Blood-Aqueous Barrier Changes After the Use of Prostaglandin Analogues in Patients With Pseudophakia and Aphakia

A 6-Month Randomized Trial

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Objectives: To investigate the effects of prostaglandin analogues on the blood-aqueous barrier and to evaluate the occurrence of cystoid macular edema in aphakic or pseudophakic patients with glaucoma.

Methods: In this randomized, masked-observer, 6-month clinical trial, patients with primary open-angle, pseudophakic, or aphakic glaucoma were treated once daily with bimatoprost (n=16), latanoprost (n=15), or travoprost (n=17) or twice daily with unoprostone (n=16) or lubricant drops (control group) (n=16). Blood-aqueous barrier status, which was assessed using a laser flare meter; intraocular pressure; the occurrence of angiographic cystoid macular edema; and conjunctival hyperemia were evaluated.

Results: Mean flare values were significantly higher in the bimatoprost, latanoprost, and travoprost groups throughout follow-up (P < .02). Four latanoprost-treated eyes, 1 bimatoprost-treated eye, and 1 travoprost-treated eye developed cystoid macular edema; all cases resolved after discontinuation of the prostaglandin analogue and treatment with topical diclofenac sodium. Mean intraocular pressure reductions after 6 months were higher for the latanoprost (26%), bimatoprost (28%), and travoprost (29%) groups than for the control (3%) and unoprostone (14%) groups (P < .05). Bimatoprost induced significantly higher hyperemia scores than latanoprost, unoprostone, and placebo (P < .01).

Conclusion: Bimatoprost, latanoprost, and travoprost use may lead to disruption of the blood-aqueous barrier in patients with pseudophakia and aphakia.


Several years after the observation that prostaglandin (PG) F₂, was a potent ocular hypotensive substance, latanoprost, unoprostone, travoprost, and bimatoprost were developed and became widely used in the treatment of primary open-angle glaucoma and ocular hypertension. Although these drugs have structural differences, they share similar characteristics and are often referred to as PG analogues.

Many adverse effects have been reported with PG analogues, including conjunctival hyperemia, iris hyperpigmentation, and eyelash growth. However, among the serious PG-induced adverse effects are the disruption of the blood-aqueous barrier and the development of cystoid macular edema (CME). CME has also been reported in patients with pseudophakic or aphakic glaucoma being treated with bimatoprost, travoprost, or unoprostone.

To the best of our knowledge, there are no published clinical studies that compare the safety of topical PG analogues in patients with pseudophakia or aphakia. The primary objectives of this study are to investigate the effects of PG analogues on the blood-aqueous barrier and to evaluate the occurrence of angiographic CME in patients with aphakic or pseudophakic glaucoma.

METHODS

This 6-month, randomized, masked-observer clinical trial was conducted at the Glaucoma Service of the University of Campinas. The study was performed in accordance with the Declaration of Helsinki after receiving approval from the ethics committee of the University of Campinas. Written informed consent was obtained from each patient before inclusion in the study.
Patients were eligible for participation if they met the following inclusion criteria: age older than 18 years, pseudophakia or aphakia, intraocular pressure (IOP) greater than the target level (determined by V.P.C.), and a diagnosis of primary open-angle, pseudophakic, or aphakic glaucoma. Pseudophakic and aphakic glaucoma were defined in individuals with pseudophakia and aphakia with no history of glaucoma before cataract surgery. Patients were excluded from the study if they had a history of uveitis or CME, substantial ocular irritation at baseline, or a history of intraocular surgery or a laser procedure within 6 months of baseline. We also excluded individuals who had been treated with PG analogues in the past and those who had undergone other ocular surgery except for cataract or glaucoma. Finally, the presence of systemic disorders that could be associated with uveitis or CME (i.e., diabetes mellitus and rheumatologic diseases), pregnancy, lactation, and inadequate contraception (in females) were also exclusion criteria.

If patients were eligible but were using any antiglaucoma medications (except PG analogues), hypertensive therapy was discontinued. Required washout periods before the baseline visit were 4 weeks for β-adrenergic antagonists, 2 weeks for adrenergic agonists, and 5 days for cholinergic agonists and carbonic anhydrase inhibitors. A safety check with IOP measurement was required after 2 weeks for all patients undergoing a 4-week washout. At that time, patients whose IOPs had risen to levels deemed to be detrimental were excluded from the study. No other IOP-reducing therapy was permitted during the study. If both eyes of a patient were eligible for study inclusion, the same medication was prescribed for both eyes, although only 1 eye per patient was included in the analysis.

Study medications, packaged in commercially available, labeled containers, were as follows: 0.005% latanoprost (Xalatan; Pfizer Inc, New York, NY), 0.03% bimatoprost (Lumigan; Allergan Inc, Irvine, Calif), 0.004% travoprost (Travatan; Alcon Inc, Ft Worth, Tex), and 0.12% unoprostone (Rescula; Novartis AG, Basel, Switzerland). Before dispensing, latanoprost and unoprostone were stored refrigerated at 2°C to 8°C, and patients were instructed to conserve them under refrigeration. Bimatoprost and travoprost were stored at room temperature.

To investigate the effects of benzalkonium chloride, the preservative used in all PG analogues, we included in the study a control group of patients with pseudophakic and aphakic glaucoma who had reached IOP control after trabeculectomy without the need for medication. These patients received a lubricant drop (Tears Naturale; Alcon Inc) containing 0.01% benzalkonium chloride.

To preserve masking, a designated unmasked coordinator (A.S.)—who did not perform any study evaluations or assessments—received randomization codes, dispensed the medications, and instructed the patients on how to use and store the containers. The Web program Research Randomizer v3.0 (http://www.randomizer.org) was used for random assignment. Patients were randomized to the once-daily use (at 8 PM) of bimatoprost, latanoprost, or travoprost or to the twice-daily use (at 8 AM and 8 PM) of unoprostone or placebo. New bottles of study medications were dispensed by the unmasked coordinator to all treatment groups every month to ensure that patients were using medications within the label-specified timeframe and to preserve masking.

Study visits occurred at baseline; after 7 and 15 days; and after 1, 2, 3, 4, 5, and 6 months of treatment. At baseline, the medical records of each patient were analyzed, and the following data were obtained: age, race, diagnosis, the presence of an intraocular lens, posterior capsule status, previous ocular procedures, and the interval between cataract surgery and baseline. At each visit, all patients underwent Snellen visual acuity procedures, and the interval between cataract surgery and baseline, the study medications were dispensed by the unmasked coordinator (A.S.)—who did not perform any study evaluations or assessments—received randomization codes, dispensed the medications, and instructed the patients on how to use and store the containers. The Web program Research Randomizer v3.0 (http://www.randomizer.org) was used for random assignment. Patients were randomized to the once-daily use (at 8 PM) of bimatoprost, latanoprost, or travoprost or to the twice-daily use (at 8 AM and 8 PM) of unoprostone or placebo. New bottles of study medications were dispensed by the unmasked coordinator to all treatment groups every month to ensure that patients were using medications within the label-specified timeframe and to preserve masking.

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A laser flare meter (FM 500; Kowa Co Ltd, Tokyo, Japan) was used to determine the status of the blood-aqueous barrier at all follow-up visits by the same masked investigator (E.S.A.). The flare measurements were repeated 7 times, the highest and lowest values were excluded, and the mean of the 5 remaining values was adopted as a “flare value” for statistical analysis. According to information provided by the manufacturer, flare readings greater than 26 photon counts per millisecond (p/μs) are indicative of a disruption in the blood-aqueous barrier.

The IOP was measured using a Goldmann applanation tonometer by the same investigator (E.S.A.) at all visits. Three measurements were performed in each eye, and the mean of 3 values was used for statistical analysis. At baseline and during follow-up, a masked investigator (A.S.) graded the conjunctival hyperemia according to a scale. Each eye was compared with standard photographs showing conjunctival hyperemia of grades 0, 1, 2, and 3 (none, mild, moderate, and severe, respectively) (Figure 1); the scale included values of 0, 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0.

Fluorescein angiography (FA) was performed to investigate the occurrence of CME at baseline and at 1 and 6 months of follow-up, or if a patient showed decreased visual acuity at any time during follow-up. If CME was detected, the patient was instructed to discontinue the medication, and a nonsteroidal anti-inflammatory drug, diclofenac sodium (Voltaren; Novartis), was prescribed (4 times a day for 4 weeks). Then, FA was again performed to evaluate whether the CME had resolved. The FAs were analyzed by a single masked retina specialist, who graded them as normal (no fluorescein leakage) or abnormal (fluorescein leakage compatible with CME).

Before the study, it was determined that a sample size of 14 patients in each treatment group had 90% power to detect a 20% difference in aqueous flare measurements between the groups at a significance level of α = 0.05, using the estimated variability determined in a previous study.20

Categorical variables were analyzed using the Fisher exact test or the χ² test. Continuous variables were analyzed using analysis of variance when the values were normally distributed. If statistically significant differences were detected, the Tukey test for multiple comparisons was used to identify the site(s) of difference. When values were not normally distributed and the variances were not homogeneous, we used the Kruskal-Wallis test, followed by the Wilcoxon 2-sample test if statistically significant differences were found. Within-group changes from baseline were analyzed using paired t tests.
nonparametric Spearman rank correlation test was used to evaluate the relationship between mean flare values and hyperemia scores. $P < .05$ was considered statistically significant.

**RESULTS**

Eighty patients were included in the study: 16 in the bimatoprost group, 15 in the latanoprost group, 17 in the travoprost group, 16 in the unoprostone group, and 16 in the control group. Full details on patient flow through the study and exit status are given in Figure 2. Demographic and clinical characteristics of the treatment groups are given in Table 1. There were no statistically significant differences among groups regarding sex, age, race, cup-disc ratio, diagnosis, number of previous intraocular procedures, lens status, posterior capsule status, and interval between cataract surgery and baseline.

Table 2 lists the amount of aqueous flare at baseline and at each follow-up visit for the treatment groups. In the control group, the mean flare value was significantly lower compared with baseline throughout follow-up, except at 1 month ($P = .14$). Comparing the PG analogues, although there were no significant differences at baseline ($P = .38$), mean flare values were significantly higher in the bimatoprost, latanoprost, and travoprost groups throughout follow-up compared with the unoprostone group.

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**Table 1. Demographic and Clinical Characteristics of the Treatment Groups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo Group (n = 16)</th>
<th>Unoprostone Group (n = 16)</th>
<th>Bimatoprost Group (n = 16)</th>
<th>Latanoprost Group (n = 15)</th>
<th>Travoprost Group (n = 17)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>64.7 ± 14.2</td>
<td>68.9 ± 13.5</td>
<td>69.6 ± 13.5</td>
<td>66.7 ± 15.4</td>
<td>65.8 ± 13.6</td>
<td>.82</td>
</tr>
<tr>
<td>Sex, M/F, No.</td>
<td>9/7</td>
<td>10/6</td>
<td>8/8</td>
<td>7/8</td>
<td>9/8</td>
<td>.92</td>
</tr>
<tr>
<td>Race, white/black, No.</td>
<td>16/0</td>
<td>11/5</td>
<td>10/6</td>
<td>12/3</td>
<td>13/4</td>
<td>.11</td>
</tr>
<tr>
<td>Cup-disc ratio, mean ± SD</td>
<td>0.61 ± 0.19</td>
<td>0.57 ± 0.18</td>
<td>0.70 ± 0.20</td>
<td>0.61 ± 0.18</td>
<td>0.68 ± 0.19</td>
<td>.29</td>
</tr>
<tr>
<td>Diagnosis, POAG/PG, No.</td>
<td>9/7</td>
<td>6/10</td>
<td>11/5</td>
<td>7/8</td>
<td>10/7</td>
<td>.45</td>
</tr>
<tr>
<td>No. of previous intraocular operations, mean ± SD</td>
<td>1.43 ± 0.51</td>
<td>1.12 ± 0.34</td>
<td>1.12 ± 0.34</td>
<td>1.13 ± 0.35</td>
<td>1.11 ± 0.33</td>
<td>.08</td>
</tr>
<tr>
<td>Lens status, pseudophakic/aphakic, No.</td>
<td>15/1</td>
<td>15/1</td>
<td>14/2</td>
<td>13/2</td>
<td>15/2</td>
<td>.93</td>
</tr>
<tr>
<td>Posterior capsule status, intact/ruptured, No.</td>
<td>9/7</td>
<td>9/7</td>
<td>8/8</td>
<td>8/7</td>
<td>8/9</td>
<td>.98</td>
</tr>
<tr>
<td>$\Delta t$, Mean ± SD, y</td>
<td>3.23 ± 3.23</td>
<td>3.54 ± 2.48</td>
<td>2.01 ± 2.48</td>
<td>3.39 ± 2.58</td>
<td>3.29 ± 3.09</td>
<td>.70</td>
</tr>
</tbody>
</table>

Abbreviations: PG, pseudophakic/aphakic glaucoma; POAG, primary open-angle glaucoma; $\Delta t$, interval between cataract surgery and baseline.

**Table 2. Aqueous Flare Values for Each Treatment Group at Baseline and Throughout Follow-up**

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo Group</th>
<th>Unoprostone Group</th>
<th>Bimatoprost Group</th>
<th>Latanoprost Group</th>
<th>Travoprost Group</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>10.45 ± 4.33</td>
<td>8.36 ± 2.87</td>
<td>8.80 ± 3.51</td>
<td>6.81 ± 2.75</td>
<td>7.96 ± 3.59</td>
<td>.07</td>
</tr>
<tr>
<td>7 d</td>
<td>9.23 ± 3.55</td>
<td>8.63 ± 2.91</td>
<td>18.55 ± 16.77</td>
<td>11.08 ± 6.43</td>
<td>14.75 ± 7.32</td>
<td>.01*</td>
</tr>
<tr>
<td>15 d</td>
<td>9.53 ± 3.85</td>
<td>8.32 ± 2.79</td>
<td>20.81 ± 17.03</td>
<td>12.75 ± 8.82</td>
<td>15.27 ± 7.56</td>
<td>.003*</td>
</tr>
<tr>
<td>1 mo</td>
<td>9.66 ± 4.27</td>
<td>8.60 ± 2.78</td>
<td>20.35 ± 20.28</td>
<td>12.58 ± 9.76</td>
<td>14.10 ± 6.77</td>
<td>.01*</td>
</tr>
<tr>
<td>2 mo</td>
<td>9.11 ± 3.71</td>
<td>8.21 ± 2.24</td>
<td>23.69 ± 37.64</td>
<td>10.46 ± 6.94</td>
<td>13.76 ± 6.90</td>
<td>.003*</td>
</tr>
<tr>
<td>3 mo</td>
<td>9.69 ± 3.93</td>
<td>8.21 ± 2.84</td>
<td>15.08 ± 7.60</td>
<td>9.80 ± 5.12</td>
<td>15.03 ± 7.71</td>
<td>.002*</td>
</tr>
<tr>
<td>4 mo</td>
<td>9.50 ± 3.34</td>
<td>8.61 ± 2.91</td>
<td>14.97 ± 7.78</td>
<td>9.56 ± 5.19</td>
<td>15.18 ± 7.23</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>5 mo</td>
<td>9.20 ± 3.85</td>
<td>7.28 ± 2.69</td>
<td>14.16 ± 6.73</td>
<td>9.67 ± 4.27</td>
<td>15.58 ± 7.76</td>
<td>&lt;.001*</td>
</tr>
</tbody>
</table>

*Statistically significant difference between groups (analysis of variance).
Table 3. Intraocular Pressures for Each Treatment Group at Baseline and Throughout Follow-up

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo Group</th>
<th>Unoprostone Group</th>
<th>Bimatoprost Group</th>
<th>Latanoprost Group</th>
<th>Travoprost Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>14.8 ± 2.5</td>
<td>21.2 ± 2.4</td>
<td>20.2 ± 2.3</td>
<td>20.3 ± 2.3</td>
<td>20.5 ± 2.7</td>
</tr>
<tr>
<td>7 d</td>
<td>14.4 ± 2.7</td>
<td>18.7 ± 2.2</td>
<td>15.2 ± 2.4</td>
<td>15.7 ± 2.0</td>
<td>15.1 ± 2.2</td>
</tr>
<tr>
<td>15 d</td>
<td>14.0 ± 2.4</td>
<td>18.2 ± 2.3</td>
<td>14.8 ± 2.1</td>
<td>15.1 ± 1.5</td>
<td>14.7 ± 2.1</td>
</tr>
<tr>
<td>1 mo</td>
<td>14.3 ± 2.4</td>
<td>18.2 ± 2.2</td>
<td>14.5 ± 1.9</td>
<td>14.7 ± 1.6</td>
<td>14.5 ± 1.7</td>
</tr>
<tr>
<td>2 mo</td>
<td>14.7 ± 2.8</td>
<td>17.9 ± 1.9</td>
<td>14.3 ± 2.2</td>
<td>14.9 ± 1.6</td>
<td>14.2 ± 1.9</td>
</tr>
<tr>
<td>3 mo</td>
<td>14.4 ± 3.0</td>
<td>17.7 ± 2.0</td>
<td>14.4 ± 1.9</td>
<td>15.0 ± 1.8</td>
<td>14.3 ± 1.9</td>
</tr>
<tr>
<td>4 mo</td>
<td>14.4 ± 2.6</td>
<td>18.1 ± 1.9</td>
<td>14.5 ± 2.3</td>
<td>15.0 ± 1.7</td>
<td>14.3 ± 2.0</td>
</tr>
<tr>
<td>5 mo</td>
<td>14.4 ± 2.2</td>
<td>18.1 ± 2.1</td>
<td>14.5 ± 1.9</td>
<td>15.0 ± 1.6</td>
<td>14.5 ± 2.0</td>
</tr>
<tr>
<td>6 mo</td>
<td>14.3 ± 2.4</td>
<td>17.9 ± 1.9</td>
<td>14.3 ± 2.2</td>
<td>14.9 ± 1.7</td>
<td>14.2 ± 1.8</td>
</tr>
</tbody>
</table>

*P < .001 for all; statistically significant difference between groups (analysis of variance).

prostone group (P < .02). However, there were no significant differences in mean flare measurements among eyes receiving bimatoprost, latanoprost, and travoprost at all times (P > .07). Within-group analyses showed no significant differences in flare values among patients treated with unoprostone (P > .24), whereas patients receiving bimatoprost (P < .03), latanoprost (P < .02), and travoprost (P < .01) showed significant increases in mean flare values compared with baseline at all times.

Although patients treated with bimatoprost, latanoprost, and travoprost demonstrated statistically significant increases in mean flare values, only 1 patient in the latanoprost group (7%) and 1 in the bimatoprost group (6%) had anterior uveitis detected by slitlamp examination (P = .52). Both patients also developed CME. If we consider aqueous flare values greater than 26 p/ms as indicative of uveitis, 2 patients in the bimatoprost group (12%), 2 in the latanoprost group (13%), and 2 in the travoprost group (12%) had this complication (P = .36).

When we evaluated the effect of posterior capsule status on mean flare values during follow-up, we observed that among patients treated with bimatoprost, the mean aqueous flare value was significantly higher in eyes with an absent or ruptured posterior capsule (18.70 vs 12.37 p/ms; P = .04). Levels of aqueous flare did not differ in eyes with vs without a broken posterior capsule in the latanoprost group (12.11 vs 9.81 p/ms; P = .48), the travoprost group (13.87 vs 15.79 p/ms; P = .51), the unoprostone group (7.68 vs 8.97 p/ms; P = .66), or the placebo group (7.28 vs 11.07 p/ms; P = .20).

No patient had angiographic CME at baseline. Four latanoprost-treated eyes (27%), 1 bimatoprost-treated eye (6%), and 1 travoprost-treated eye (6%) developed CME. The incidence was significantly higher in eyes receiving latanoprost than in the other groups (P = .03). Comparing latanoprost vs unoprostone and latanoprost vs placebo, the incidence of angiographic CME was significantly higher with latanoprost (P = .04). However, there was no significant difference between the incidence of CME when latanoprost-treated eyes were compared with those receiving bimatoprost (P = .17) or travoprost (P = .16). Three patients treated with latanoprost and 1 receiving travoprost developed CME at 1 month. One patient in the bimatoprost group developed CME at 2 months, and 1 patient in the latanoprost group developed CME at 6 months. Only 1 patient treated with latanoprost had CME associated with visual acuity loss (visual acuity decreased from 0.2 to 0.05). After resolution of the CME, his visual acuity improved to 0.2. All cases of CME resolved after discontinuation of the PG analogue and the use of diclofenac for 1 month.

Of the 6 patients who developed CME, 5 (83%) had an absent or ruptured posterior capsule. However, there was no significant difference between the incidence of CME in eyes with a ruptured or absent posterior capsule (13.2%) and eyes with an intact posterior capsule (2.4%) (P = .10). The mean ± SD flare values were significantly higher in patients who developed CME (30.23 ± 30.32 p/ms) compared with those who did not (11.69 ± 6.92 p/ms) (P = .03).

At baseline, mean IOP was significantly lower in the control group (P < .001), but the PG analogue groups had similar mean IOP levels (P = .71) (Table 3 and Figure 3). Within-group analyses showed no significant differences in mean IOPs among eyes receiving placebo, except at 15 days, when there was a significant decrease in mean IOP (P = .03). Patients treated with PG analogues showed significant IOP reductions at all times compared with baseline (P < .001).

Overall, mean IOP reductions after 6 months were 3% (0.4 mm Hg) for the placebo group, 14% (3.1 mm Hg)
for the unoprostone group, 26% (5.4 mm Hg) for the latanoprost group, 28% (5.8 mm Hg) for the bimatoprost group, and 29% (5.9 mm Hg) for the travoprost group. Patients receiving unoprostone had significantly higher IOP reductions than the control group (P < .05), but the mean hypotensive effect was significantly lower than that of the other PG analogues at all times (P < .05). Mean IOP reductions did not differ among the bimatoprost, latanoprost, and travoprost groups throughout follow-up (P > .05).

Changes in hyperemia scores throughout follow-up are displayed in Table 4 and Figure 4. At baseline, all patients were classified as having no hyperemia. There was a significant increase in hyperemia scores in the latanoprost, bimatoprost, and travoprost groups 1 week after baseline. Hyperemia scores reached their peak 15 days after baseline and started to decrease 1 month after therapy was initiated. Twelve patients in the bimatoprost group (75%), 8 in the travoprost group (47%), 6 in the latanoprost group (40%), 4 in the unoprostone group (25%), and 1 in the control group (6%) showed conjunctival hyperemia during follow-up (P < .001). Median (range) hyperemia scores during follow-up were 0 (0-0.5) for placebo, 0 (0-1.0) for unoprostone, 0 (0-1.0) for latanoprost, 0 (0-2.0) for travoprost, and 0.28 (0-3.0) for bimatoprost (P < .001).

Comparing the treatment groups at all times, we observed that the hyperemia scores were significantly higher in patients treated with bimatoprost compared with those treated with unoprostone or placebo throughout follow-up (P < .04). Bimatoprost-treated eyes had significantly higher grades of hyperemia than travoprost-treated eyes at 1 month (P < .04) and 2 months (P < .04). Compared with the latanoprost group, eyes receiving bimatoprost showed significantly higher hyperemia scores from 7 days to 2 months (P < .04). Patients treated with travoprost had significantly higher hyperemia scores than those treated with unoprostone at 15 days (P < .03) and than the control group at 7 days (P < .009), 15 days (P < .01), and 1 month (P < .03). Control eyes showed significantly lower hyperemia scores than latanoprost-treated eyes at 15 days (P < .01) and 1 month (P < .03). There were no significant differences regarding hyperemia scores between the unoprostone and placebo (P > .14), latanoprost and travoprost (P > .12), and latanoprost and unoprostone (P > .13) groups. The bimatoprost group had a significantly higher number of eyes (n = 8, 50%) with peak hyperemia scores of 1 or greater than the latanoprost (n = 1, 7%) (P < .02), travoprost (n = 2, 12%) (P < .03), unoprostone (n = 1, 6%) (P < .02), and control (n = 0) (P < .002) groups. There was a weak correlation between mean flare values and hyperemia scores according to the Spearman rank correlation test (r = 0.143; P < .005).

In this study, all the PG analogues statistically significantly reduced IOP in pseudophakic or aphakic eyes with glaucoma. Our findings suggest that bimatoprost, latanoprost, and travoprost administered once daily, however, are significantly more effective in reducing IOP than unoprostone administered twice daily. Twice-daily unoprostone use was associated with a 14% reduction in IOP from baseline after 6 months, which is in accordance with previous studies. The ocular hypotensive effects of latanoprost (26%), bimatoprost (28%), and travoprost (29%) did not differ statistically. Although the study was not primarily designed to compare the hypotensive effects of PG analogues, our sample had 80% power to detect IOP differences greater than 1.07 mm Hg among the groups at a significance level of α = .05.

The intensity of ocular hyperemia (the number of eyes with a peak hyperemia score ≥ 1) was also greater in the
bimatoprost group compared with the latanoprost, unoprostone, and control groups. This finding agrees with previous comparative studies that evaluated hyperemia after the use of topical PG analogues. Stewart et al evaluated conjunctival hyperemia after short-term use of latanoprost, bimatoprost, and travoprost in 28 healthy adults in a crossover study with a washout interval of 1 week. The results suggested that latanoprost therapy may cause significantly less short-term conjunctival hyperemia on average than bimatoprost and travoprost use in healthy adults. Parrish et al compared latanoprost, bimatoprost, and travoprost use in 410 patients with primary open-angle glaucoma or ocular hypertension. Masked investigators’ assessments of hyperemia were similar across treatments at baseline. However, at weeks 2 and 12, mean hyperemia scores were significantly lower for latanoprost-treated than for bimatoprost-treated patients. Hyperemia was consistently rated lowest in the latanoprost group and highest in the bimatoprost group, with patients in the travoprost group receiving intermediate mean ratings.

To investigate the effects of PG analogues on the blood-aqueous barrier, we used the laser flare meter, an objective, noninvasive, and reproducible technique, to quantitatively measure flare in the anterior chamber in vivo. In a randomized, double-masked trial, Miyake et al studied the occurrence of blood-aqueous barrier changes and angiographic CME in eyes undergoing phacoemulsification and intraocular lens implantation that received latanoprost in the early postoperative period. The authors also used the laser flare meter and reported that latanoprost therapy led to a disruption of the blood-aqueous barrier and significantly increased the incidence of angiographic CME. Furthermore, they demonstrated that these adverse effects were prevented when nonsteroidal anti-inflammatory drops were given concurrently.

The present study demonstrates that the use of bimatoprost, travoprost, and latanoprost in pseudophakic or aphakic eyes may lead to a disruption in the blood-aqueous barrier. These abnormalities were not detected in the control and unoprostone groups. We also demonstrated that disruption of the blood-aqueous barrier is not associated with the degree of conjunctival hyperemia but is significantly associated with the development of CME.

Several isolated studies have retrospectively described the development of CME in patients with pseudophakia or aphakia using PG analogues. Lima et al described 3 of 185 patients with pseudophakia or aphakia who experienced visually significant CME while using latanoprost for a mean of 10 months. Watanabe et al reported the development of visually significant CME 1 month after the use of topical latanoprost in 1 pseudophakic eye with glaucoma and a ruptured posterior capsule. The CME disappeared 2 weeks after the discontinuation of latanoprost therapy and the use of topical 0.1% betamethasone disodium and 0.1% diclofenac sodium.

Most reported cases of latanoprost-associated CME occurred in patients with coexisting ocular or systemic conditions that increase the risk of CME. These conditions include a history of CME or anterior uveitis, epiretinal membrane, vein occlusion, complicated cataract surgery, absent or ruptured posterior capsular support, the presence of an anterior chamber intraocular lens, and diabetes mellitus. Wand and Gaudio described 3 cases of CME related to PG analogues. All 3 patients had previous cataract and filtration surgery and an absent or open posterior capsule. Decreased vision of at least 2 Snellen lines caused by angiographically confirmed CME was noted in each of the 3 patients, who were receiving unoprostone, travoprost, and bimatoprost.

Apart from these isolated case reports, only 1 short-term, prospective study describes the occurrence of CME in latanoprost-treated eyes early after cataract surgery. Of the 37 eyes receiving latanoprost and fluorometholone in the postoperative period, 30 (81%) developed angiographic CME. In previous retrospective studies, that evidenced PG-related CME, FA was performed when the patient complained about visual acuity loss. Hence, it is possible that some of these patients already had angiographic CME or a disruption in the blood-aqueous barrier before starting PG analogue therapy.

The present study is the first to prospectively evaluate the long-term effects of all commercially available PG analogues on the blood-aqueous barrier in aphakic and pseudophakic eyes with glaucoma. Pretreatment measurements of aqueous flare and FAs were performed to ensure that no patient had a disruption of the blood-aqueous barrier before taking the PG analogue, and no patient with a history of uveitis or CME was allowed to participate in the study. Notwithstanding, we demonstrated that latanoprost, bimatoprost, and travoprost are capable of inducing CME in pseudophakic or aphakic eyes even in lower risk cases. The fact that only 1 of the 6 patients with angiographic CME had visual complaints suggests that the incidence of CME in patients with pseudophakia and aphakia treated with PG analogues may be higher than previously recognized.

Although the precise pathogenesis of CME is not yet fully understood, a variety of mechanisms are proposed to explain the disruption of the blood-retinal barrier. The concentration of benzalkonium chloride is 0.02% in latanoprost, 0.015% in travoprost and unoprostone, 0.01% in placebo, and 0.005% in bimatoprost. The facts that bimatoprost induced blood-aqueous barrier changes with a lower concentration of benzalkonium chloride and that unoprostone did not result in blood-aqueous barrier changes despite a higher concentration of benzalkonium chloride suggest that the preservative was not responsible for the changes we observed. Numerous clinical trials support the role of inflammatory mediators, such as PGs, in this disruption, with evidence that anti-inflammatory agents may prevent or affect the recovery of CME after cataract surgery. It has been shown that PGF2α may induce the release of endogenous PGs from the iris and ciliary muscles of mammals, including humans. The facts that patients who developed CME had significantly higher mean flare values than those who did not develop this complication and that the discontinuation of the PG analogues associated with the use of diclofenac induced CME recovery are compatible with a PG-mediated break in the blood-retinal barrier. Nevertheless, there must be other factors involved because most of even the high-risk eyes receiving ocular PG ana-
logues do not develop CME.24 Broken or absent posterior capsules are known as risk factors for the development of CME in pseudophakic or aphakic eyes.25,26 Our study indicated borderline statistical significance in the association between CME and broken posterior capsules, possibly a consequence of the small sample sizes included in the analysis.

Receptor binding studies have demonstrated that bimatoprost, latanoprost, and travoprost have high affinity for the FP receptor, whereas the affinity of unoprostone for the FP receptor is 100-fold lower. It is not clear whether binding to the PG FP receptor may be involved in the pathogenesis of PG-induced CME, but this could explain the higher incidence of CME and the significant increase in aqueous flare in patients treated with bimatoprost, latanoprost, and travoprost compared with unoprostone-treated patients.

There is not a single medication or surgical treatment without potential adverse effects and complications. It is fundamental to be aware of the potential risks of any therapy we recommend and to choose an adequate treatment plan with the best benefit-risk ratio for our patients. In this study, we confirmed that the use of bimatoprost, latanoprost, and travoprost may lead to the disruption of the blood-aqueous barrier and the development of CME in pseudophakic and aphakic eyes, even in the absence of a history of uveitis or CME. We recommend caution when prescribing bimatoprost, travoprost, and latanoprost to patients with aphakic or pseudophakic eyes with glaucoma. When therapy with one of these PG analogues is started in such a patient, careful monitoring of the blood-aqueous barrier status (by slitlamp examination) and visual acuity is advocated.

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