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

Kensaku Miyake, MD; Ichiro Ota, MD; Kumiko Maekubo, MD; Satomi Ichihashi, MD; Sampei Miyake, MD

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.


USE OF prostaglandin F\textsubscript{2\alpha} and its prodrug forms effectively lowers intraocular pressure (IOP).\textsuperscript{5,12} Results of further studies\textsuperscript{5,8} using human volunteers, however, reveal that topical application of these drugs leads to severe conjunctival hyperemia, foreign body sensation, and headache. Stjernschantz and Resul\textsuperscript{3} found that a group of phenyl-substituted compounds had the least number of adverse effects. Based on these findings, a clinical trial was conducted to determine the effects of latanoprost (PhXA41), an analog of the group mentioned above, as an antiglaucoma agent, and positive results with minimal findings on its clinical adverse effects were reported.\textsuperscript{6,8}

Although the major mechanism of latanoprost in lowering IOP is thought to be an increase in uveoscleral outflow,\textsuperscript{9-12} the drug’s physiologic mechanisms and adverse effects are not fully understood. With experimental animals, although there was a slight difference among various types of animals, the effects of latanoprost therapy on aqueous humor dynamics, blood-aqueous barrier function, and blood-retinal barrier function were minimal.\textsuperscript{13-16} In human eyes, in addition to
finding no sign of latanoprost therapy causing disruption of the blood-aqueous barrier.\textsuperscript{7,15} Administration of the drug also had no effect on cystoid macular edema (CME) formation in long-standing pseudophakic eyes.\textsuperscript{16}

The studies discussed above, however, were conducted in animal eyes or in human eyes without any eye disorders except for glaucoma and long-standing pseudophakias. Because prostaglandins are believed to play a role as inflammatory mediators,\textsuperscript{19-21} we evaluated the effects of latanoprost administration on the blood-ocular barrier in diseased eyes with abnormal activity and transport of endogenous prostaglandins.

Results of studies\textsuperscript{22-27} indicate that endogenous prostaglandins, synthesized at the anterior uvea, are involved in disrupting the blood-aqueous barrier and in inducing CME after cataract extraction. Results of recent
studies²⁸,²⁹ 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 prostaglandins³⁰ is reduced during the time the inflammatory reaction remains active after lens extraction.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.

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 mentioned36), 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).
In this study, we confirmed that use of latanoprost eye-
drops leads to disruption of the blood-aqueous barrier and
significantly increases the incidence of angiographic CME soon after cataract extraction and IOL im-
plantation in eyes with glaucoma and its related condi-
tions. These adverse effects, however, can be prevented when latanoprost is given concurrently with nonsteroi-
dal eyedrops. Use of latanoprost eyedrops was never re-
ported 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 pseu-
dophakias.13-18 Thus, it is worthwhile to discuss the mecha-
nism by which latanoprost disrupts the blood-ocular bar-
der. 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. Fur-
thermore, we discovered that blood-aqueous barrier dis-
ruption was prevented to the same level in eyes receiv-
ing 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 present results should not neglect nonspecific actions, such as inducing inflammation and hyperper-
meability of the vessels, of prostaglandin F2α, including latanoprost, exist within the entire eye and in the lens epithe-
cial cells.39 Therefore, it is highly likely that accelerated production of inflammatory mediators, which results from latanoprost encouraging proliferation and meta-
plasia 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 bar-
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The present results should not neglect nonspecific actions, such as inducing inflammation and hyperper-
meability of the vessels, of prostaglandin F2α, and relating compounds.20,21 Further studies are necessary to prove the above-mentioned hypothesis that latanoprost acts in-
directly in enhancing postsurgical inflammation and also that latanoprost modifies biosynthesis of chemical me-
diators during lens epithelial cell proliferation and pseudo-
dematplasia. Direct detection of inflammatory chemical me-
diators in a culture medium using lens epithelial cells and with latanoprost may be meaningful.

There is an active transport function of prostaglan-
dins at the anterior uvea.28 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 sur-

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

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 35)</th>
<th>Group B (n = 37)</th>
<th>Group C (n = 36)</th>
<th>Group D (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD IOP Reduction, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>21.9 ± 4.1</td>
<td>21.3 ± 5.6</td>
<td>20.3 ± 4.9</td>
<td>21.9 ± 4.9</td>
</tr>
<tr>
<td>At 5 wk after operation</td>
<td>15.5 ± 3.2</td>
<td>15.8 ± 3.3</td>
<td>18.6 ± 2.9</td>
<td>18.2 ± 3.5</td>
</tr>
</tbody>
</table>

*See Table 1 for description of drug treatment groups. 

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

<table>
<thead>
<tr>
<th>Grading</th>
<th>Group A (n = 35)</th>
<th>Group B (n = 37)</th>
<th>Group C (n = 36)</th>
<th>Group D (n = 37)</th>
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</thead>
<tbody>
<tr>
<td>0°</td>
<td>32</td>
<td>7</td>
<td>34</td>
<td>24</td>
</tr>
<tr>
<td>I°</td>
<td>2</td>
<td>15</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>II°</td>
<td>1</td>
<td>10</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>III°</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>2</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 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.

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REFERENCES

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 and the Marchi osmic-acid method for nerve-fibre changes. Two hours after injection no changes were found. Retinas examined on the third day after several toxic doses had been given, revealed degenerative changes in a few ganglion cells (vacuolation, paleness and absence of chromophilic granules, breaking down of the cell body), and changes in the nerve fibres (a deposition in the nerve-fibre layer of large globsules of a myelin-like character). On the 9th and 17th days more ganglion cells were found affected and more myelin globules were present. On the 17th day the first changes in the optic nerve were noticed, consisting in a breaking down of the medullary sheaths of a number of fibres. On the 42d and 47th days, a large cavities, and the myelin globules were noticed, consisting in a breaking down of the medullary sheaths of a number of fibres. On the 42d and 47th days, and the degeneration of the nerve fibre layer and the nerve-fibre layer had almost entirely disappeared, leaving large cavities, and the myelin globules were noticed, consisting in a breaking down of the medullary sheaths of a number of fibres.