Effect of Topical Hypotensive Medications for Preventing Intraocular Pressure Increase after Cataract Surgery in Eyes with Glaucoma

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• PURPOSE: To compare the effects of a topical intraocular pressure (IOP)-lowering medication for preventing an IOP increase after cataract surgery in eyes with glaucoma.

• DESIGN: Randomized clinical study.

• METHODS: A total of 165 eyes of 165 patients with primary open-angle glaucoma or pseudoexfoliation glaucoma scheduled for phacoemulsification were randomly assigned to 1 of 3 groups to receive each medication immediately postoperatively: 1) prostaglandin $F_{2\alpha}$ analog (travoprost), 2) β-blocker (timolol maleate), or 3) carbonic anhydrase inhibitor (brinzolamide). Intraocular pressure (IOP) was measured using a rebound tonometer at 1 hour preoperatively, at the end of surgery, and at 2, 4, 6, 8, and 24 hours postoperatively. The incidence of eyes exhibiting a marked IOP increase to greater than 25 mm Hg was compared among the groups.

• RESULTS: At 1 hour preoperatively and at the end of surgery, mean IOP did not differ significantly among the groups. Mean IOP increased significantly between 4 and 8 hours postoperatively and then decreased at 24 hours postoperatively in all groups ($P < .0001$). Mean IOP was significantly lower in the brinzolamide group than in the travoprost or timolol group at 4, 6, and 8 hours postoperatively ($P \leq .0374$) and did not differ significantly among groups at 2 and 24 hours postoperatively. The incidence of an IOP spike was significantly lower in the brinzolamide group than in the travoprost and timolol groups ($P = .0029$).

• CONCLUSIONS: Brinzolamide reduces the short-term IOP increase after cataract surgery more effectively than travoprost or timolol in eyes with glaucoma, suggesting that brinzolamide is preferable for preventing an IOP spike. (Am J Ophthalmol 2019;205:91–98. © 2019 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)

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INCREASED INTRAOCULAR PRESSURE (IOP) FREQUENTLY occurs in the immediate postoperative period after cataract surgery in eyes with primary open-angle glaucoma (POAG) or pseudoexfoliation glaucoma.[1–6] A high IOP spike may worsen glaucomatous optic neuropathy and injure corneal endothelial cells and is, thus, a serious concern. Therefore, surgeons should aim to prevent short-term IOP increases that occur immediately after cataract surgery in eyes with glaucoma.

Previous studies have examined the effects of topical IOP-lowering medications, including prostaglandin $F_{2\alpha}$ analogs (PGFs),[7–10] β-blockers,[1,11,12] carbonic anhydrase inhibitors (CAIs),[3,7,9,13–15] and α-adrenergic agonists,[15–19] for preventing an IOP increase after cataract surgery in eyes with or without glaucoma. Whether topical agents effectively prevent IOP increases, however, remains controversial, because the exact time courses of the short-term IOP increase were not described in these studies. Recent studies revealed that oral acetazolamide administered just before surgery significantly reduces IOP increases throughout the immediate postoperative period in eyes with POAG and pseudoexfoliation syndrome.[3,5,6] Oral acetazolamide has many potential systemic side effects, however, including urinary retention, polyuria, thirst, and drowsiness. Accordingly, a topical IOP-lowering drug would be safer than oral acetazolamide for preventing a postoperative IOP increase.

The present study compared the effects of 3 topical IOP-lowering medications, travoprost (PGF), timolol maleate (β-blocker), and brinzolamide (CAI), for preventing a short-term IOP increase after phacoemulsification in eyes with POAG or pseudoexfoliation glaucoma. Because these IOP-lowering agents are currently most commonly used worldwide,[20] it is clinically important to clarify whether one of these agents is more effective for lowering IOP immediately after cataract surgery in eyes with glaucoma.

SUBJECTS AND METHODS

• STUDY DESIGN: This prospective randomized clinical study was an exploratory study to compare the prophylactic effect of 3 topical IOP-lowering medications against an IOP increase immediately after cataract surgery in eyes with POAG or pseudoexfoliation glaucoma, conducted

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between October 9, 2016, and September 28, 2018, at the Hayashi Eye Hospital in Fukuoka, Japan. This study adhered to the tenets of the Declaration of Helsinki. The Institutional Review Board of the Hayashi Eye Hospital approved the study design, and written informed consent was obtained from all patients. The study is registered in the University Hospital Medical Information Network (UMIN000034416).

• **PATIENTS:** On October 9, 2016, clinical research coordinators began screening all consecutive eyes with medically well-controlled POAG or pseudoexfoliation glaucoma that were being treated with topical hypotensive agents (IOP, ≤21 mm Hg at 2 continuous prior visits) and were scheduled for phacoemulsification with implantation of a hydrophobic acrylic intraocular lens (IOL) at the Hayashi Eye Hospital. Exclusion criteria were eyes with any ocular pathology other than cataract and glaucoma; eyes with a pupillary diameter less than 5.0 mm after mydriasis; eyes of diabetic subjects; eyes scheduled for planned extracapsular or intracapsular cataract extraction; a history of previous ocular surgery or inflammation; patients with contraindication for topical administration of PGFs, β-blockers, or CAIs; patient refusal; any anticipated difficulties with examination or follow-up; and patients who were included in another study. Screening was continued until 165 patients were recruited.

• **SAMPLE SIZE DETERMINATION:** The sample size needed for a statistical power of more than 80% to detect a clinically meaningful magnitude of difference in IOP among eyes that received 1 of 3 topical IOP-lowering medications was determined on the basis of data from a pilot study. Assuming that a difference in IOP of 4 mm Hg is clinically meaningful, it was calculated that 53 eyes per group were required based on the standard deviation of the pilot study. Assuming a possible 5% loss to follow-up, it was determined that 55 eyes were necessary for each group.

• **RANDOMIZATION:** The day before surgery, 165 eyes of 165 patients were randomly assigned to receive either travoprost (travoprost group), timolol maleate (timolol group), or brinzolamide (brinzolamide group). When both eyes were scheduled to undergo surgery, the first-operated eye was recruited. The study coordinator generated a randomization code with equal numbers (1:1:1 ratio) using computer software and assigned each patient to 1 of the 3 groups according to this code. The coordinator communicated the patient group assignments to the nurse in charge of administering the topical medication. To ensure allocation concealment, the study coordinator kept the assignment schedule concealed until all data were collected. The examiners, all nurses other than the nurse in charge, operating room staff, surgeons, and data analyst were unaware of the group to which each patient was assigned.

• **ADMINISTRATION OF TOPICAL IOP-LOWERING MEDICATIONS:** Any IOP-lowering medication that was prescribed preoperatively was stopped the day before surgery. The topical PGF used was travoprost 0.004% (Travatanz; Novartis Pharma K.K., Tokyo, Japan); the β-blocker used was timolol maleate 0.5% (Timoptol; Santen Pharmaceutical, Tokyo, Japan); and the topical CAI used was brinzolamide 1% (Azopt; Novartis Pharma K.K.). The nurse in charge administered these topical medications immediately after surgery.

• **SURGICAL TECHNIQUES:** Two surgeons (M.Y., S.M.) performed all surgeries using surgical procedures described previously.[5,6] For phacoemulsification, the surgeon performed a 2.2- or 2.4-mm clear corneal incision (CCI). First, 2 side ports were created with a slit knife approximately 90 degrees away from the main CCI. Through one side port a continuous curvilinear capsulorhexis was performed using a bent needle or anterior capsule forceps. Then, a single-plane CCI was started at the limbus without conjunctival incision, using a steel keratome. After thorough hydrodissection, phacoemulsification of the nucleus and cortical aspiration were conducted. Without enlarging the CCI, the capsular bag was inflated with 1% sodium hyaluronate (Hyaguard; Nihon Tenganyaku Kenkyusyo, Nagoya, Japan), after which the hydrophobic acrylic IOL was placed into the capsular bag by using a Monarch II injector with D-cartridge (Alcon Laboratories, Fort Worth, Texas, USA). The ophthalmic viscoelastic material was then thoroughly evacuated. The CCI and side ports were hydrated using a balanced saline solution to close the incisions. Upon completion of the surgery, the IOP was adjusted to between 15 and 25 mm Hg with stromal hydration by procedures described previously.[5,6] Briefly, examiners experienced in the use of a rebound tonometer (ICare tonometer; Tiolat, Helsinki, Finland) measured the IOP. When the IOP did not range between 15 and 25 mm Hg, it was increased to at least 30 mm Hg by injecting balanced saline solution into the anterior chamber and corneal stroma around the CCI and side ports. After the IOP was increased, it was then lowered again by carefully draining the anterior chamber fluid through a side port by using a cannula to obtain an IOP within the range of 15 to 25 mm Hg. All IOLs were implanted in the capsular bag.

• **OUTCOME MEASUREMENTS:** Patients underwent examination of IOP, visual acuity, and static visual field sensitivity before and after surgery. IOP was measured using the ICare rebound tonometer at 1 hour preoperatively, at the end of surgery, and at 2, 4, 6, 8, and 24 hours postoperatively. Details of the IOP measurement method have been described previously.[21,22] Briefly, the ICare software was programmed for 6 measurements. The highest and lowest readings were discarded, and mean IOP was calculated

TABLE 1. Comparison of Patient Characteristics at Baseline and Surgical Factors Among the 3 Study Groups

	Travoprost Group	Timolol Group	Brinzolamide Group	*P* Value
Patient characteristics at baseline				
Age (y)	72.3 ± 6.8	70.2 ± 8.5	71.5 ± 8.1	.3864[a]
Men/women	20/35	17/37	15/39	.6278[a]
Left/Right	21/34	27/27	31/23	.1282[a]
Corneal astigmatism (D)	1.01 ± 0.62	0.94 ± 0.64	1.02 ± 0.75	.7798[a]
MRSE (D)	−2.40 ± 4.48	−3.93 ± 6.88	−2.56 ± 6.00	.3281[a]
logMAR corrected visual acuity	0.39 ± 0.32	0.38 ± 0.25	0.34 ± 0.21	.5424[a]
Number (%) of eyes with pseudoexfoliation Glaucoma	7 (12.7%)	5 (9.3%)	4 (7.4%)	.6378[a]
Surgical factors				
Nuclear opalescence	2.26 ± 0.48	2.28 ± 0.56	2.26 ± 0.48	.9723[a]
Surgery times (min)	7.15 ± 2.16	6.78 ± 2.15	6.66 ± 1.80	.4367[a]
Cumulated dissipated energy (millijoules)	6.53 ± 2.88	6.91 ± 4.67	6.53 ± 5.11	.8680[a]
Infusion volume (ml)	41.27 ± 12.03	40.65 ± 11.33	40.38 ± 9.99	.9123[a]

D = diopter; logMAR = logarithm of minimal angle of resolution; MRSE = manifest spherical equivalent value.
[a]No statistically significant differences among groups.

from the remaining readings. The ICare tonometer accounts for the relationship among all measurements obtained by estimating the standard deviation to ensure a coherent final result. When the device detected the existence of any discrepancy among measurements, an error sign was displayed. In this study, IOP was measured with the patients in the supine position, and the same examiner measured the IOP for each patient. Measurements were repeated 3 times at each time point to ensure reliability of the IOP readings, and the mean value was used for analysis. The reliability and reproducibility of the data obtained using the ICare tonometer were previously reported.[21–24]

Distance-corrected visual acuity was measured on decimal charts before and after surgery. Decimal visual acuity was converted to the logarithm of minimal angle of resolution (logMAR) scale for statistical analyses. The refractive spherical and cylindrical powers were examined using an autorefractometer (model KR-7100; Topcon, Tokyo, Japan). Manifest spherical equivalent value was determined as the spherical power plus one-half the cylindrical power. Nuclear opalescence of the lens was graded using the Lens Opacities Classification System III.[25] Static visual field sensitivity was measured with the 30-2 program of the Humphrey Visual Field Analyzer (Zeiss Meditec, Dublin, California, USA) within 6 months before and after surgery. All examinations were performed by experienced ophthalmic technicians unaware of the purpose of the study.

• **STATISTICAL ANALYSES:** The normality of the data distribution was evaluated by inspecting a histogram. IOP, manifest spherical equivalent value, logMAR visual acuity, and other continuous variables followed a normal distribution, and therefore parametric tests were used for the analyses. Temporal changes in mean IOP in each group were tested by using repeated measures analysis of variance. When a significant difference was detected among the time intervals, the differences in mean IOP between each time interval pair were compared using a paired *t* test. In this study, the IOP was intentionally adjusted to range between 15 and 25 mm Hg with surgical techniques at the end of surgery. Because previous studies revealed that the postoperative IOP is independent of the adjusted IOP at the end of surgery,[5,6,26,27] the IOP at the end of surgery was excluded from the analysis.

Preoperative IOP value, age, and sex-adjusted mean IOP at 2, 4, 6, 8, and 24 hours after surgery in the 3 groups were calculated using a linear mixed model that included an interaction term between time points and medications with time points as a categorical variable (PROC MIXED with REPEATED statement and no RANDOM statement; SAS, Cary, North Carolina, USA). Mean IOPs were compared among the 3 groups at each time point. Covariance structure of the linear mixed model was selected based on the Akaike information criterion index among the unstructured, compound symmetry, and autoregressive structures. Because the Akaike information criterion index was smallest with unstructured covariance structure, the unstructured model was adopted.

The incidence of a marked IOP increase was compared among groups using the Kaplan-Meyer survival analysis with 2 criteria: 1) IOP increase to greater than 25 mm Hg, and 2) IOP values 2-fold greater than the preoperative IOP value. Differences were tested using the log-rank test. The survival curves for each pair of the 3 groups were also compared.

Manifest spherical equivalent value, logMAR visual acuity, and other continuous variables were compared among

TABLE 2. Comparison of IOP-Lowering Medications Prescribed Preoperatively and Preoperative Mean ± SD in the 3 Study Groups

	Travoprost Group	Timolol Group	Brinzolamide Group	*P* Value
Prostaglandin $F_{2\alpha}$ analog	31 (66.7%)	33 (60.0%)	31 (66.7%)	.8702[a]
β-blocker	16 (36.7%)	21 (23.3%)	20 (30.0%)	.5215[a]
Topical carbonic anhydrase inhibitor	12 (21.8%)	10 (26.7%)	5 (9.3%)	.2963[a]
Brimonidine	3 (0.0%)	7 (3.3%)	3 (6.7%)	.2545[a]
Others	0 (0%)	1 (1.9%)	2 (3.7%)	.3554[a]
Total number of intraocular pressure-lowering medications	0.91 ± 0.93	1.11 ± 0.93	0.87 ± 0.73	.3023[a]
Mean deviation (decibels)	−8.47 ± 7.33	−8.54 ± 6.29	−7.67 ± 6.39	.8069[a]
Pattern standard deviation (decibels)	6.23 ± 4.73	7.23 ± 5.53	6.14 ± 4.22	.5615[a]

[a]No statistically significant differences among groups.

the 3 groups using a one-way analysis of variance, and categorical variables were compared among groups using the chi-square goodness of fit test. When a statistically significant difference was detected among groups, the differences between each group pair was compared using the unpaired *t* test for continuous variables and the chi-square or Fisher exact test for categorical variables. Differences with a *P* value less than .05 were considered statistically significant.

RESULTS

OF THE 165 PATIENTS, 2 PATIENTS (1.2%) WERE EXCLUDED from the analysis. One patient refused to undergo examinations, and 1 patient experienced a complicated surgery. Accordingly, 163 patients (98.8%) remained for the analysis. Because the ocular appearances were identical, the examiners were unaware of which topical agent was administered to each patient. In addition, because the perioperative medications and surgical procedures were similar among groups, the patients were unaware which topical agent was administered. The randomization assignment schedule was concealed until all data were collected; therefore, the data analysts did not know which topical agent was administered to each patient.

Baseline patient characteristics and surgical factors of the 3 groups are shown in Table 1. Mean ± standard deviation (SD) age of the patients was 72.0 ± 8.0 years, and there were 52 men and 111 women. The mean age, sex, ratio of left and right eyes, preoperative manifest spherical equivalent value, preoperative visual acuity, type of glaucoma, nuclear opalescence, surgery times, and other baseline characteristics and surgical factors did not differ significantly among the 3 groups. The total numbers and types of topical IOP-lowering medications prescribed before surgery did not differ significantly among the 3 groups (Table 2). In the last examination at 6 months before surgery using the Humphrey Visual Field Analyzer 30-2 program, the mean deviation and pattern standard deviation values did not differ significantly among the groups (Table 2).

Mean IOP changed significantly over time in all groups ($P < .0001$) (Figure 1). Mean IOP at 2, 4, 6, and 8 hours postoperatively was significantly higher than the preoperative IOP and the IOP at 24 hours postoperatively in all groups ($P \leq .0003$). Each pair of postoperative time points at 2, 4, 6, and 8 hours was compared in each group. In the travoprost group, mean IOP at 8 hours postoperatively was significantly higher than the IOP at 2 hours postoperatively ($P = .0039$). In the timolol group, mean IOP at 4, 6, and 8 hours postoperatively was significantly higher than the IOP at 2 hours ($P \leq .0015$). In the brinzolamide group, mean IOP did not differ significantly among the groups at 2, 4, 6, and 8 hours postoperatively, indicating that IOP did not increase significantly during hours 2 to 8 postoperatively.

The differences in mean IOP among the 3 groups were compared using a linear mixed model analysis (Figure 2). After adjusting for preoperative IOP, age, and sex, mean IOP at 2 hours postoperatively did not differ significantly among the 3 groups. At 4, 6, and 8 hours postoperatively, mean IOP was significantly lower in the brinzolamide group than in the travoprost or timolol group ($P \leq .0374$), and no significant differences were detected between the travoprost and timolol groups. At 24 hours postoperatively, mean IOP did not differ significantly among the 3 groups.

Kaplan-Meyer survival analysis showed the incidence of IOP increase to greater than 25 mm Hg and an IOP increase 2-fold greater than preoperative IOP value were significantly different among the 3 groups ($P \leq .0393$) (Figure 3). The number (percentage) of eyes that exhibited an IOP increase greater than 25 mm Hg was 6 eyes (11.1%) in the brinzolamide group, 15 eyes (27.8%) in the timolol group, and 22 eyes (40.0%) in the travoprost group. Comparisons between each group pair revealed that the incidence of an IOP increase greater than 25 mm Hg and of an IOP increase 2-fold greater than the preoperative IOP was significantly lower in the brinzolamide group than in the travoprost group.

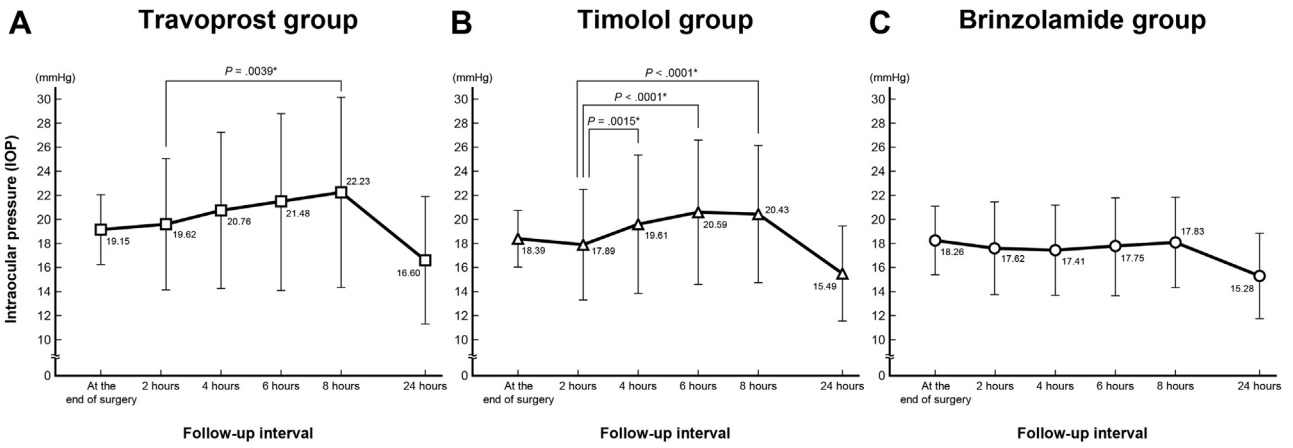

FIGURE 1. Longitudinal changes in the mean ± SD intraocular pressure (IOP) in eyes that received (A) travoprost (travoprost group), (B) timolol maleate (timolol group), or (C) brinzolamide (brinzolamide group). In all groups, mean IOP at 2, 4, 6, and 8 h postoperatively was significantly higher than the preoperative IOP and the IOP at 24 h postoperatively. Each pair of postoperative time intervals was compared at 2, 4, 6, and 8 hours in each group. (A) In the travoprost group, mean IOP at 8 h postoperatively was significantly higher than the IOP at 2 hours. (B) In the timolol group, the IOP at 4, 6, and 8 h postoperatively was significantly higher than the IOP at 2 hours. (C) In the brinzolamide group, the IOP did not change significantly among the 2-, 4-, 6-, and 8-hour intervals postoperatively.

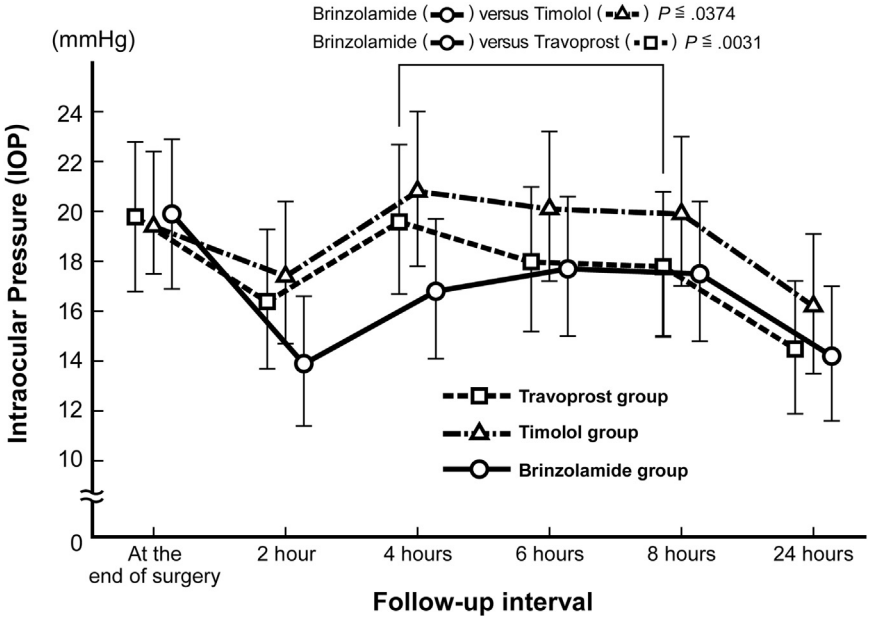

FIGURE 2. Preoperative intraocular pressure (IOP), age, and sex-adjusted mean ± SD IOPs were compared among eyes that received travoprost (travoprost group), timolol maleate (timolol group), and brinzolamide (brinzolamide group) at 2, 4, 6, 8, and 24 hours postoperatively by using a linear mixed model. Preoperative IOP, age, and sex-adjusted mean IOP at 2 and 24 hours postoperatively did not differ significantly among the 3 groups. At 4, 6, and 8 hours postoperatively, the mean IOP was significantly lower in the brinzolamide group than in the travoprost or timolol group, and no significant differences were detected between the travoprost and timolol groups.

DISCUSSION

THE FINDINGS OF THE PRESENT STUDY SHOWED THAT MEAN IOP in eyes with POAG or pseudoexfoliation glaucoma markedly increased between 4 and 8 hours after uncomplicated phacoemulsification surgery and returned to the preoperative IOP level at 24 hours postoperatively. This IOP elevation was attenuated most prominently in eyes that

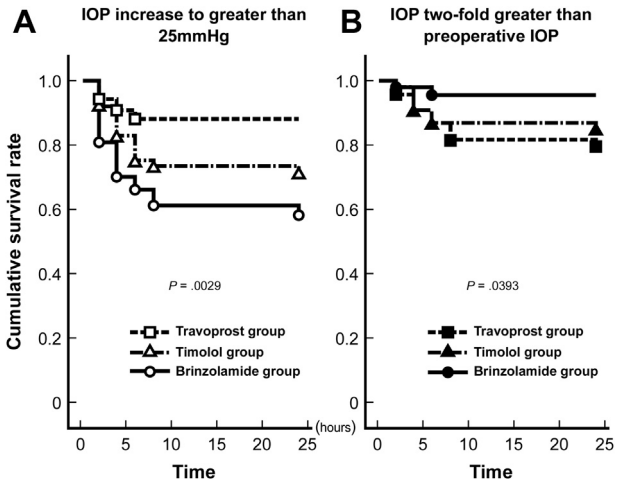

FIGURE 3. Comparison of the incidence of a marked intraocular pressure (IOP) increase among eyes that received travoprost (travoprost group), timolol maleate (timolol group), and brinzolamide (brinzolamide group) based on Kaplan-Meyer survival analysis with 2 criteria: (A) an IOP increase greater than 25 mm Hg, and (B) a 2-fold greater IOP increase than the preoperative IOP value. The incidence of a marked IOP increase differed significantly among the 3 groups with both criteria. Comparisons between each group pair revealed that the incidence was significantly lower in the brinzolamide group than in the travoprost group.

received topical brinzolamide. Furthermore, mean IOP at 4, 6, and 8 hours postoperatively was significantly lower in eyes that received brinzolamide immediately after surgery than in eyes that received travoprost or timolol, whereas mean IOP did not differ significantly between eyes that received travoprost and eyes that received timolol. Additionally, the incidence of a marked IOP increase was significantly lower in eyes that received brinzolamide than in eyes that received travoprost or timolol. These findings suggest that brinzolamide more effectively reduces the short-term IOP elevation than timolol or travoprost in eyes with glaucoma.

Patient characteristics at baseline and surgical factors did not differ significantly among groups. Additionally, the type of glaucoma, number and types of hypotensive medications prescribed before surgery, and visual field sensitivity before surgery were similar among the groups. Thus, because baseline and surgical factors that could possibly affect the short-term IOP increase were not different among groups, the lower IOP in the immediate postoperative periods in the brinzolamide group is attributed to the IOP-lowering effect of brinzolamide.

A marked IOP increase often occurs within 24 hours after cataract surgery in eyes with glaucoma[1–6,12,19] or in healthy eyes.[7–18] This short-term IOP elevation is not so harmful to healthy eyes but may enhance optic nerve damage in glaucomatous eyes, particularly in eyes with advanced glaucoma. Some studies reported that systemic administration of oral acetazolamide reduces the IOP increase in eyes with or without glaucoma[3,5,6,28,29] and that the IOP-lowering effect of oral acetazolamide is greater than that of topical CAI.[3,28,29] Oral acetazolamide has many systemic side effects, however, including urinary retention, thirst, drowsiness, and polyuria; thus, topical IOP-lowering agents are safer for prophylaxis against an IOP increase. The IOP increase-reducing effects of many topical agents, such as PGFs,[7–10] β-blockers,[1,11,12] CAIs,[3,7,9,13–15] and α-adrenergic agonists,[15–19] have been examined, but the prophylactic effects of these topical agents are conflicting. To date, no study has evaluated which topical agent is the most effective among the topical agents commonly used to treat postoperative increase in IOP. The present study revealed that brinzolamide, a topical CAI, reduced the short-term postoperative IOP increase most effectively among the topical hypotensive drugs currently preferred.

The findings of the present study may be due to differences in the peak time and intensity of the IOP-lowering effects of the 3 topical agents evaluated. A meta-analysis showed that the IOP-lowering effect of PGFs is the most intensive among these agents, but the peak time of the effect is at 12 hours after administration.[20] In contrast, the peak time of the effect of β-blockers and CAIs is at 2 hours after administration.[20] Thus, β-blockers and CAIs could more rapidly reduce an immediate IOP increase. Furthermore, comparison of the intensity of the IOP-lowering effect between β-blockers and CAIs revealed that the effect of β-blockers is more intensive than that of the CAI dorzolamide.[20,30] The evidence regarding which of the IOP-lowering effects is more intensive between β-blockers and another CAI, brinzolamide, however, is conflicting.[31,32] The present study revealed that topical brinzolamide was more effective than timolol for reducing the short-term IOP increase after cataract surgery.

The present study has several limitations. First, IOP was not examined between 8 and 24 hours postoperatively due to the difficulty in measuring IOP during the night. Because mean IOP did not change significantly among 4, 6, and 8 hours after surgery in all groups, however, it is unlikely that the IOP markedly increased later than the time intervals examined. Second, complete washout of the preoperatively prescribed medication was not performed. Because many eligible patients had severe optic nerve damage, however, a long-term interruption of the IOP-lowering medications was not permissible. Furthermore, there were no significant differences in the types and number of the preoperative medications among groups, thus, the lack of a complete washout would not likely have affected the results of the present study. Third, the prophylactic effect of brimonidine was not examined in this study. A meta-analysis, however, reported that travoprost and timolol more effectively reduce IOP than brimonidine.[20] Other studies revealed that therapy with travoprost and brinzolamide combined more effectively reduced IOP than a combination of travoprost

and brimonidine therapy.[33,34] On the basis of these previous findings, the effects of travoprost, timolol, and brinzolamide were compared in the present study.

In conclusion, mean IOP in patients with POAG or pseudoexfoliation glaucoma at 4 to 8 hours after phacoemulsification was significantly lower in eyes that received topical brinzolamide than in eyes that received travoprost or timolol maleate. The incidence of an IOP spike was lower in eyes with brinzolamide than in eyes with travoprost or timolol. Thus, in glaucomatous eyes, brinzolamide, a topical CAI, was more effective than travoprost, a PGF, or timolol maleate, a β-blocker, for reducing the short-term IOP increase postoperatively. Although oral acetazolamide also prevents an IOP increase,[3,5,6] this medication is contraindicated for patients with renal pathology or urethral calculus. Accordingly, in glaucoma patients undergoing cataract surgery, brinzolamide would be preferable to travoprost or timolol for preventing an IOP spike. The optimal number of times and optimal time points for topical brinzolamide administration, however, remain unclear. Further studies are needed to assess the optimal number of times and optimal time points for administering brinzolamide in eyes with glaucoma undergoing cataract surgery.

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REFERENCES

1. Levkovitch-Verbin H, Habot-Wilner Z, Burla N, et al. Intraocular pressure elevation within the first 24 hours after cataract surgery in patients with glaucoma or exfoliation syndrome. *Ophthalmology* 2008;115(1):104–108.
2. Ahmed II, Kranemann C, Chipman M, Malam F. Revisiting early postoperative follow-up after phacoemulsification. *J Cataract Refract Surg* 2002;28(1):100–108.
3. Fogagnolo P, Centofanti M, Figus M, et al. Short-term changes in intraocular pressure after phacoemulsification in glaucoma patients. *Ophthalmologica* 2012;228(3):154–158.
4. Slabaugh MA, Bojikian KD, Moore DB, Chen PP. Risk factors for acute postoperative intraocular pressure elevation after phacoemulsification in glaucoma patients. *J Cataract Refract Surg* 2014;40(4):538–544.
5. Hayashi K, Yoshida M, Manabe SI, Yoshimura K. Prophylactic effect of oral acetazolamide against intraocular pressure elevation after cataract surgery in eyes with glaucoma. *Ophthalmology* 2017;124(5):701–708.
6. Hayashi K, Yoshida M, Sato T, Manabe SI, Yoshimura K. Intraocular pressure elevation after cataract surgery and its prevention by oral acetazolamide in eyes with pseudoexfoliation syndrome. *J Cataract Refract Surg* 2018;44(2):175–181.
7. Rainer G, Menapace R, Schmetterer K, Findl O, Georgopoulos M, Vass C. Effect of dorzolamide and latanoprost on intraocular pressure after small incision cataract surgery. *J Cataract Refract Surg* 1999;25(12):1624–1629.
8. Lai JS, Loo A, Tham CC, Ho SY, Lam DS. Preoperative latanoprost to prevent ocular hypertension after phacoemulsification and intraocular lens implantation. *J Cataract Refract Surg* 2001;27(11):1792–1795.
9. Ermis SS, Ozturk F, Inan UU. Comparing the effects of travoprost and brizolamide on intraocular pressure after phacoemulsification. *Eye* 2005;19(3):303–307.
10. Unal M, Yücel I. Effect of bimatoprost on intraocular after cataract surgery. *Can J Ophthalmol* 2008;43(6):712–716.
11. Fry LL. Comparison of the postoperative intraocular pressure with Betagan, Betoptic, Timoptic, Iopidine, Diamox, Pilopine Gel, and Miostat. *J Cataract Refract Surg* 1992;18(1):14–19.
12. Barak A, Desatnik H, Ma-Naim T, Ashkenasi I, Neufeld A, Melamed S. Early postoperative intraocular pressure pattern in glaucomatous and nonglaucomatous patients. *J Cataract Refract Surg* 1996;22(5):607–611.
13. Dayanir V, Ozcura F, Kir E, Topaloğlu A, Ozkan SB. Aktunç T Medical control of intraocular pressure after phacoemulsification. *J Cataract Refract Surg* 2005;31(3):484–488.
14. Zohdy GA, Rogers ZA, Lukaris A, Sells M, Roberts-Harry TJ. A comparison of the effectiveness of dorzolamide and acetazolamide in preventing post-operative intraocular pressure rise following phacoemulsification surgery. *J R Coll Surg Edinb* 1998;43(5):344–346.
15. Cetinkaya A, Akman A, Akova YA. Effect of topical brinzolamide 1% and brimonidine 0.2% on intraocular pressure after phacoemulsification. *J Cataract Refract Surg* 2004;30(8):1736–1741.
16. Whitehouse G. Brimonidine and postoperative pressure spikes in cataract surgery. *Clin Exp Ophthalmol* 2000;28(5):364–366.
17. Rainer G, Menapace R, Findl O, Petternel V, Kiss B, Georgopoulos M. Effect of topical brimonidine on intraocular pressure after small incision cataract surgery. *J Cataract Refract Surg* 2001;27(8):1227–1231.
18. Katsimpris JM1, Siganos D, Konstas AG, Kozobolis V, Georgiadis N. Efficacy of brimonidine 0.2% in controlling acute postoperative intraocular pressure elevation after phacoemulsification. *J Cataract Refract Surg* 2003;29(12):2288–2294.
19. Kandarakis A, Soumplis V, Karampelas M, et al. Efficacy of brimonidine in preventing intraocular pressure spikes following phacoemulsification in glaucoma patients. *Eur J Ophthalmol* 2010;20(6):994–999.
20. van der Valk R, Webers CA, Schouten JS, Zeegers MP, Hendrikse F, Prins MH. Intraocular pressure-lowering effects

of all commonly used glaucoma drugs: a meta-analysis of randomized clinical trials. *Ophthalmology* 2005;112(7):1177–1185.
21. Nakamura M, Darhad U, Tatsumi Y, et al. Agreement of rebound tonometer in measuring intraocular pressure with three types of applanation tonometers. *Am J Ophthalmol* 2006;142(2):332–334.
22. Salim S, Du H, Wan J. Comparison of intraocular pressure measurements and assessment of intraobserver and interobserver reproducibility with the portable ICare rebound tonometer and Goldmann applanation tonometer in glaucoma patients. *J Glaucoma* 2013;22(4):325–329.
23. Jablonski KS, Rosentreter A, Gaki S, Lappas A, Dietlein TS. Clinical use of a new position-independent rebound tonometer. *J Glaucoma* 2013;22(9):763–767.
24. Rao A, Kumar M, Prakash B, Varshney G. Relationship of central corneal thickness and intraocular pressure by iCare rebound tonometer. *J Glaucoma* 2014;23(6):380–384.
25. Chylack LT, Wolfe JK, Singer DM, et al. The Lens Opacities Classification System III: The Longitudinal Study of Cataract Study Group. *Arch Ophthalmol* 1993;111(6):831–836.
26. Hayashi K, Yoshida M, Manabe S, Yoshimura K. Effect of high pressurization versus normal pressurization on changes in intraocular pressure immediately after clear corneal cataract surgery. *J Cataract Refract Surg* 2014;40(1):87–94.
27. Hayashi K, Tsuru T, Yoshida M, Hirata A. Intraocular pressure and wound status in eyes immediately after scleral tunnel incision and clear corneal incision cataract surgery. *Am J Ophthalmol* 2014;158(2):232–241.
28. Maus TL, Larsson LI, McLaren JW, Brubaker RF. Comparison of dorzolamide and acetazolamide as suppressors of aqueous humor flow in humans. *Arch Ophthalmol* 1997;115(1):45–49.
29. Portellos M, Buckley EG, Freedman SF. Topical versus oral carbonic anhydrase inhibitor therapy for pediatric glaucoma. *J AAPOS* 1998;2(1):43–47.
30. Boyle JE, Ghosh K, Gieser DK, Adamsons IA. A randomized trial comparing the dorzolamide-timolol combination given twice daily to monotherapy with timolol and dorzolamide. Dorzolamide-Timolol Study Group. *Ophthalmology* 1998;105(10):1945–1951.
31. Hollo G, Chiselita D, Petkova N, et al. The efficacy and safety of timolol maleate versus brindolamide each given twice daily added to travoprost in patients with ocular hypertension or primary open-angle glaucoma. *Eur J Ophthalmol* 2006;16(6):816–823.
32. Pfeiffer N, TATS (Travatan Adjunctive Treatment Study) group. Timolol versus brinzolamide added to travoprost in glaucoma or ocular hypertension. *Graefes Arch Clin Exp Ophthalmol* 2011;249(7):1065–1071.
33. Feldman RM, Tanna AP, Gross RL, et al. Comparison of the ocular hypotensive efficacy of adjunctive brimonidine 0.15% or brinzolamide 1% in combination with travoprost 0.004%. *Ophthalmology* 2007;114(7):1248–1254.
34. Reis R, Queiroz CF, Santos LC, Avila MP, Magacho L. A randomized, investigator-masked, 4-week study comparing timolol maleate 0.5%, brinzolamide 1%, and brimonidine tartrate 0.2% as adjunctive therapies to travoprost 0.004% in adults with primary open-angle glaucoma or ocular hypertension. *Clin Ther* 2006;28(4):552–559.