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Comparison of Diclofenac and Fluorometholone in Preventing Cystoid Macular Edema After Small Incision Cataract Surgery: A Multicentered Prospective Trial

Kensaku Miyake,* Kanjiro Masuda,† Shiroaki Shirato,‡ Tetsuro Oshika,‡ Koichiro Eguchi,§ Hyouzi Hoshi, ‖ Yoshinao Majima,¶ Wataru Kimura** and Fumihiko Hayashi††

**Miyake Eye Hospital, Nagoya, Japan; †Kanto Rosai Hospital, Kawasaki, Japan; ‡Department of Ophthalmology, The Tokyo University School of Medicine, Tokyo, Japan; §Eguchi Eye Hospital, Hakodate, Japan; ‖Imaizumi-West Hospital, Koriyama, Japan; ¶Fujita Health University School of Medicine, Toyoake, Japan; **Kimura Eye and Internal Medicine Hospital, Kure, Japan; ††Hayashi Eye Hospital, Hakata, Japan*

Purpose: To compare a nonsteroidal topical solution (0.1% diclofenac) to a steroidal topical solution (0.1% fluorometholone) in preventing cystoid macular edema (CME) and disruption of the blood–aqueous barrier.

Methods: A multicentered, prospective clinical trial was performed on eyes undergoing phacoemulsification followed by implantation of a foldable acrylic intraocular lens by the envelope technique. The presence and degree of cystoid macula edema (CME) was determined by fluorescein angiography. A breakdown of the blood–aqueous barrier was determined by laser flare-cell photometry.

Results: Five weeks after surgery, CME was present in 3 of 53 eyes (5.7%) receiving diclofenac and in 29 of 53 eyes (54.7%) receiving fluorometholone. This difference was statistically significant ($P < .001$). The amount of flare in the anterior chamber at 3 days, 1, 2, 5, and 8 weeks after surgery was also significantly lower ($P < .01$–$P < .001$) in the diclofenac group. The degree of flare at 3 days, 1, 2, 5, and 8 weeks after surgery was significantly higher in eyes with CME ($P < .001$).

Conclusions: These findings suggest that diclofenac effectively prevents CME following cataract surgery and that CME is closely related to the breakdown of the blood–aqueous barrier. **Jpn J Ophthalmol 2000;44:58–67** © 2000 Japanese Ophthalmological Society

Key Words: Blood–aqueous barrier, cyclooxygenase inhibitor, cystoid macular edema, diclofenac eye drops, steroid eye drops.

Introduction

The mechanism of blood–aqueous barrier disruption and the development of cystoid macular edema (CME) following phacoemulsification and implantation of a foldable intraocular lens (IOL), designed for small incision cataract surgery, has not been determined. In addition, the effectiveness of nonsteroidal anti-inflammatory topical solutions in preventing these disorders has not been resolved.

In the late 1970s,[1–5] Japanese ophthalmologists were the first to apply nonsteroidal eye drops to maintain mydriasis during cataract surgery and prevent postoperative inflammation or CME. This procedure has been accepted throughout the world.

Miyake and associates initially introduced the nonsteroidal drug treatment along with modifica-

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Correspondence and reprint requests to: Kensaku MIYAKE, MD, Shohzankai Medical Foundation, Miyake Eye Hospital, 1070-Kami 5, Higashiozone-cho, Kita-ku, Nagoya 462-0823, Japan

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tions of the surgical technique to prevent CME during the intracapsular cataract extraction era.[2–4] Other nonsteroidal drugs have also been found to be effective.[6–18] In the study of these drugs, however, only a limited number of double-masked and/or multicenter studies have been conducted.[6,8,9,17] The results of a recent international meta-analysis of medical prophylaxis and treatment of CME after cataract surgery have also indicated that most of the randomized clinical trials performed to date have problems related to quality. This suggests that a well-designed randomized clinical trial is needed.[19]

There has not been any prospective multicentered study to date, especially in Japan. Previous findings suggest that CME is correlated with the postoperative disruption of the blood–aqueous barrier.[3] Because of the differences in the severity of inflammation among different races,[20] additional studies are necessary in Japan to further evaluate drugs affecting the blood–aqueous barrier in the eyes of Japanese patients.

A prospective multicentered study was performed to compare a nonsteroidal topical solution to a steroidal topical solution in preventing CME and disruption of the blood–aqueous barrier in eyes undergoing the most current cataract surgical procedures.

Materials and Methods

The following eight institutions participated in the multicentered open trials: Miyake Eye Hospital, Kanto Rosai Hospital, Tokyo University Hospital, Eguchi Eye Hospital, Imaizumi-West Hospital, Fujita Health University Hospital, Kimura Eye and Internal Medicine Hospital, and Hayashi Eye Hospital.

The effect of 0.1% diclofenac, which is a phenylacetic acid derivative, was compared to 0.1% fluorometholone, prepared from 0.1% solvent (Flumethron®; Santen, Osaka). The efficacy of these drugs in preventing CME and blood–aqueous barrier disruption following cataract surgery was investigated. Diclofenac (0.1%) equivalent intraocular penetrating power and stronger titer than indomethacin[2] is prepared from 0.1% solvent (Diclod®; Wakamoto, Tokyo).

Five to 15 consecutive patients were enrolled at each site according to the study protocol. The inclusion criteria were: (1) patient must be between 60 and 70 years of age; (2) unilateral cataract surgery is indicated, and (3) a period of 6 months is necessary for surgery of the contralateral eye when bilateral surgery is indicated. The exclusion criteria were: (1) patient shows signs of acute ocular inflammation or inflammatory disease within 1 month of the initiation of the study, (2) eyes allergic to diclofenac or fluorometholone, (3) eyes allergic to fluorescein, (4) eyes previously underwent any intraocular surgery, (5) eyes with a history of trauma, (6) eyes with pseudo-exfoliation syndrome, (7) eyes suffering from or with a history of uveitis or glaucoma, (8) eyes with complications from diabetic mellitus or kidney disorders, (9) patients with severe cardiac incompetence, myocardial infarction, or cerebrovascular disorders, and (10) patients with hypertension.

The study was conducted in accordance with the Declaration of Helsinki and received approval from the Institutional Review Board of each site. After explaining in detail the purpose of the study and the method of fluorescein fundus angiography, informed consent was obtained from all patients.

The assigned solution was given to each patient at 3 hours, 2 hours, 1 hour, and 30 minutes, prior to surgery, and 3 times a day for 8 consecutive weeks following surgery. Other drugs taken concurrently included oral and topical antimicrobial medications.

The following items were evaluated: patient's medical background, surgical procedures, visual acuity, intraocular pressure, amount of anterior chamber flare and cells measured by laser flare-cell photometry, and the severity of CME determined by fluorescein fundus angiography. Table 1 summarizes the results of each of these evaluations when appropriate.

Table 1. Schedule of Study

		After Surgery					
	Before Surgery	1 Day	3 Days	1 Week	2 Weeks	5 Weeks	8 Weeks
FA						○	
LFCM							
Flare value	○	○	○	○	○	○	○
Cell value	○	○	○	○	○	○	○
Visual acuity	○	○	○	○	○	○	○
Intraocular pressure	○	○		○		○	○

FA: Fluorescein fundus angiography; LFCM: Laser flare cell metry.

Table 2. Background of Patients

	Diclofenac Group	Fluorometholone Group	Statistical Analysis
Age (yrs)*	66.32 ± 3.14	65.62 ± 3.10	$P = .654^{\dagger}$
No. of eyes			
Male	26	25	$P = .846^{\dagger}$
Female	27	28	

*Values are mean ± SD.
†Difference is not significant.

Table 3. Surgical Data

	Diclofenac Group	Fluorometholone Group	Statistical Analysis
Operation time (minutes)	14.0 ± 3.9	15.1 ± 5.0	$P = .214$*
Hardness of crystalline lens	2.5 ± 0.9	2.3 ± 0.6	$P = .302$*
U/S time (seconds)	78.3 ± 52.4	68.4 ± 33.5	$P = .249$*
Irrigating solution (mL)	107.9 ± 46.7	99.3 ± 56.9	$P = .393$*

Values are mean ± SD.
U/S: Ultra Sound.
*Difference is not significant.

As described elsewhere,[2] CME was evaluated in a double-masked fashion by one of the authors (KM) at 5 weeks after surgery. Briefly, 0° refers to an angiogram showing no fluorescein leakage, I°, an angiogram disclosing minimal fluorescein leakage into the cystic space but not surrounding the entire fovea; II°, an angiogram revealing fluorescein leakage surrounding nearly the entire fovea but is less than 2.0 mm in diameter; and III°, an angiogram showing fluorescein leakage surrounding the fovea and is larger than 2.0 mm in diameter.

The surgical technique used in this study consisted of a continuous curvilinear capsulorrhexis (CCC), phacoemulsification and implantation of a foldable acrylic IOL (AcrySofR; Alcon Laboratories, Fort Worth, TX, USA) into the lens capsule through a small incision. The incision was either sutured or remained sutureless.

Statistical Analysis

The background of the patients and surgical data were analyzed using the chi-square method and Student *t*-test. We also used the following for statistical analysis: Student *t*-test for visual acuity, the paired *t*-test for intraocular pressure, the Mann–Whitney *U*-test for the incidence of CME, and the Welch *t*-test for aqueous flare and cells. At all times, $P < .05$ was considered to be significant and the data are presented as mean ± SD unless stated otherwise.

Results

Of the 118 eyes initially included in the study, 59 eyes were assigned to the diclofenac group and 59 to the fluorometholone group. However, 6 eyes from each group were dropped from the study because of the following: 1 from the diclofenac group and 2 from the fluorometholone group due to complications, 5 from the diclofenac group and 4 from the fluorometholone group due to either poor health or a positive reaction to the intradermal fluorescein test, not permitting fluorescein fundus angiography. Finally, 53 eyes from the diclofenac group and 53 eyes from the fluorometholone group, a total of 106 eyes, completed the study. There was no statistically significant difference in age or sex between the two groups (Table 2).

Table 3 summarizes the surgical data; there was no statistically significant difference between the two groups in duration of surgery, hardness of the crystalline lens, phacoemulsification time, or amount of irrigating solution. The hardness of the lens was clas-

Table 4. Postoperative Visual Acuity

	Before Surgery		After Surgery											
			1 Day		3 Days		1 Week		2 Weeks		5 Weeks		8 Weeks	
Diclofenac group	0.37 ± 0.2 (n = 36)	$P =$	0.9 ± 0.2 (n = 30)	$P =$	1.1 ± 0.2 (n = 34)	$P =$	1.1 ± 0.2 (n = 34)	$P =$	1.1 ± 0.2 (n = 32)	$P =$	1.1 ± 0.2 (n = 31)	$P =$	1.1 ± 0.2 (n = 27)	$P =$
Fluorometholone group	0.4 ± 0.3 (n = 40)	.441*	0.9 ± 0.2 (n = 37)	.730*	0.9 ± 0.3 (n = 34)	.730*	0.9 ± 0.3 (n = 36)	.002†	1.0 ± 0.3 (n = 36)	.410*	1.0 ± 0.3 (n = 32)	.127*	1.0 ± 0.3 (n = 29)	.248*

Values are mean ± SD.
*Difference is not significant.
†Difference is statistically significant.

Table 5. Intraocular Pressure (mm Hg)

	Before Surgery	After Surgery					
		1 Day	3 Days	1 Week	2 Weeks	5 Weeks	8 Weeks
Diclofenac group	12.67 ± 2.80 (n = 51)	12.84 ± 3.34 $P = .895$* (n = 51)	11.54 ± 2.47 $P = .008$† (n = 50)	11.73 ± 2.94 $P = .029$† (n = 52)	11.75 ± 2.95 $P = .027$† (n = 44)	11.40 ± 2.80 $P = .0007$† (n = 52)	11.37 ± 2.64 $P = .0002$† (n = 49)
Fluorometholone group	12.94 ± 3.03 (n = 53)	12.43 ± 3.46 $P = .138$* (n = 49)	10.56 ± 2.99 $P = .000005$† (n = 46)	11.06 ± 3.05 $P = .00001$† (n = 52)	11.71 ± 3.06 $P = .0010$† (n = 45)	11.14 ± 2.68 $P = .0000002$† (n = 51)	11.85 ± 3.12 $P = .0024$† (n =48)

Values are mean ± SD.
*Difference is not significant.
†Statistically significant changes compared to preoperative values.

sified using the Emery-Little classification; balanced salt solution was used for irrigation.

There was also no significant difference between the two groups in changes in visual acuity (Table 4).

Both groups of eyes showed significantly lower intraocular pressure at 3 days, and 1, 2, 5, and 8 weeks after surgery when compared to their preoperative value ($P < .05$–$P < .001$), as shown in Table 5.

A comparison of the degree of flare between the two groups is shown in Table 6. At 3 days, and 1, 2, 5, and 8 weeks after surgery, the fluorometholone group showed a statistically significantly increase in flare ($P < .01$–$P < .001$). The degree of flare in eyes with and without CME within each group is shown in Table 7. At 3 days, and 1, 2, 5, and 8 weeks after surgery, eyes with CME in both groups demonstrated a statistically significantly increase in flare ($P < .001$). The flare in eyes with and without CME in the fluorometholone group is shown in Table 8. At 3 days, and 1, 2, and 5 weeks after surgery, eyes with CME showed a statistically significantly increase in flare ($P < .05$–$P < .01$).

The number of cells in the anterior chamber of the two groups is shown in Table 9. At 1 and 2 weeks after surgery, the fluorometholone group had a statistically significantly greater number of cells ($P < .05$).

The incidence of CME in the two groups is shown in Table 10. Three of 53 eyes (5.7%) in the diclofenac group and 29 of 53 eyes (54.7%) in the fluorometholone group revealed CME formation. This difference was statistically significant ($P < .001$).

Discussion

Figure 1 is a schematic flow chart demonstrating the mechanism of CME formation following cataract surgery, which was presented by Miyake in 1977.[2,22] It shows that due to either the secretion of prostaglandins or the disruption of the blood–aqueous barrier, various prostaglandins and other inflammatory mediators, synthesized mainly in the iris, accumulate in the aqueous humor. Aging, diabetes mellitus, systemic vascular diseases, glaucoma, and uveitis are conditions that lead to a predisposition to disruption of the blood–aqueous barrier. Such an accumulation may also be caused by reduced active transport of prostaglandins in the iris-ciliary body.[23,24] The accumulated substances travel through the vitreous cavity to reach the retinal vessels where they increase the permeability of the vessels, leading to CME formation. For this reason, the fragility of the retinal vessels where CME is induced, namely the blood–retinal barrier, is also an important factor in considering CME formation. Aging, hypertension, and diabetes mellitus are also predisposing factors to CME formation.

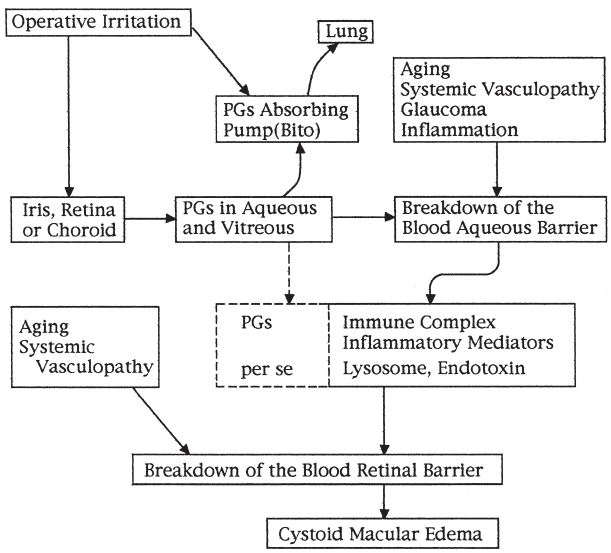

Figure 1. Hypothesis on mechanism of cystoid macular edema formation following cataract surgery.

Table 6. Aqueous Flare (Photon Counts/msec)

	Before Surgery		After Surgery											
			1 Day		3 Days		1 Week		2 Weeks		5 Weeks		8 Weeks	
Diclofenac group	8.15 ± 7.64 (n = 53)	P = .886*	16.59 ± 14.10 (n = 52)	P = .064*	12.77 ± 9.97 (n = 53)	P = 9.1×10^{-6}†	10.48 ± 3.48 (n = 52)	P = .00001†	10.65 ± 5.24 (n = 51)	P = .0002†	8.04 ± 4.38 (n = 52)	P = .0067†	6.60 ± 2.78 (n = 49)	P = .0003†
Fluorometholone group	7.95 ± 7.06 (n = 53)		24.01 ± 24.75 (n = 52)		31.63 ± 26.73 (n = 52)		30.36 ± 30.12 (n = 51)		18.17 ± 12.80 (n = 53)		11.01 ± 6.28 (n = 50)		9.67 ± 4.95 (n = 47)	

Values are mean ± SD.
*Difference is not significant.
†Difference is statistically significant.

Table 7. Aqueous Flare in Eyes With and Without Cystoid Macular Edema (CME) in the Both Groups (photon counts/msec)

	Before Surgery		After Surgery											
			1 Day		3 Days		1 Week		2 Weeks		5 Weeks		8 Weeks	
Eyes without CME	8.36 ± 8.56 (n = 74)	P = .363*	18.68 ± 22.01 (n = 72)	P = .172*	13.75 ± 9.43 (n = 74)	P = 7.8×10^{-11}†	13.40 ± 13.89 (n = 73)	P = 9.8×10^{-7}†	11.21 ± 7.60 (n = 51)	P = 6.3×10^{-7}†	7.88 ± 4.09 (n = 72)	P = 2.4×10^{-6}†	6.99 ± 3.48 (n = 67)	P = .00007†
Eyes with CME	7.34 ± 2.92 (n = 32)		23.95 ± 15.86 (n = 32)		42.08 ± 29.96 (n = 31)		37.16 ± 32.31 (n = 30)		21.84 ± 12.40 (n = 32)		13.38 ± 6.71 (n = 30)		10.68 ± 4.85 (n = 29)	

Values are mean ± SD.
*Difference is not significant.
†Difference is statistically significant.

Table 8. Aqueous Flare (Photon Counts/msec) in Eyes With and Without Cystoid Macular Edema (CME) in Fluorometholone Group

	Before Surgery		After Surgery											
			1 Day		3 Days		1 Week		2 Weeks		5 Weeks		8 Weeks	
Eyes without CME	8.92 ± 10.10 (n = 24)	P = .412*	21.70 ± 32.51 (n = 24)	P = .747*	18.56 ±11.86 (n = 24)	P = .001†	19.75 ± 22.74 (n = 24)	P = .017†	13.12 ± 10.88 (n = 24)	P = .008†	8.87 ± 5.59 (n = 23)	P = .025†	8.35 ± 4.88 (n = 20)	P = .117†
Eyes with CME	7.14 ± 2.73 (n = 29)		25.08 ± 16.20 (n = 29)		42.85 ± 30.78 (n = 28)		39.79 ± 33.04 (n = 27)		22.35 ± 12.93 (n = 29)		12.84 ± 6.35 (n = 27)		10.66 ± 4.89 (n = 27)	

Values are mean ± SD.
*Difference is not significant.
†Difference is statistically significant.

Table 9. Aqueous Cells

	Before Surgery		After Surgery											
			1 Day		3 Days		1 Week		2 Weeks		5 Weeks		8 Weeks	
Diclofenac group	0.51 ± 1.19 (n = 52)	P = .260*	6.37 ± 9.84 (n = 50)	P = .133*	3.38 ± 8.03 (n = 51)	P = .052*	0.85 ± 1.43 (n = 50)	P = .015†	0.41 ± 0.61 (n = 50)	P = .022†	0.09 ± 0.19 (n = 50)	P = .056*	0.38 ± 1.85 (n = 48)	P = .532*
Fluorometholone group	0.29 ± 0.73 (n = 53)		10.02 ± 13.75 (n = 48)		7.25 ± 11.28 (n = 48)		3.90 ± 8.47 (n = 50)		1.19 ± 2.27 (n = 52)		0.31 ± 0.77 (n = 48)		0.21 ± 0.43 (n = 27)	

Values are mean ± SD.
*Difference is not significant.
†Difference is statistically significant.

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Table 10. Incidence of Cystoid Macular Edema (CME) (No. of Eyes)

	0°	I°	II°	III°	Incidence of CME (%)	Statistical Analysis
Diclofenac group	50	2	1	0	5.7	$P =$
Fluorometholone group	24	9	16	4	54.7	3.4×10^{-8}*

*Difference is statistically significant.

The major characteristic of this hypothesis is that it emphasizes the blood–aqueous barrier disruption as the causative and/or the coexisting factor of CME. While its role as the causative factor is described above, the blood–aqueous barrier disruption has been confirmed to coexist in eyes with CME and other ocular disorders, including pigmentary retinal degeneration, intraocular tumors, vein occlusion, and diabetic retinopathy.[25] This suggests that in eyes with these diseases and CME, the ocular barriers have been disrupted by chemical mediators.[25]

As for the CME induced following cataract surgery, Miyake reported on the significance of blood–aqueous barrier disruption based on his early series of patients undergoing ICCE,[3] although studies have not been performed to confirm this. In the present study, the authors have used laser flare-cell photometry in every case to measure the blood–aqueous barrier function at various postoperative periods. These measurements showed that the breakdown of the blood–aqueous barrier was significantly more severe in eyes with CME than in those without CME. The disruption lasted for several weeks after surgery (Table 7 and 8), which supports the hypothesis that the blood–aqueous barrier disruption plays a major role as a factor causing and coexisting with CME. The correlation between the severity of disruption and CME is clinically significant because it indicates that predisposing factors, such as complications, inappropriate surgical maneuvers, and long-standing uveitis or diabetes mellitus can all lead to CME formation.

Diclofenac, the nonsteroidal drug, is an effective cyclooxygenase inhibitor.[21] Only 3 eyes receiving this drug developed mild CME, and when this incidence is compared to that in the fluorometholone group, diclofenac can be regarded as a drug that significantly blocks CME formation (Table 10). This outcome is clinically significant. Because the fifth postoperative week was found to reveal the highest incidence of CME during the natural course of CME after cataract surgery,[3] the severity of CME was determined for the two groups at 5 weeks after surgery. Compared to previous findings in similar evaluations,[2–4,6–19] the combination of diclofenac and the most recent surgical techniques consisting of a small incision, phacoemulsification, and foldable acrylic IOL implantation, seems to effectively block CME formation, and this is especially important in eyes predisposed to blood–retinal barrier disruption due to diabetes mellitus, uveitis, and other disorders.

New findings on cyclooxygenase continue to be introduced today. It was previously thought to be just one enzyme; recent studies confirmed that there are two types of cyclooxygenase.[26,27] Cyclooxygenase-1 exists in all tissue and is responsible for the biosynthesis of prostaglandins related to the homeostasis of normal tissue. On the other hand, cyclooxygenase-2, which appears when the inflammatory site is stimulated by proliferative factors, such as interleukin 1β or endotoxin, biosynthesizes prostaglandins related to inflammation. Steroidal anti-inflammatory drugs, previously believed to inhibit phospholipase A2, which is necessary for disseminating arachidonic acid from the cell membrane, have now been confirmed to play a major role in selectively inhibiting cyclooxygenase-2.[28,29] On the contrary, nonsteroidal anti-inflammatory drugs nonselectively inhibit both cyclooxygenase-1 and -2.[30,31,32]

Because of the more recent understanding of these drugs, it is worthwhile to compare the effect of steroidal and nonsteroidal anti-inflammatory drugs in the prevention of inflammation, including CME after cataract surgery. The findings from the present study and previous data indicate that nonsteroidal anti-inflammatory solutions are more effective than steroidal solutions, such as 1% predonisolone,[33,34] 0.1% dexamethasone[35,36] or 0.1% fluorometholone (present study). Topical steroid should be effective, but there has been no scientific evidence reported to date. Ohtsuka and associates have recently compared the degree of aqueous flare in the postoperative eyes treated with one of the following topical solutions: 0.1% ketorolac, 0.1% betamethasone and 0.3% ofloxacin.[37] They found that postoperative inflammation was most severe in eyes treated with antibiotics, followed by steroid and nonsteroid medication.[37] The principal reason for this is perhaps that a lower amount of topically applied steroid reaches various ocular regions, such as the anterior chamber and the iris-ciliary region. A second reason may be that the nonselective inhibition of cyclooxygenase by nonsteroidal solutions also blocks cyclooxygenase-1 prostaglandins. Blocking not only cyclooxygenase-2 prostaglandins but also cyclooxygenase-1 prostag-

landins may be more effective physiologically in preventing inflammation following cataract/IOL implantation procedure. Steroidal drugs have been developed as selective cyclooxygenase inhibitors.[28,29] The only problem concerning nonsteroidal eye drops is their side effects, causing corneal epithelial defect[38] and decreasing corneal sensitivity.[39]

Various inflammatory mediators, including prostaglandins, are believed to originate mainly from the iris and the uvea.[40,41] The data from recent studies indicate that trauma to lens epithelial cells and their healing process also contribute to the secretion of these mediators.[42,43] Using baboon eyes to perform experimental IOL implantation procedures, Miyake and associates found that the amount of prostaglandin E_2 in the aqueous humor at 1 and 8 days after surgery had significantly increased in eyes fitted with a PMMA IOL in the capsular bag compared to eyes without IOL implantation.[42] In a cell culture study using lens epithelial cells, Nishi and associates showed that the amount of prostaglandin E_2 and interleukin had increased in the culture media along with metaplasia of the these cells.[43] Further, Tsuboi and associates reported that the degree of flare in the aqueous humor was higher at early postoperative periods in eyes with in-the-bag fixation of the lens than out-of-the-bag fixation. This finding was more apparent in eyes with smaller CCC.[44] These results suggest that during cell metaplasia, induced when the IOL comes into contact with lens epithelial cells, various inflammatory mediators, including prostaglandin, are biosynthesized. In the same study using baboon eyes, Miyake and associates were able to confirm that topical application of indomethacin is effective in preventing the biosynthesis of prostaglandins even when the lens epithelial cells and the IOL are in contact.[42] These past studies also indicate that topical application of nonsteroidal anti-inflammatory solutions must be continued for a relatively long time following surgery or until the healing process of lens epithelial cells has been completed. For this reason, these drugs were applied for 8 consecutive weeks following surgery in the present study. Because nonsteroidal anti-inflammatory drugs may possibly inhibit metaplasia of lens epithelial cells, some surgeons have continued to apply diclofenac for 3 consecutive months following surgery.[45]

The arachidonic acid cascade is not the only chemical mediator related to postoperative inflammation. Other substances such as complement,[46] platelet-activating factor (PAF),[47] lysozome,[48] cytokines,[49,50] nitric monoxide,[51] and endothelin[52] are also believed to be involved. Interleukin 6, which is one of the cytokines derived from lymphocytes, has recently been studied in detail.[49,50] Malecaze and associates discovered that in 12 patients undergoing cataract surgery, the amount of interleukin 6 had increased significantly in the aqueous humor, and our data supported their clinical findings.[49] As explained above, cytokines produce cyclooxygenase-2,[28,29] and PAF interacting with interleukin and prostaglandins is believed to be responsible for inflammatory reactions.[47,52] Moreover, there are recent studies reporting that endothelin induces the arachidonic acid cascade but that cyclooxygenase inhibitors do prevent the inflammation of the anterior chamber induced by endothelin.[53,54]

In summary, there seems to be more than one mediator inducing inflammation, including postoperative inflammation. Clinically, we should focus our attention on developing drugs that effectively block these mediators without causing major side effects.

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