ChBVol, which is proportional to the number of red blood cells, are independent measurements. ChBFlow is calculated with an instrument, using these two parameters in the following formula: ChBFlow = constant × ChBVel × ChBVol.[28]

A diode laser beam (670 nm) with an intensity of 40 μW was delivered through a fundus camera (model PRO-1; Kowa, Tokyo, Japan), and the diameter of the probing laser beam was approximated to be 150 μm at the fundus. Before measuring, the pupil was fully dilated with tropicamide 0.5% and phenylephrine hydrochloride 0.5% eye drops (Mydrin P; Santen).

During ChBFlow measurement at the fovea, an area of the posterior retina (50° in diameter) was illuminated with a retinal irradiance of approximately 0.03 mW/cm^2 and at a wavelength of 570 μm. This light enabled observation of the position of the laser on the fovea. Subjects were asked to fixate on the probing laser. ChBFlow corresponds mainly to choriocapillaris flow, as described previously by Riva et al.[26]

Proper fixation during measurements was ascertained by direct observation of the foveola through the fundus camera. Two continuous 30-second measurements of the choroidal circulation were obtained. Analysis of these data was performed by one of the two authors (KN or SH) in a masked manner using a computer (NeXT, no longer manufactured) incorporating a software specifically developed for the analysis of Doppler signals from ocular tissues. The examiner selected suitable parts of the recordings that showed stable circulatory parameters, which were approximately between 10 and 20 seconds for each measurement. The average of two measurements was used as the data of each eye.

Brachial artery systolic and diastolic blood pressures (SBP and DBP, respectively) were determined by sphygmomanometer before blood flow measurements. Intraocular pressure (IOP) was measured with a Goldmann applanation tonometer. Mean arterial blood pressure (MBP) was calculated using the following formula: MBP = DBP + ⅓(SBP − DBP). Mean perfusion pressure (MPP) of the eye studied was estimated using the following formula: MPP = ⅔(MBP − IOP).

All data are expressed as the mean ± SD. Statistical significance was determined with one of the following: Student's *t*-test, the χ^2 test, the Mann-Whitney U test, or one-way ANOVA. Student's *t*-test was adjusted by the Bonferroni post hoc test. $P < 0.05$ was considered statistically significant.

TABLE 2. Patients' Profiles and Surgical Characterization

	Diclofenac Group	Fluorometholone Group	*P*
Age (y)	65.4 ± 7.0	65.8 ± 7.1	0.841 (NS)
Eyes (*n*)			
Male	13	10	
Female	12	15	
Duration of surgery (min)	10.9 ± 2.1	11.0 ± 2.3	0.847 (NS)
Ultrasound time (s)	2.0 ± 1.6	1.5 ± 1.1	0.202 (NS)
Irrigation solution (mL)	68.1 ± 35.8	65.2 ± 35.5	0.776 (NS)
Hardness of crystalline lens	2.6 ± 0.7	2.5 ± 0.7	0.553 (NS)

Data are expressed as the mean ± SD. Statistical analysis was performed by Student's *t*-test.

TABLE 3. Changes in IOP, MBP, and MPP before and after Surgery

	Before Surgery	After Surgery				*P*
		2 Days	1 Week	2 Weeks	5 Weeks	
IOP						
Diclofenac	12.7 ± 2.3	12.2 ± 2.9	12.7 ± 2.3	12.8 ± 2.4	13.3 ± 1.9	0.657 (NS)
Fluorometholone	14.1 ± 2.2	13.2 ± 3.0	13.0 ± 1.7	13.6 ± 2.7	14.2 ± 2.8	0.308 (NS)
MBP						
Diclofenac	91.3 ± 11.0	89.4 ± 7.9	86.2 ± 10.4	88.9 ± 11.8	93.1 ± 8.3	0.168 (NS)
Fluorometholone	89.5 ± 11.3	92.1 ± 8.0	87.8 ± 8.6	90.6 ± 9.7	87.0 ± 8.2	0.297 (NS)
MPP						
Diclofenac	48.2 ± 7.6	47.4 ± 5.9	44.7 ± 7.0	46.9 ± 8.1	48.8 ± 5.4	0.298 (NS)
Fluorometholone	45.5 ± 7.0	48.6 ± 4.3	46.4 ± 5.2	46.9 ± 7.1	43.7 ± 4.8	0.056 (NS)

Data are expressed as the mean mm Hg ± SD. Statistical analysis was performed by one-way ANOVA. NS, intragroup comparison not significant.

RESULTS

Originally randomized for the study was a total of 62 eyes or 31 eyes each in both the diclofenac and fluorometholone groups; however, since 6 eyes from each group had to be excluded, 25 eyes from each group remained in the study. The reasons for exclusion in the diclofenac group were as follows: one eye showed sensitivity to fluorescein sodium, three eyes presented insufficient pupil dilation, and two eyes had glaucoma. The causes in the fluorometholone group were as follows: Three eyes presented insufficient pupil dilation, one eye had uveitis, one subject had diabetes, and one subject had hypertension. There was no significant difference in age and sex between the two groups (Table 2). Table 2 also describes surgical details; again, there was no significant difference between the two groups in duration of the entire procedure, hardness of the lens, duration of the ultrasound time, and the amount of irrigating solution used. There was no significant difference in postoperative visual acuity between the two groups: 1.1 ± 0.2 ($n = 25$) and 1.0 ± 0.3 ($n = 25$) at 2 weeks, and 1.1 ± 0.2 ($n = 25$), and 1.0 ± 0.3 ($n = 25$) at 5 weeks each in the diclofenac and fluorometholone groups, respectively.

Table 3 details the changes in IOP, MBP, and MPP, before and after surgery in both groups. There were no significant differences. Table 4 summarizes the incidence of CME at 2 and 5 weeks after surgery. At 2 weeks, the incidence trended to be lower ($P = 0.08$) and was significantly less ($P = 0.001$) in the diclofenac group. Table 5 compares the amount of aqueous flare between the two groups before surgery and at 1, 2, and 5 weeks after surgery. At 1 and 2 weeks after surgery, the fluorometholone group showed significantly a higher level of flare ($P < 0.05$). This comparison is also presented in Figure 1.

Table 6 presents the postoperative change in ChBVel, ChBVol, and ChBFlow determined by LDF. At 1 and 2 weeks after surgery, fluorometholone group showed significantly lower ChBFlow and ChBVol ($P < 0.05$). At 5 weeks after surgery, the fluorometholone group showed a significantly lower ChBVel ($P < 0.05$). ChBFlow, ChBVel, and ChBVol at 5 weeks in both groups were not significantly different from those of the control group except for ChBVel in the fluorometholone group. These comparisons are also presented in Figure 1.

The incidence of CME and ChBFlow, ChBVel, and ChBVol were similar in the diclofenac and control groups.

Postoperative correlation among ChBFlow, amount of aqueous flare, and incidence of CME is summarized as follows. In the fluorometholone group, the incidence of CME was higher at 2 and 5 weeks after surgery than in the diclofenac group. ChBFlow diminished along with elevation of aqueous flare 1 to 2 weeks after surgery. In the diclofenac group, decrease in ChBFlow and increase in aqueous flare, together with occurrence of CME, were minimal.

TABLE 4. CME Frequency and Severity after Surgery

	CME Grade				Ratio of Occurrence
	0	1	2	3	
Two weeks after surgery					
Diclofenac	25	0	0	0	0/25 (0%)
Fluorometholone	21	3	1	0	4/25 (16%)
Five weeks after surgery					
Diclofenac	24	1	0	0	1/25 (4%)
Fluorometholone	13	5	4	3	12/25 (48%)

CME was graded on the Miyake scale, by using fluorescein fundus angiography.

DISCUSSION

Chronological change in the disruption of the BAB, incidence of CME, and ChBFlow was studied in eyes undergoing cataract/IOL implantation surgery. Although blood flow of the choriocapillaries at the fovea diminished 1 to 2 weeks after surgery, we confirmed that this was effectively prevented by topical NSAIDs. These topical drugs, at the same time, prevented BAB disruption and the occurrence of CME. These findings may suggest that discussing the correlation among the three phenomena—disruption of the BAB, incidence of CME, and ChBFlow—is interesting in understanding the clinical entity of pseudophakic CME.

Development of CME and macular edema is generally related to disruption of the inner BRB and disruption or dysfunction of the outer BRB.[21–24,29–33] While disruption of the inner BRB can be confirmed by a common method of fluorescein angiography, that of the outer BRB existing in the RPE, for the most part, can only be speculated. Bresnick hypothesized that the transport function of water from the retina to the choroids in the outer BRB either prevents or compensates macular edema from becoming clinically evident.[21] Electron microscopic findings of monkey eyes with experimentally induced CME[23] and vitreous fluorometric results of human eyes with CME[24] suggest disruption or dysfunction of both the inner and the outer BRB.

Let us next study and compare the chronological change of the three phenomena evaluated in this study: disruption of the BAB, incidence of CME, and ChBFlow. Disruption of the BAB 1 to 2 weeks after surgery was significantly larger in eyes treated with steroidal drops than in those with NSAID drops. This

TABLE 5. Postoperative Aqueous Flare

	Before Surgery	After Surgery			
		2 Days	1 Week	2 Weeks	5 Weeks
Diclofenac	8.9 ± 6.5	12.6 ± 3.9	8.9 ± 2.2	9.2 ± 3.5	8.1 ± 3.8
Fluorometholone	9.7 ± 9.6	15.4 ± 5.7	24.4 ± 18.9	16.7 ± 12.3	9.0 ± 3.0
P	0.999 (NS)	0.276 (NS)	0.001*	0.025*	0.999 (NS)

Data are expressed as the mean ± SD. Statistical analysis was performed by using Student's *t*-test with the Bonferroni adjustment, in which the probability was multiplied by the number of comparisons. NS, not significant between groups.

* Statistically significant ($P < 0.05$).

outcome matches the results of a previous experiment done with baboon eyes, which showed a higher amount of PGs in the aqueous humor at 1 week after cataract/IOL implantation surgery than at 1 day after surgery.[34] Eyes receiving steroidal drops also showed diminished ChBFlow 1 to 2 weeks after surgery. In other words, the amount of PGs in the aqueous, the value of aqueous flare and the trend of ChBFlow all revealed a similar chronological trend. This suggests that soluble mediators such as PGs may be related to the two phenomena. CME hardly occurs immediately after surgery, but its incidence increases at ~5 weeks after surgery.[18] This incidence can be effectively inhibited by NSAID drops. Since all three phenomena are prevented by NSAID application, it is worthwhile to study their correlation. Soluble mediators such as PGs synthesized by residual lens epithelial cells or uveal cells accumulate in the aqueous[34,35] and lead to disruption of the BAB and inner BRB. These mediators somehow diffuse into the choroids to diminish ChBFlow, for example, through the uveoscleral flow.[36] Further studies are needed, however, to clarify how these mediators relate to choroidal blood flow.

In conducting LDF, the results may be affected by cataract or other forms of hazy media, as well as insufficient mydriasis and the type of IOL implanted. In our study, we used as the control otherwise normal, 3-month or longer postoperative pseudophakic subjects. The incidence of CME was highest at 5 weeks after surgery,[18] but the ChBFlow at this period showed no difference between the NSAID and steroid groups, leading us to believe CME did not significantly influence the measurement.

In conclusion, we confirmed that in eyes undergoing cataract/IOL implantation surgery, ChBFlow diminishes temporarily for 1 to 2 weeks after surgery and that this effect is

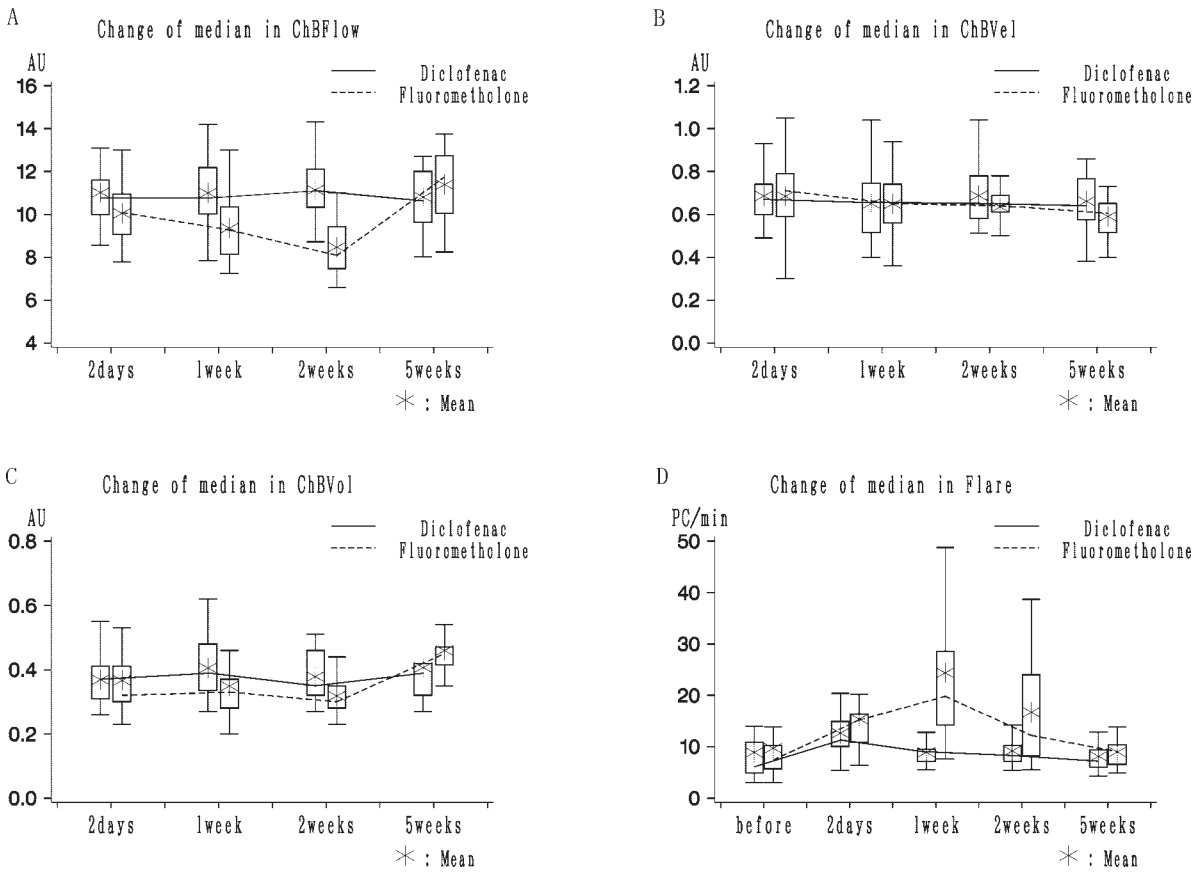

FIGURE 1. Changes in ChBFlow (**A**), ChBVel (**B**), ChBVol (**C**), and aqueous flare (**D**) after IOL surgery. Box-and-whisker plots show the levels of ChBFlow, ChBVel, ChBVol, and aqueous flare in patients with cataract after IOL surgery. *Solid line*: diclofenac group median; *dashed line*: fluorometholone group median; *vertical bars*: range and horizontal boundaries of box represent the first and third quartiles.

TABLE 6. Changes in ChBFlow, ChBVel, and ChBVol after IOL Surgery

	After Surgery				*P*
	2 Days	1 Week	2 Weeks	5 Weeks	(Intragroup)
ChBFlow					
Diclofenac	11.03 ± 1.94	11.01 ± 1.74	11.15 ± 1.43	10.80 ± 1.67	0.911 (NS)
Fluorometholone	10.05 ± 1.57	9.35 ± 1.51	8.47 ± 1.27	11.40 ± 1.61	0.000*
P	0.226 (NS)	0.003*	0.000*	0.852 (NS)	
ChBVel					
Diclofenac	0.69 ± 0.11	0.65 ± 0.16	0.69 ± 0.14	0.66 ± 0.13	0.707 (NS)
Fluorometholone	0.68 ± 0.18	0.65 ± 0.14	0.63 ± 0.09	0.59 ± 0.09	0.103 (NS)
P	1.000 (NS)	1.000 (NS)	0.444 (NS)	0.105 (NS)	
ChBVol					
Diclofenac	0.37 ± 0.07	0.41 ± 0.09	0.38 ± 0.08	0.41 ± 0.12	0.367 (NS)
Fluorometholone	0.37 ± 0.12	0.35 ± 0.10	0.32 ± 0.07	0.46 ± 0.09	0.000*
P	1.000 (NS)	0.170 (NS)	0.022*	0.346 (NS)	

Data are expressed as the mean arbitrary units ± SD. Statistical significance was determined by one-way ANOVA for intragroup comparisons and by Student's *t*-test with the Bonferroni adjustment, for comparisons between the two groups (diclofenac and fluorometholone). NS, inter- or intragroup comparisons not significant.

* Statistically significant ($P < 0.05$).

prevented by NSAID drops. NSAIDs, at the same time, inhibit disruption of the BAB and CME formation, suggesting that ChBFlow affected by chemical mediators such as PGs is related to CME formation. Our findings provide consideration when studying the mechanism of CME and macular edema related to various ocular disorders. For example, dysfunction of the outer BRB is discussed as one of the causative factors of diabetic macular edema.[21,22] ChBFlow has been measured in patients with diabetes or diabetic retinopathy, and there are reports informing diminished ChBFlow is related to diabetic macular edema, although the findings have not been uniform.[37–41] Further studies are necessary to clarify the relationship between reduced ChBFlow and the outer BRB.

References

1. Cieplinski W, Ciesielski TE, Haine C, et al. Diseases of the uveal tract. In: Duke-Elder WS, ed. *Systems of Ophthalmology*. Vol 9. London: Henry Kimpton; 1971:213–215.
2. Wolter JR. The histopathology of cystoid macular edema. *Albrecht Von Graefes Arch Klin Exp Ophthalmol*. 1981;216:85–101.
3. Irvine SR. A newly defined vitreous syndrome following cataracts surgery: interpreted according to recent concepts of the structure of the vitreous. *Am J Ophthalmol*. 1953;36:599–619.
4. Reese AB, Jones IS, Cooper WC. Macular changes secondary to vitreous traction. *Trans Am Ophthalmol Soc*. 1966;64:123–134.
5. Tolentino FI, Schepens CL. Edema of posterior pole after cataract extraction: a biomicroscopic study. *Arch Ophthalmol*. 1965;74:781–786.
6. Gass JD, Norton EW. Cystoid macular edema and papilledema following cataract extraction: a fluorescein fundoscopic and angiographic study. *Arch Ophthalmol*. 1966;76:646–661.
7. Binkhorst CD. Corneal and retinal complications after cataract extraction: the mechanical aspect of endophthalmodonesis. *Ophthalmology*. 1980;87:609–617.
8. Fine BS, Brucker AJ. Macular edema and cystoid macular edema. *Am J Ophthalmol*. 1981;92:466–481.
9. Henry MM, Henry LM, Henry LM. A possible cause of chronic cystic maculopathy. *Ann Ophthalmol*. 1977;9:455–457.
10. Roper DL, Nisbet RM. Effect of hyaluronidase on the incidence of cystoid macular edema. *Ann Ophthalmol*. 1978;10:1673–1678.
11. Worst JG. Biotoxic effects of aqueous humour: a unifying pathogenetic theory, based on certain hypothetic biotoxic factors in aqueous [in German]. *Klin Monatsbl Augenheilkd*. 1975;167:376–384.
12. Miyake K, Ibaraki N. Prostaglandins and cystoid macular edema. *Surv Ophthalmol*. 2002;47(suppl 1):S203–S218.
13. Miyake K. Indomethacin in the treatment of postoperative cystoid macular edema. *Surv Ophthalmol*. 1984;28(suppl):554–568.
14. Miyake K. Prevention of cystoid macular edema after lens extraction by topical indomethacin: I. A preliminary report. *Albrecht Von Graefes Arch Klin Exp Ophthalmol*. 1977;203:81–88.
15. Yannuzzi LA, Landau AN, Turtz AI. Incidence of aphakic cystoid macular edema with the use of topical indomethacin. *Ophthalmology*. 1981;88:947–954.
16. Flach AJ. Cyclo-oxygenase inhibitors in ophthalmology. *Surv Ophthalmol*. 1992;36:259–284.
17. Rossetti L, Chaudhuri J, Dickersin K. Medical prophylaxis and treatment of cystoid macular edema after cataract surgery: the results of a meta-analysis. *Ophthalmology*. 1998;105:397–405.
18. Miyake K. Prevention of cystoid macular edema after lens extraction by topical indomethacin: II, a control study in bilateral extraction. *Jpn J Ophthalmol*. 1978;22:80–94.
19. Terasaki H, Miyake K, Miyake Y. Reduced oscillatory potentials of the full-field electroretinogram of eyes with aphakic or pseudophakic cystoid macular edema. *Am J Ophthalmol*. 2003;135:477–482.
20. Miyake K. Cystoid macular edema as part of diffuse intraocular symptoms [in Japanese]. *Folia Ophthalmol Jpn*. 1995;46:219–231.
21. Bresenick GH. Diabetic maculopathy: a critical review highlighting diffuse macular edema. *Ophthalmology*. 1983;90:1301–1317.
22. Eagle RC. Mechanisms of maculopathy. *Ophthalmology*. 1984;91:613–625.
23. Tso MOM, Shin CY. Experimental macular edema after lens extraction. *Invest Ophthalmol Vis Sci*. 1977;16:381–392.
24. Miyake K. Vitreous fluorophotometry in aphakic or pseudophakic eyes with persistent cystoid macular edema. *Jpn J Ophthalmol*. 1985;29:146–152.
25. Emery JM, Mclntyre DJ. *Patient Selection in Extracapsular Cataract Surgery.* St. Louis: Mosby-Year Book, Inc; 1983:95–100.
26. Riva CE, Cranstoun SD, Grunwald JE, Petrig BL. Choroidal blood flow in the foveal region of the human ocular fundus. *Invest Ophthalmol Vis Sci*. 1994;35:4273–4281.
27. Grunwald JE, Metelitsina TI, DuPont JC, Ying GS, Maguire MG. Reduced foveolar choroidal blood flow in eyes with increasing AMD severity. *Invest Ophthalmol Vis Sci*. 2005;46:1033–1038.
28. Riva CE. Basic principles of laser Doppler flowmetry and application to the ocular circulation. *Int Ophthalmol*. 2001;23:183–189.
29. Cunha-Vas JG, Travassos A. Breakdown of the blood-retinal barriers and cystoid macular edema. *Surv Ophthalmol*. 1984;28(suppl):485–492.

30. Wallow IH, Engerman RL. Permeability and patency of retinal blood vessels in experimental diabetes. *Invest Ophthalmol Vis Sci*. 1977;16:447–461.
31. Brightman MW, Hori M, Rapoport SL, et al. Osmotic opening of tight junctions in cerebral endothelium. *J Comp Neurol.* 1973;152:317–325.
32. Mormor MF, Abodul-Rahim AS, Cohen DS. The effect of metabolic inhibitors on retinal adhesion and subretinal fluid resorption. *Invest Ophthalmol Vis Sci*. 1980;19:893–903.
33. Cunha-Vaz JG, Maurice DM. The active transport of fluorescein by the retinal vessels and the retina. *J Physiol*. 1967;191:467–486.
34. Miyake K, Mibu H, Horiguchi M, Shirasawa E. Inflammatory mediators in postoperative aphakic and pseudophakic baboon eyes. *Arch Ophthalmol*. 1990;108:1764–1767.
35. Nishi O, Nishi K, Imanishi M. Synthesis of interleukin-1 and prostaglandin E2 by lens epithelial cells of human cataracts. *Br J Ophthalmol*. 1992;76:338–341.
36. Bill A. The aqueous humor drainage mechanism in the cynomolgus monkey (Macaca irus) with evidence for unconventional routes. *Invest Ophthalmol Vis Sci*. 1965;4:911–919.
37. Geyer O, Neudorfer M, Snir T, et al. Pulsatile ocular blood flow in diabetic retinopathy. *Acta Ophthalmol Scand*. 1999;77:522–525.
38. Langham ME, Grebe R, Hopkins S, et al. Choroidal blood flow in diabetic retinopathy. *Exp Eye Res*. 1991;52:167–173.
39. Mackinnon JR, O'Brien C, Swa K, et al. Pulsatile ocular blood flow in untreated diabetic retinopathy. *Acta Ophthalmol Scand*. 1997;75:661–664.
40. Schmidt KG, von Ruckmann A, Kemkes-Matthes B, et al. Ocular pulse amplitude in diabetes mellitus. *Br J Ophthalmol*. 2000;84:1282–1284.
41. Nagaoka T, Kitaya N, Sugawara R, et al. Alteration of choroidal circulation in the foveal region in patients with type 2 diabetes. *Br J Ophthalmol*. 2004;88:1060–1063.