Latanoprost Accelerates Disruption of the Blood-Aqueous Barrier and the Incidence of Angiographic Cystoid Macular Edema in Early Postoperative Pseudophakias

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Objective: To study the effect of latanoprost, a prostaglandin analog, on the blood-aqueous barrier and angiographic cystoid macular edema (CME) formation in early postoperative pseudophakias.

Patients and Methods: Included in the study were eyes with ocular hypertension, normal-tension glaucoma, or primary open-angle glaucoma undergoing surgery for cataract. The study consisted of a randomized double-masked trial for latanoprost and an open-label controlled trial for determining the effects of diclofenac sodium or fluorometholone eyedrop use on latanoprost or its placebo. We compared 4 groups of eyes with concurrent application of latanoprost and diclofenac (group A), latanoprost and fluorometholone (group B), latanoprost placebo and diclofenac (group C), and latanoprost placebo and fluorometholone (group D). A laser flare cell meter was used to determine the severity of blood-aqueous barrier disruption, and fluorescein angiography was performed to determine angiographic CME formation. Mean diurnal intraocular pressure differences were compared on the preoperative baseline day and in the fifth postoperative week. Latanoprost (0.005%) or its placebo was given once a day starting 2 days before surgery until the fifth postoperative week. Diclofenac or fluorometholone eyedrops were given 4 times a day before surgery on the day of surgery and 3 times a day until the fifth postoperative week.

Results: In group B compared with group D, the amount of flare 3 days and 1 and 2 weeks after surgery and the incidence of angiographic CME in the fifth postoperative week were significantly higher. These 2 factors were significantly higher in group B than in group A (P < .05) and in group D than in group C (P < .01). There was no significant difference in these factors between groups A and C. The intraocular pressure decline was significant in groups A and B compared with groups C and D (P < .05), but there was no significant difference between groups A and B and between groups C and D.

Conclusions: Latanoprost therapy enhances disruption of the blood-aqueous barrier and increases the incidence of angiographic CME formation in early postoperative pseudophakias. Because administration of nonsteroidal eyedrops such as diclofenac seems to prevent the adverse effects of latanoprost therapy while maintaining its effect to lower intraocular pressure, we suggest their concurrent application.

PATIENTS AND METHODS

To study the effect of latanoprost on disruption of the blood-aqueous barrier and on the incidence of angiographic CME formation after cataract and IOL surgery, eyes with ocular hypertension, normal-tension glaucoma, or primary open-angle glaucoma were entered in the double-masked controlled trial using latanoprost (0.005% Xalatan, Pharmacia & Upjohn, Kalamazoo, Mich) and its placebo, which was sterile phosphate-buffered saline solution prepared in the hospital pharmacy. At the same time, a study on the effect of concurrent application of either diclofenac sodium (a non-steroidal drug; 0.1%Diclod, Wakamoto Pharmaceutical Co Ltd, Tokyo, Japan) or fluorometholone (a steroid drug; 0.1%Flumetholon, Santen Pharmaceutical Co Ltd, Osaka, Japan) was conducted. Flurometholone, which has similar anti-inflammatory effects as betamethasone sodium phosphate or dexamethasone sodium phosphate but is less likely to cause steroid glaucoma, was chosen for an ethical reason. However, because fluorometholone is a milky-white substance, making it difficult to conduct this part of the study as a double-masked trial, we performed it as an open-label study.

Latanoprost and its placebo were randomly assigned; and fluorometholone and diclofenac were also randomly assigned to latanoprost or its placebo.

Groups of 40 eyes (160 eyes total) receiving latanoprost and diclofenac (group A), latanoprost and fluorometholone (group B), latanoprost placebo and diclofenac (group C), and latanoprost placebo and fluorometholone (group D) initially entered the study. Inclusion criteria for these 160 consecutive patients required the patient to be older than 40 years and to have cataract and ocular hypertension, normal-tension glaucoma, or primary open-angle glaucoma; only 1 eye from each patient was considered for the trial during follow-up (5 weeks). Exclusion criteria were as follows: eyes unable to obtain a pupil diameter larger than 4 mm when mydriasis was induced for operation; eyes reacting to administration of diclofenac, fluorometholone, latanoprost, or fluoroscine sodium; eyes with a previous history of ocular surgery; and patients with other ocular or systemic disorders except glaucoma and cataract.

This study was conducted in accordance with the Declaration of Helsinki after receiving approval from the Institutional Review Board of the Miyake Eye Hospital, Nagoya, Japan. Written informed consent was obtained from each patient before inclusion in the study and after sufficient explanation about the nature of the study and the method in which fluorescein angiography is performed.

In all patients, surgery consisted of creating a 3-mm clear corneal incision and placing 1 suture if necessary. After continuous curvilinear capsulorhexis and phacoemulsification, an acrylic foldable IOL (Acrysof, Alcon Laboratories Inc, Fort Worth, Tex) was implanted inside the lens capsule. All surgical procedures were performed by 1 of 2 surgeons (K.M. or I.O.).

In patients who had been taking medication for glaucoma, the antiglaucoma treatment was discontinued 2 weeks before initiation of the study to wash out the drug. Treatment with either latanoprost or placebo was started 2 days before surgery and was given once a day at 8 AM until the fifth postoperative week. In addition, either fluorometholone or diclofenac was given 4 times on the day of surgery (3, 2, and 1 hour and 30 minutes before surgery) and then 3 times a day until the fifth postoperative week. Other drugs taken concurrently included oral and topical antimicrobial medications.

Examination and observation criteria included patient background, surgical detail, visual acuity, IOP, amount of aqueous flare as measured by a laser flare cell meter, and presence of angiographic CME as determined by fluorescein angiography.

Visual acuity was measured 1 to 3 days before surgery and 1 and 3 days and 1, 2, and 5 weeks after surgery. The fluctuation in IOP was evaluated using the average diurnal IOP measured 4 times a day—at 8 AM, 12 PM, 4 PM, and 8 PM—3 days before surgery as the baseline, comparing it with the average found in the fifth postoperative week. A laser flare cell meter (FC1000, Kowa Co Ltd, Tokyo) was used to determine the severity of blood-aqueous barrier disruption 4 to 6 days before surgery and 1 and 3 days and 1, 2, and 5 weeks after surgery.

Fluorescein angiography was performed to determine angiographic CME formation in the fifth postoperative week after IOP measurement. The late phase (15 minutes after intravenous injection of 10% sodium fluorescein) of fluorescein angiograms was graded by 1 of us (S.M.) using the method previously mentioned in a double-masked manner. Briefly, $0^\circ$ means there is no sign of fluorescein leakage; $I^\circ$, there is a slight fluorescein leakage into the cystic space but not sufficient enough to enclose the entire foveal center; $II^\circ$, there is a complete circular accumulation of the fluorescein in the cystic space but its diameter is less than 2.0 mm; and $III^\circ$, the circular accumulation of the fluorescein is larger than 2.0 mm in diameter. The Figure shows a representative example of each grade.

Patient age, surgical data, visual acuity, aqueous flare amount, and IOP among the 4 groups were analyzed using 1-way analysis of variance. Furthermore, if there were differences in each comparison, we used the Tukey test for multiple comparisons to specify the site of difference. The reduction of IOP in each group was analyzed using the paired t test. The distribution of sex, types of glaucoma, antiglaucoma medications, and family history of glaucoma were analyzed using the chi-square method. The incidence of angiographic CME was analyzed using the Fisher exact test. At all times, $P<.05$ was considered significant; the data are presented as mean±SD unless stated otherwise.
studies\textsuperscript{28,29} suggest that the synthesis of prostaglandins and cytokine may also be related to the wound healing process, proliferation, and metaplasia of lens epithelial cells after surgery. In addition, the active transport of prostaglandins\textsuperscript{30} is reduced during the time the inflammatory reaction remains active after lens extraction.\textsuperscript{31} How external prostaglandins such as latanoprost may affect these pseudophakic eyes under these circumstances also remains unclear.

In this study, we applied latanoprost eyedrops or its placebo to glaucomatous eyes to evaluate the early postoperative effects of latanoprost on the blood-aqueous barrier function and on the incidence of angiographic CME after cataract extraction and intraocular lens (IOL) implantation. The effects of concurrently applied steroidal or nonsteroidal eyedrops were also investigated. Because many eyes undergoing cataract surgery often have glaucoma, this study was relevant from both clinical and basic points of view.

\section*{RESULTS}

Because continuous curvilinear capsulorhexis failed in 1 eye from group A, the posterior capsule ruptured in 1 eye from group C, and several patients from each group did not meet the follow-up requirements (such as fluorescein angiography) because of health or social reasons, 35 eyes from group A, 37 eyes from group B, 36 eyes from group C, and 37 eyes from group D (145 eyes total) remained in the study. Included in the follow-up group were several patients unable to meet all laser flare cell metric evaluations and visual acuity measurements because of social or physical reasons.
Table 1 shows demographic and clinical characteristics of the patients. There was no significant difference in age, sex, type of glaucoma, history of drug use, and family history among patients in the 4 groups of eyes.

Table 2 summarizes surgical data. Again, there was no significant difference in operation time, hardness of the lens (classified using the method previously mentioned), ultrasound time, and amount of irrigating solution used among the 4 groups.

Table 3 summarizes the results of corrected visual acuity measurements. There was no significant difference among the 4 groups in fluctuation of visual acuity after surgery.

Table 4 summarizes the changes in IOP. Before surgery, there was no significant difference in IOP among the 4 groups of eyes. All 4 groups revealed significant decline in IOP in the fifth postoperative week compared with preoperative diurnal IOP, which is used as the baseline (P<.01). Furthermore, compared with the 2 groups of eyes receiving placebo (groups C and D), the amount of decline was significantly larger in the 2 groups receiving latanoprost (groups A and B) (P<.05), although there was no significant difference between the former 2 groups and between the latter 2 groups.

Table 5 lists the incidence of angiographic CME formation in the fifth postoperative week. The incidence was significantly higher in eyes receiving fluorometholone (groups B and D) than in those receiving diclofenac (groups A and C) (P<.01) and was significantly higher in eyes receiving latanoprost and fluorometholone (group B) compared with those receiving placebo and fluorometholone (group D) (P<.01). However, there was no significant difference in the incidence between eyes receiving latanoprost and diclofenac (group A) and those receiving placebo and diclofenac (group C).

Table 6 lists the amount of aqueous flare. None of the 4 groups showed any differences in the amount of flare determined before surgery and 1 day after surgery. In 2 groups of eyes receiving fluorometholone (groups B and D), the amount of flare 3 days and 1, 2, and 5 weeks after surgery was significantly higher compared with the other 2 groups receiving diclofenac (groups A and C) (P<.05),
except when comparing groups C and D 2 weeks after surgery. There was no significant difference in the flare amount throughout the study between eyes receiving latanoprost and diclofenac (group A) and those receiving placebo and diclofenac (group C); however, the amount of flare was significantly higher in eyes receiving latanoprost and fluorometholone (group B) compared with those receiving placebo and fluorometholone (group D) 3 days and 1 and 2 weeks after surgery (P<.05).

In this study, we confirmed that use of latanoprost eyedrops leads to disruption of the blood-aqueous barrier and significantly increases the incidence of angiographic CME soon after cataract extraction and IOL implantation in eyes with glaucoma and its related conditions. These adverse effects, however, can be prevented when latanoprost is given concurrently with nonsteroidal eyedrops. Use of latanoprost eyedrops was never reported to induce disruption of the blood-aqueous and blood-retinal barriers in experimental animal eyes and in human eyes or to lead to CME in long-standing pseudophakias.13-18 Thus, it is worthwhile to discuss the mechanism by which latanoprost disrupts the blood-aqueous barrier 1 to 2 weeks after surgery. In other words, latanoprost, an external prostaglandin F2α, including latanoprost, exist within the entire eye and in the lens epithelial cells.39 Therefore, it is highly likely that accelerated production of inflammatory mediators, which results from latanoprost encouraging proliferation and metaplasia of lens epithelial cells, enhances disruption of the blood-aqueous barrier 1 to 2 weeks after surgery. In other words, latanoprost, an external prostaglandin F2α, is not the actual mediator to disrupt the blood-aqueous barrier. If latanoprost is directly related to blood-aqueous barrier disruption, the disruption 1 day after surgery should be more severe in eyes receiving the drug. Furthermore, we discovered that blood-aqueous barrier disruption was prevented to the same level in eyes receiving nonsteroidal and latanoprost eyedrops compared with those receiving nonsteroidal eyedrops and placebo. This denies any direct relationship of latanoprost therapy in inducing barrier disruption and supports recent findings from studies reporting that latanoprost therapy has only a minimum effect, if any, on blood-aqueous barrier function.13,14,17,18

The receptors of prostaglandin F2α, including latanoprost, exist within the entire eye and in the lens epithelial cells.39 The present results should not neglect nonspecific actions, such as inducing inflammation and hyperpermeability of the vessels, of prostaglandin F2α and related compounds.20,21 Further studies are necessary to prove the above-mentioned hypothesis that latanoprost acts indirectly in enhancing postsurgical inflammation and also that latanoprost modifies biosynthesis of chemical mediators during lens epithelial cell proliferation and metaplasia. Direct detection of inflammatory chemical mediators in a culture medium using lens epithelial cells and with latanoprost may be meaningful.

There is an active transport function of prostaglandins at the anterior uvea.30 Immediately after cataract surgery, and especially when there is a vitreous prolapse, this function (also known as Bito pump) is lost.31 The loss of this transport function may also be related to and explain the enhanced disruption of the blood-aqueous barrier after latanoprost instillation. If so, however, the disruption should be most severe immediately after surgery.

**Table 4. Reduction of Intraocular Pressure (IOP)**

<table>
<thead>
<tr>
<th>Mean ± SD IOP Reduction, mm Hg</th>
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<tbody>
<tr>
<td>Group A (n = 35)</td>
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<tr>
<td>Mean diurnal IOP</td>
</tr>
<tr>
<td>At baseline</td>
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<tr>
<td>At 5 wk after operation</td>
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</tbody>
</table>

*See Table 1 for description of drug treatment groups.

**Table 5. Incidence of Cystoid Macular Edema (CME)**

<table>
<thead>
<tr>
<th>Incidence of CME, No. of Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grading</td>
</tr>
<tr>
<td>0°</td>
</tr>
<tr>
<td>I°</td>
</tr>
<tr>
<td>II°</td>
</tr>
<tr>
<td>III°</td>
</tr>
</tbody>
</table>

*See Table 1 for description of drug treatment groups. P<.01 group A vs group B, group C vs group D, and group B vs group D.
surgery and thus cannot explain why the elevation in the flare level was most significant 3 days and 1 to 2 weeks after surgery, as stated above. We therefore conclude that in pseudophakias receiving latanoprost, diminished active transport of prostaglandins plays a small role, if any, in inducing blood-aqueous barrier disruption. In our study, we encountered an increased incidence of angiographic CME in eyes receiving latanoprost shortly after cataract and IOL surgery, but this phenomenon was significantly prevented by concurrent application of nonsteroidal eyedrops. The magnitude of blood-aqueous barrier disruption is directly proportional to the incidence of angiographic CME. Thus, the increased incidence of angiographic CME because of latanoprost therapy is understandable because the drug was confirmed to indirectly disrupt the blood-aqueous barrier. Again, latanoprost itself is probably not the major factor related to angiographic CME formation, but its instillation affects the wound healing process of lens epithelial cells, resulting in biosynthesis of prostaglandins and other mediators that eventually lead to angiographic CME; we speculate that these same mediators are involved in blood-aqueous barrier disruption as well.

Although latanoprost is effective in decreasing IOP and may become the first choice of drug in treating varieties of glaucoma, it is a prostaglandin analog, necessitating careful selection of patients for indication and close monitoring of the intraocular conditions of each eye during drug use. Results of our study confirm that latanoprost given to pseudophakic eyes shortly after surgery disrupts the blood-aqueous barrier and increases the incidence of angiographic CME formation. However, these complications can be minimized and still maintain the effect in reducing IOP when latanoprost is applied concurrently with nonsteroidal eyedrops. These results suggest a possible solution to one of the few clinical problems of latanoprost therapy.

In this study, we were unable to determine how long the nonsteroidal eyedrops should be applied concurrently. If we assume that use of latanoprost modifies the wound healing process of lens epithelial cells, which is a relatively a long-term phenomenon, the period of application should generally be long. Even a longer duration of application may be indicated in eyes in which the blood-ocular barrier is predisposed by aging, diabetes mellitus, and other factors, making the eye more vulnerable to latanoprost therapy. Fragile blood-ocular barrier is often associated with eyes with broken posterior lens capsules. In these eyes, use of latanoprost should again be done with care. Recently, Rowe and associates reported a pseudophakic eye that disclosed angiographic CME at an early postoperative stage and recurrent angiographic CME a year after topical latanoprost application. This finding suggests that the blood-ocular barrier remains fragile to latanoprost application even a year after surgery.

Accepted for publication September 15, 1998.
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REFERENCES


Table 6. Aqueous Flare*

<table>
<thead>
<tr>
<th>Mean ± SD Aqueous Flare, PC/ms (No. of Eyes)</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before operation</strong></td>
<td>8.2 ± 3.0 (35)</td>
<td>8.4 ± 4.2 (37)</td>
<td>8.6 ± 5.7 (36)</td>
<td>8.9 ± 5.7 (37)</td>
</tr>
<tr>
<td><strong>Postoperative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1 d</td>
<td>19.8 ± 9.4 (35)</td>
<td>22.0 ± 9.8 (37)</td>
<td>19.1 ± 7.9 (36)</td>
<td>20.9 ± 7.8 (37)</td>
</tr>
<tr>
<td>3 d</td>
<td>14.6 ± 4.6 (35)</td>
<td>50.7 ± 28.1 (37)</td>
<td>13.7 ± 6.1 (36)</td>
<td>30.7 ± 19.1 (37)</td>
</tr>
<tr>
<td>1 wk</td>
<td>12.9 ± 4.1 (34)</td>
<td>66.4 ± 55.3 (35)</td>
<td>11.7 ± 4.6 (36)</td>
<td>27.9 ± 36.2 (36)</td>
</tr>
<tr>
<td>2 wk</td>
<td>11.7 ± 5.3 (34)</td>
<td>55.6 ± 68.3 (35)</td>
<td>12.0 ± 6.5 (35)</td>
<td>18.5 ± 7.8 (35)</td>
</tr>
<tr>
<td>5 wk</td>
<td>9.6 ± 2.1 (35)</td>
<td>15.4 ± 7.6 (37)</td>
<td>9.0 ± 1.8 (36)</td>
<td>12.8 ± 5.7 (37)</td>
</tr>
</tbody>
</table>

*See Table 1 for description of drug treatment groups. PC indicates photon count; braced data, P < .05 for comparison between these groups.
A look at the past . . .

Half an hour after a toxic dose of quinine is given to a dog, the retinal vessels become greatly constricted and vision is completely lost. After two or three days, a fair degree of vision returns, as a rule, and remains unless another dose is given.

In this investigation a number of dogs were killed at periods ranging from two hours to seven weeks after the first injection of quinine, and the eyes, optic nerves, brains and cords were examined by the Nissl methylene-blue method for cell changes in the retina. In the ganglion-cell layer and the nerve-fibre layer had almost entirely disappeared, leaving large cavities, and the myelin globules were no longer present. Many of the fibres of the optic nerve were broken down, and the degeneration of the nerve could be traced up to the termination of its fibres in the external geniculate body and pulvinar.