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Prophylactic Effect of Oral Acetazolamide against Intraocular Pressure Elevation after Cataract Surgery in Eyes with Glaucoma

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Purpose: To confirm the prophylactic effect of oral acetazolamide against increased intraocular pressure (IOP) in the period immediately after cataract surgery in eyes with primary open-angle glaucoma (POAG) and to evaluate the appropriate administration time of oral acetazolamide to prevent IOP elevation.

Design: Randomized clinical study.

Participants: Ninety eyes of 90 patients with well-controlled POAG scheduled for phacoemulsification.

Methods: Eyes were assigned randomly to 1 of 3 groups: (1) oral acetazolamide (500 mg) administration 1 hour preoperatively, (2) oral acetazolamide (500 mg) administration 3 hours postoperatively, or (3) no acetazolamide administration. Intraocular pressure was measured using a rebound tonometer 1 hour preoperatively, at the conclusion of surgery (adjusted in the range between 15 and 25 mmHg), and 1, 3, 5, 7, and 24 hours postoperatively. The incidence of eyes with IOP elevation more than 100% above the preoperative IOP was compared.

Main Outcome Measures: Postoperative IOP and incidence of eyes with marked IOP elevation.

Results: Mean IOP 1 hour preoperatively and that at the conclusion of surgery did not differ significantly among groups. In all groups, mean IOP was significantly elevated from 3 to 7 hours postoperatively, and then decreased at 24 hours. At 1 and 3 hours postoperatively, mean IOP was significantly lower in the group receiving oral acetazolamide preoperatively than in the other 2 groups (postoperative administration or no administration; $P \leq 0.0031$). At 5, 7, and 24 hours postoperatively, the IOP was significantly lower in both the preoperative and postoperative administration groups than in the nonadministration group ($P \leq 0.0224$). Intraocular pressure elevation of more than 100% occurred in 1 eye (3.3%) in the preoperative administration group, 7 eyes (23.3%) in the postoperative administration group, and 8 eyes (26.6%) in the nonadministration group; the incidence was significantly lower in the preoperative administration group ($P = 0.0459$).

Conclusions: Eyes with POAG experienced short-term IOP elevation from 3 to 7 hours after phacoemulsification. Oral acetazolamide administration 1 hour preoperatively significantly reduced the IOP elevation from 1 to 24 hours, while administration 3 hours postoperatively reduced the IOP elevation at 5 hours or more after surgery. *Ophthalmology 2017;■:1–8 © 2016 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Intraocular pressure (IOP) markedly increases in a high percentage of patients with glaucoma in the immediate or early period after cataract surgery.[1–5] Short-term IOP elevation may occur within 7 hours after surgery, although in most studies, the IOP was not measured periodically.[3–7] Because marked IOP elevation may worsen glaucomatous optic nerve damage, surgeons should consider prophylaxis against a short-term IOP spike in eyes with glaucoma. According to a United Kingdom–wide consultant survey, 37.4% of ophthalmic surgeons routinely prescribe an antiglaucoma medication for eyes that are to undergo cataract surgery.[8]

Several studies have evaluated the prophylactic effects of many types of topical antiglaucoma medications, including prostaglandin $F_{2\alpha}$ analogs, topically active carbonic anhydrase inhibitor II, β-blockers, or topical α-adrenergic agonists, against immediate postoperative IOP increases, but the findings regarding their short-term effectiveness are conflicting.[4,6,9–13] In contrast, prophylactic administration of oral acetazolamide has a rapid and substantial effect against short-term IOP spikes.[14–18] Indeed, in a United Kingdom–wide consultant survey, 87% of responders who routinely prescribe prophylactic medications prefer oral acetazolamide administration to topical agents.[8] However, in most studies and in clinical situations, antiglaucoma medications, including oral acetazolamide, are used just before or after cataract surgery. Because the exact time course of short-term IOP elevation after cataract surgery remains controversial, the optimal time for administration of antiglaucoma medications to protect against postoperative IOP elevation is unclear.

The purpose of the present study was to examine the time course of short-term IOP elevation in eyes with glaucoma after cataract surgery, to assess the prophylactic effect of oral acetazolamide against IOP elevation, and to determine the optimal time for administering acetazolamide using a

http://dx.doi.org/10.1016/j.ophtha.2016.12.027
ISSN 0161-6420/17

linear mixed model. Because the time course of the short-term IOP elevation may differ depending on the type of glaucoma, only patients with primary open-angle glaucoma (POAG) were recruited for this study.

Methods

Patients

This was a prospective, randomized clinical study. On September 9, 2014, a clinical research coordinator began screening all consecutive eyes with medically well-controlled POAG (IOP $\leq$21 mmHg at 2 continuous visits before surgery) that were scheduled for phacoemulsification with intraocular lens implantation at the Hayashi Eye Hospital. Exclusion criteria were eyes with any pathologic features other than cataract and POAG; eyes with pseudoexfoliation syndrome; eyes scheduled for planned extracapsular or intracapsular cataract extraction; eyes with a history of ocular surgery or inflammation; patients with contraindication for oral acetazolamide; patient declining to participate; and any anticipated difficulties with examination or follow-up. Eyes with an IOP higher than 21 mmHg at 2 prior continuous visits and included in another study also were excluded from the present study. Screening was continued until 90 patients were recruited, on May 10, 2016. This research adhered to the tenets of the Declaration of Helsinki. The Institutional Review Board/Ethics Committee of the Hayashi Eye Hospital, Fukuoka, Japan, where this study was conducted, approved the study protocol, and all patients provided written informed consent to participate. This study was registered in the University Hospital Medical Information Network (identifier, 000017556).

Randomization

All 90 enrolled patients were assigned randomly to 1 of 3 groups (n = 30/group) the day before surgery: (1) eyes that were to undergo oral acetazolamide administration 1 hour before surgery (preoperative administration group), (2) eyes that were to undergo oral acetazolamide administration 3 hours after surgery (postoperative administration group), or (3) eyes that were not to undergo administration (nonadministration group). The coordinator of this study generated a randomization code with equal numbers (1:1:1 ratio) using random number tables and assigned each patient to 1 of the 3 groups according to this code. The coordinator informed a nurse who was in charge of oral acetazolamide administration which group the patient had been assigned to. To ensure allocation concealment, the coordinator kept the assignment schedule concealed until all data were collected. The examiners, all nurses other than the nurse in charge, operating room staff, surgeon, and data analyst were unaware of the groups to which the patients had been assigned.

Oral Acetazolamide Administration

Any topical antiglaucoma hypotensive medication that was prescribed before surgery was stopped the day before surgery. The nurse in charge administered 500 mg oral acetazolamide (Diamox; Sanwa Kagaku Kenkyusho, Nagoya, Japan) to patients in the preoperative administration group 1 hour before surgery or the same dose of oral acetazolamide to patients in the postoperative administration group 3 hours after surgery. The immediate release formulation of oral acetazolamide was administered.

Surgical Techniques

One surgeon (M.Y.) performed all of the cataract surgeries. Each eye received a 2-ml injection of 2% Xylocaine (AstraZeneka, Osaka, Japan) into the sub-Tenon's capsule at the beginning of surgery. Clear corneal incision cataract surgery was performed using standardized techniques and instruments essentially as described previously.[19] After making 2 side ports with a knife, a continuous curvilinear capsulorrhexis was performed through a side port using a bent needle. A 2.2-mm single-plane clear corneal incision was made with a steel keratome from the posterior margin of the cornea. After thorough hydrodissection, phacoemulsification of the nucleus and aspiration of the residual cortex was conducted. The lens capsule was inflated with 1% sodium hyaluronate (Hyaguard; Nihon Tenganyaku Kenkyusyo, Nagoya, Japan) for implantation of a single-piece hydrophobic acrylic intraocular lens (SN60WF; Alcon Laboratories, Fort Worth, TX), after which the intraocular lens was placed into the capsular bag using a Monarch II injector with a C cartridge (Alcon). The viscoelastic material then was evacuated thoroughly. The clear corneal wound and side ports were hydrated using a balanced saline solution. At the conclusion of surgery, IOP was adjusted to range between 15 and 25 mmHg with stromal hydration using the method described previously.[20] In brief, an examiner trained to use a rebound tonometer (Icare; Tiolat, Helsinki, Finland) measured the IOP using the Icare rebound tonometer. When the IOP was not in the range between 15 and 25 mmHg, the IOP was increased to approximately 30 mmHg by injecting balanced saline solution into the anterior chamber and corneal stroma around the wound and side ports to close these incisions. After raising the IOP, it was reduced by draining the anterior chamber fluid through a side port using the cannula to obtain an IOP within the range of 15 to 25 mmHg.

Outcome Measures

All patients underwent IOP measurement and examinations of wound status and flare intensity in the immediate and early periods after cataract surgery. The IOP was measured using the Icare rebound tonometer 1 hour before surgery, at the conclusion of surgery, and 1, 3, 5, 7, and 24 hours after surgery. The details of this tonometer were described previously.[21] In brief, the Icare tonometer includes a solenoid magnetized probe and processing electronics. The probe moves toward the cornea at a speed of approximately 0.2 m/second. After the initial propulsion pulse is completed, the probe impacts the corneal surface, decelerates, and rebounds from the corneal surface. Signal processing electronics and microcontrollers register the probe's deceleration time upon corneal impact. The software is programmed for 6 measurements; the highest and lowest readings are discarded, and mean IOP is calculated from the remaining readings. The software can detect whether an incorrect measurement is obtained. In these cases, the tonometer shows an error message and does not accept the readings as correct. Additionally, the Icare tonometer considers the relationship among all measurements obtained by estimating the standard deviation to ensure a coherent final result. When the device detects the existence of any discrepancy among measurements, an error sign is displayed. In the present study, IOP was measured with the patients lying in the supine position. The same examiner performed all IOP measurements for each patient. To ensure reliability of the IOP readings, the measurements were repeated 3 times, and the mean value was used for analysis. When any type of error sign was displayed or in the event of a discrepancy between 1 IOP reading and the other 2 readings, the reading was excluded and another measurement was obtained. Many studies