Early Aqueous Suppressant Therapy on Hypertensive Phase Following Glaucoma Drainage Device Procedure: A Randomized Prospective Trial

Simon K. Law, MD, PharmD, Helen L. Kornmann, MD, PhD, JoAnn A. Giaconi, MD, Allen Kwong, BS, Eric Tran, BA, and Joseph Caprioli, MD

Purpose: To prospectively evaluate the effect of early aqueous suppression (therapy) on hypertensive phase (HP) and intraocular pressure (IOP) control after implantation of silicone Ahmed glaucoma valve (AGV).

Materials and Methods: Patients who underwent AGV implantation were randomized to initiate therapy (including β-blockers, α-agonists, or carbonic anhydrase inhibitors) when postoperative IOP > 10 mm Hg (low-IOP initiation group) or > 17 mm Hg (moderate-IOP initiation group). HP was defined as an IOP > 21 mm Hg during the first 6 postoperative months, after an initial IOP reduction to < 22 mm Hg in the first postoperative week. Primary outcome measures included the occurrence of HP and IOP control.

Results: Fifty-two eyes (50 patients) underwent AGV implantation. Average follow-up was 21.9 ± 10.7 months. HP was observed in 21 eyes (40.4%) with average peak IOP of 30 ± 8 mm Hg, onset at 32 ± 30 days, and duration of 15 ± 32 days. One year postoperatively, those eyes with HP had higher IOP than eyes that did not develop HP (15.1 ± 5.2, 11.4 ± 4.3, respectively; $P = 0.021$) and required more additional glaucoma surgeries (28.6%, 3.2%, respectively; $P = 0.013$). The peak IOP at week 3 postoperatively in the low-IOP initiation group (26 eyes) was significantly lower than in the moderate-IOP initiation group (26 eyes; 15.7 ± 3.6, 20.6 ± 8.9, respectively; $P = 0.012$). Eyes with therapy started after HP onset had significantly higher postoperative IOP from 2 to 4 months. Therapy initiated before the development of HP was not associated with a higher complication rate.

Conclusions: Aqueous suppression initiated in the early postoperative period while IOPs were still in the low-teens and was able to reduce the incidence of IOP spike associated with the HP without an increased complication rate.

Key Words: hypertensive phase, glaucoma drainage device, intraocular pressure, glaucoma

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Glaucoma drainage devices (GDDs) are designed to reduce intraocular pressure (IOP) by allowing aqueous humor through a tube to the subconjunctival space, which is maintained by an episcleral end-plate. Fibrous encapsulation of the end-plate produces a reservoir into which aqueous humor pools.[1,2] Aqueous humor is reabsorbed into the systemic circulation through the fibrous encapsulation by diffusion.[3] After tube implantation, an initial reduction of IOP is frequently followed by a rebound IOP increase called the hypertensive phase (HP).[4,5] Such a rise of IOP has been observed with GDDs of various designs.[6–11] For the Ahmed glaucoma valve (AGV; New World Medical Inc., Cucamonga, CA), the HP has been reported to occur about 4 to 8 weeks after the device's implantation.[5] A study on the polypropylene rigid AGV (model S-2) showed that the HP resolved in approximately 50% of patients with medical treatment, with pressure gradually returning to < 20 mm Hg in the ensuing weeks and months.[5] Aggressive management was required during the HP to avoid irreversible damage to the visual function, and medical therapy typically was begun at the onset of the HP.[12] The exact cause of the HP is unknown, although it is postulated that early exposure to inflammatory factors within aqueous humor may lead to denser fibrous encapsulation.[9] We hypothesize that earlier initiation of glaucoma therapy, particularly aqueous suppressants, may be effective in reducing the rate of HP and the magnitude and duration of IOP rise.

The purposes of this study were: (1) to prospectively evaluate HP characteristics in eyes receiving early aqueous suppressant therapy after implantation of the flexible silicone AGV (model FP-7); and (2) to analyze the effect of aqueous suppressant therapy initiation at 2 different levels of IOP (> 10 vs. > 17 mm Hg).

MATERIALS AND METHODS

This was a prospective comparative study approved by the Institutional Review Board of the University of California Los Angeles (UCLA IRB#10-001426) and registered with ClinicalTrials.gov (NCT00869141). The study was conducted according to the tenets of the Declaration of Helsinki. Informed consent was obtained from subjects before study enrollment.

Inclusion and Exclusion Criteria

All subjects requiring AGV implantation to control IOP between the ages of 18 to 85 years were invited to participate in this prospective study. Patients were excluded if they were unwilling to accept randomization, had a known allergic reaction to β-blockers, selective α-2 agonists, carbonic anhydrase inhibitors, or sulfa drugs, had medical conditions for which the use of β-blockers was contraindicated (such as unstable congestive heart failure, heart blockage, asthma, or chronic obstructive pulmonary disease), were scheduled for a

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From the Glaucoma Division, Jules Stein Eye Institute, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA.
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Reprints: Simon K. Law, MD, PharmD, Glaucoma Division, Jules Stein Eye Institute, David Geffen School of Medicine, University of California Los Angeles, 100 Stein Plaza #2-235, Los Angeles, CA 90095 (e-mail: law@jsei.ucla.edu).

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concurrent intraocular procedure with AGV implantation, or had previous GDD implanted.

Definitions

HP was defined in accordance with existing literature as IOP > 21 mm Hg during the first 6 postoperative months after an initial reduction of IOP to < 22 mm Hg during the first postoperative week, not caused by tube obstruction, retraction, or valve malfunction. Preoperative IOP was defined as the average of the last 3 IOPs within 3 months of AGV implantation.

Randomization

Patients were randomized to receive aqueous suppression when postoperative IOP reached a level > 10 mm Hg in the low-IOP initiation group or > 17 mm Hg in the moderate-IOP initiation group. An IOP of 10 mm Hg was chosen for the low-IOP initiation group based on the closing pressure of the AGV's valve mechanism, as reported in the literature. The in vitro closing pressure of the silicone AGV was shown to be 7.1 ± 5.0 mm Hg with significant variability (ranging from 1.4 to 13.5 mm Hg with 50% closed < 5 mm Hg).[13] By setting the criterion of aqueous suppression initiation slightly higher than the closing pressure, we tried to avoid postoperative hypotony and associated complications.[14] An IOP of 17 mm Hg was chosen for the moderate-IOP initiation group based on our usual clinical practice and in the hopes that aqueous suppression would begin before patients with advanced glaucoma entered the predefined HP (> 21 mm Hg). It would be unethical to deliberately allow subjects to experience an IOP spike in the HP by withholding therapy. Neither the investigators nor the patients were masked to which treatment group the subjects were randomized. A permuted variable block randomization scheme stratified by types of glaucoma (neovascular glaucoma, uveitic glaucoma, and others) was used to assure unbiased treatment assignment. Neovascular and uveitic glaucomas were stratified because of the possible relationship between postoperative inflammation intensity and fibrous encapsulation formation.[15–17]

As postoperative IOP variation is highly individual, we did not expect that aqueous suppressant therapy would be started before HP developed in all eyes. We estimated that a greater number of eyes in the moderate-IOP initiation group than in the low-IOP initiation group would develop HP before aqueous suppressant therapy could be initiated.

Surgical Technique

A flexible silicone plate AGV (model FP-7) and peribulbar anesthesia with 5 mL of 1% lidocaine and 0.75% of bupivacaine in a one-to-one mixture were used in all cases. A fornix-based flap of conjunctiva and Tenon capsule was created in the superior temporal quadrant. The AGVs were positioned in the middle of the quadrant, with the anterior edge of the plate positioned 8 to 10 mm posterior to the superotemporal corneoscleral limbus. The tube was irrigated with balanced salt solution to ensure patency. The tube was then trimmed bevel-up to extend 2 to 3 mm into the anterior chamber before insertion through a scleral track that was created with a 22-G needle into the anterior chamber. Viscoelastic material was injected through the needle track into the anterior chamber to maintain the anterior chamber before tube insertion. A commercially available processed single-layer pericardium graft (Tutoplast; IOP Inc., Costa Mesa, CA) was used to cover the scleral entry site and the anterior 8 mm of the tube by securing the graft to the episcleral surface with 9-0 polyglactin suture. The conjunctiva and Tenon capsule were closed to the limbus with the same suture.

Preoperative and Postoperative Care

Subjects underwent routine ocular examination including visual acuity measurement with Snellen acuity chart, slit-lamp examination of the anterior segment, IOP estimation by Goldmann tonometry, and ophthalmoscopy for dilated fundus examination before and after the AGV implantation procedure.

After the surgery, all subjects received an antibiotic drop to be used 4 times daily for 1 week, and a topical steroid (prednisolone acetate 1%) starting 4 times daily and tapered over 4 to 6 weeks. All subjects were monitored weekly in the first postoperative month, then every month for 6 months and yearly thereafter. Patients could be brought back sooner than the required study visits. At each visit, visual acuity and IOP were measured. Other routine ocular examination procedures were performed according to the surgeon's discretion.

Medications that primarily suppress aqueous humor production could be used in any combination according to the treating surgeon's discretion. Medications used included timolol 0.5%, dorzolamide 0.2%, brinzolamide 1%, brimonidine 0.1% or 0.15%, and oral acetazolamide or methazolamide. To protect the subjects from unnecessary exposure to high IOP, there was no restriction on additional therapy to control elevated IOPs. Any topical or systemic medical therapy and surgical therapy could be pursued.

Statistical Analysis and Sample Size Determination

It was determined that for IOP comparisons, a sample size of 25 in each arm would detect an IOP difference of 4 mm Hg (eg, mean IOP of 13 vs. 17 mm Hg, or 18 vs. 22 mm Hg) between the 2 arms with a SD of 5 mm Hg for an 80% (0.8) power at an α error of 0.05.

Primary outcome measures included IOP and HP characteristics. Secondary outcome measures included visual acuity, number of glaucoma medications, additional glaucoma surgeries, and complications. HP characteristics were evaluated and reported with descriptive statistics. They included the rate of IOP rise, the maximum IOP, and the duration of IOP rise. The effect of aqueous suppressant therapy timing was evaluated by comparing the low-IOP initiation group and moderate-IOP initiation group. Additional comparisons were performed between eyes with aqueous suppressant therapy successfully started *before* HP (IOP > 21 mm Hg) and those eyes with therapy started *after* HP had already developed. Visual acuity was modeled as the negative logarithm of the reciprocal of the minimum angle of resolution (LogMAR) for the purposes of statistical analysis. LogMAR values of 1.4, 2.7, and 3.7 were assigned to counting fingers, hand motion, and light perception vision, respectively.[18] Statistical analysis was performed using SAS software version 9.1 (SAS Inc., Cary, NC). Categorical data and continuous data were analyzed with χ^2 test or Fisher exact test and Student t test, respectively. Bonferroni correlation for multiple comparisons was applied as necessary to avoid false-positive results. P-values ≤ 0.05 were considered statistically significant. Mean values were presented with their SDs (± SD).

RESULTS

Fifty-two eyes of 50 subjects who underwent AGV implantation for IOP control were enrolled. Two subjects had both eyes enrolled with 1 eye randomized to the low-IOP initiation group and the fellow eye to the moderate-IOP initiation group. The demographic characteristics of the entire sample and individual groups are summarized in Table 1. Mean age of the entire sample was 64.3 ± 13.8 years and 50.0% were white. Ten subjects (19.2%) had neovascular glaucoma and 6 subjects (11.5%) had uveitic glaucoma. Average follow-up duration was 21.9 ± 10.7 months. Data were available for analysis from 21 eyes (80.8%) in the low-IOP initiation group and 18 eyes (69.2%) in the moderate-IOP initiation group at 12-month follow-up and 17 eyes (65.4%) in each group at 24-month follow-up. Of the 13 patients that were lost to follow-up at 12 months, medical problems were the cited reason in 3 subjects (1 had multiple sclerosis, 1 had cytomegalovirus infection, and 1 had colon cancer), poor visual potential and refusal for additional follow-up care were noted in 5 subjects (hand motion or counting fingers vision preoperatively), and 1 patient withdrew due to complications after additional glaucoma surgery (suprachoroidal hemorrhage developed after a second Ahmed valve implantation). No reason for loss to follow-up could be identified in 4 subjects who stopped returning for visits. None of these 13 subjects had complications from the primary Ahmed valve implantation. There was no significant difference in demographic characteristics between the 13 subjects who dropped out at 12 months and those who remained in the study.

Both the IOP and number of glaucoma medications were reduced by a statistically significantly amount after AGV implantation. Average IOP was reduced from 26.4 ± 8.7 mm Hg preoperatively to 13.1 ± 5.0 mm Hg at 12 months and to 12.5 ± 3.5 mm Hg at 24 months ($P < 0.0001$), whereas the number of glaucoma medications decreased from 3.7 ± 1.1 preoperatively to 2.4 ± 1.0 at 12 months and to 2.2 ± 1.1 at 24 months postoperatively ($P < 0.0001$).

TABLE 1. Demographic and Preoperative Characteristics of the Entire Sample and the Low-IOP and Moderate-IOP Initiation Groups

	Entire Sample (n = 52)	Low-IOP Initiation Group (n = 26)	Moderate-IOP Initiation Group (n = 26)	*P* of the Comparison Between Low-IOP and Moderate-IOP Initiation Groups
Mean age (y)	64.3 ± 13.8	67.5 ± 11.6	61.6 ± 15.3	0.091*
Sex				0.781†
Male	28	13	15	
Female	24	13	11	
Race				0.123‡
White	26	15	11	
Black	3	3	0	
Hispanic	8	3	5	
Asian	15	5	10	
Glaucoma subtype				0.177‡
Primary open-angle glaucoma	12	6	6	
Primary angle closure glaucoma	3	0	3	
Uveitic glaucoma	10	5	5	
Neovascular glaucoma	6	4	2	
Pseudoexfoliation glaucoma	3	3	0	
Congenital glaucoma	2	1	1	
Angle recession glaucoma	2	0	2	
Secondary open-angle glaucoma	5	4	1	
Secondary angle closure glaucoma	9	3	6	
Lens status				0.006‡
Phakia	11	1	10	
Posterior chamber intraocular lens	31	16	15	
Anterior chamber intraocular lens	5	5	0	
Aphakia	4	3	1	
Ophtec	1	1	0	
Preoperative characteristics				
Mean no. previous intraocular surgery	1.8 ± 1.3	2.2 ± 1.2	1.5 ± 1.3	0.081*
Mean preoperative visual acuity (LogMAR)	0.90 ± 0.85	0.97 ± 0.87	0.82 ± 0.83	0.529*
Mean preoperative intraocular pressure (mm Hg)	26.4 ± 8.7	28.4 ± 10.1	24.3 ± 6.6	0.092*
Mean preoperative no. glaucoma medications	3.7 ± 1.1	3.8 ± 1.0	3.5 ± 1.2	0.310*
Duration of follow-up (mo)	21.9 ± 10.7	22.1 ± 10.7	21.7 ± 11.0	0.879*

Mean values are presented with SDs (± S.D).
*Student *t* test.
†Fisher exact test.
‡χ^2 test.
IOP indicates intraocular pressure.

We also evaluated the pattern of glaucoma medication use of the entire sample. The mean number of glaucoma medications at the final visit was lower than that at postoperative month 3, but the difference was not statistically significant (2.3 ± 1.1, 2.5 ± 1.4, respectively; $P = 0.218$). Compared with postoperative month 3, the number of glaucoma medications at the final visit was greater in 13 eyes (25.0%), unchanged in 21 eyes (40.4%), and lower in 18 eyes (34.6%). At final visit, 4 eyes (7.7%) required no glaucoma medication and 6 eyes (11.5%) were only using 1 glaucoma medication.

Additional glaucoma surgeries were required in 7 eyes (13.5%). Of these 7 eyes, 5 underwent a second GDD (3 silicone AGV FP-7 and 2 Baerveldt model-250 implants) and 2 eyes had trabeculectomy with mitomycin-c application performed at the superonasal quadrant of the eye (Table 2). All additional glaucoma surgeries were performed after the HP had resolved (IOP reduced to < 21 mm Hg), at an average of 8.0 ± 6.0 months after primary AGV implantation.

Compared with preoperative values, visual acuity improved at 6, 12, and 24 months, and the difference was marginally significant at 6-month follow-up ($P = 0.046$). Complications related to AGV placement occurred in 3 eyes (5.8%), and included persistent uveitis with subsequent corneal edema in one eye, corneal edema in another eye that developed 2 years postoperatively, and one eye with strabismus related to the AGV (Table 2).

HP Characteristics and Surgical Outcomes of Silicone Ahmed Valve (Model FP-7)

HP occurred in 21 eyes (40.4%). Table 3 summarizes the characteristics of the 21 eyes that developed HP after silicone AGV placement. Average duration of HP was 15.4 ± 30.5 days. Nineteen eyes had HP resolution (IOP return to ≤21 mm Hg) in < 1 month, whereas for 2 eyes it took > 1 month to control HP (one eye had IOP > 21 mm Hg for 2 mo, and another eye for 4 mo). The average peak postoperative IOP of eyes with HP was 29.6 ± 7.7 mm Hg (range, 22 to 48 mm Hg). Aqueous suppressant therapy was initiated on average 19.2 ± 30.9 days after AGV implantation.

The postoperative IOP of eyes that developed HP (21 eyes) was higher than in those that did not have HP (31 eyes) at 2, 6, and 12 months. The differences did not remain significant with Bonferroni correction for multiple comparisons (Table 4). Aqueous suppressant therapy was initiated later in eyes with HP than in those without HP, but the difference was not statistically significant (19.2 ± 27.0, 13.6 ± 15.4 d, respectively; $P = 0.353$). A significantly higher proportion of eyes that had HP required additional glaucoma surgery than eyes that did not have a HP (28.6%, 3.2%, respectively; $P = 0.013$, Table 3).

Comparison Between Low-IOP Initiation Group and Moderate-IOP Initiation Group

There were 26 eyes each in the low-IOP initiation group and moderate-IOP initiation group. Demographic characteristics between the 2 groups were similar except for lens status, with significantly more phakic eyes in the low-IOP initiation group (1 vs. 10 eyes, respectively; $P < 0.01$, Table 1). Nine of 26 eyes (34.6%) in the low-IOP initiation group compared with 12 of 26 eyes (46.2%) in the moderate-IOP initiation group developed HP ($P = 0.286$, Table 3). The differences in the mean peak postoperative IOP and HP onset between eyes that developed HP in the 2 groups were not statistically significant.

TABLE 2. Complications and Additional Surgeries Required of the Entire Sample and the Low-IOP and Moderate-IOP Initiation Groups After Ahmed Glaucoma Valve (AGV) Implantation

	Entire Sample (% of 52 Eyes)	Low-IOP Initiation Group (% of 26 Eyes)	Moderate-IOP Initiation Group (% of 26 Eyes)	*P* of Comparison Between Low-IOP and Moderate-IOP Initiation Groups
No. eyes with complications related to AGV	3 (5.8)	1 (3.8)	2 (7.7)	0.882*
Uveitis	1 (1.9)	0	1 (3.8)	
Corneal edema	2 (3.8)	0	2 (7.7)	
Strabismus	1 (1.9)	1 (3.8)	0	
No. eyes with complications unrelated to AGV	4 (7.6)	1 (3.8)	3 (11.5)	0.305*
Progression of neovascularization	3 (5.8)	0	3 (11.5)	
Retinal detachment	1 (1.9)	1 (3.8)	0	
No. eyes required additional glaucoma surgery	7 (13.5)	3 (11.5)	4 (15.4)	0.791*
Second AGV (FP-7)	3 (5.8)	2 (7.7)	1 (3.8)	
Baerveldt-250	2 (3.8)	1 (3.8)	1 (3.8)	
Trabeculectomy	2 (3.8)	0	2 (7.7)	
Postoperative interval of additional glaucoma surgery (mo)	8.0 ± 6.0	11.1 ± 7.5	5.7 ± 4.2	0.275†
No. eyes required other nonglaucoma surgery	2 (3.8)	0	2 (7.7)	0.245*
Cataract operation	2 (3.8)	0	2 (7.7)	
Repair of retinal detachment	1 (1.9)	0	1 (3.8)	

Mean values are presented with SDs (± SD), and absolute numbers are presented with percentages (%). (Some eyes may have > 1 complication or surgery.)
*Fisher exact test.
†Student *t* test.
IOP indicates intraocular pressure.

TABLE 3. Characteristics of the HP in Eyes That Developed HP in the Low-IOP Initiation Group (Aqueous Suppressant Therapy Started When IOP > 10 mm Hg) and Moderate-IOP Initiation Group (Aqueous Suppressant Therapy Started When IOP > 17 mm Hg)

	All Eyes With HP (n = 21)	Eyes With HP in Low-IOP Initiation Group (n = 9)	Eyes With HP in Moderate-IOP Initiation Group (n = 12)	*P* of Comparison Between Low-IOP and Moderate-IOP Initiation Groups
Mean maximum postoperative IOP (mm Hg)	29.6 ± 7.7	27.1 ± 5.9	31.5 ± 8.6	0.210*
Mean interval of starting aqueous suppressant therapy postoperatively (d)	19.2 ± 30.9	3.9 ± 6.7	30.8 ± 30.9	0.020*
Mean onset of HP postoperatively (d)	31.9 ± 29.6	26.8 ± 29.1	35.8 ± 30.6	0.506*
Mean duration of HP (d)	15.4 ± 30.5	15.7 ± 36.8	15.2 ± 26.8	0.971*
Duration of HP [n (%)]				0.959†
≤ 1 wk	10 (47.6)	4 (44.4)	6 (50.0)	
≤ 1 mo	9 (42.9)	4 (44.4)	5 (41.7)	
> 1 mo	2 (9.5)	1 (11.1)	1 (8.3)	
Additional glaucoma surgery required	6 (28.6)	3 (33.3)	3 (25.0)	0.817‡

HP was defined as intraocular pressure (IOP) > 21 mm Hg during the first 6 months postoperatively after reduction of IOP to < 22 mm Hg during the first postoperative week and not caused by tube obstruction, retraction, or valve malfunction. Mean values are presented with SDs (± SD), and absolute numbers are presented with percentages (%).

*Student *t* test.

†χ^2 test.

‡Fisher exact test.

HP indicates hypertensive phase; IOP, intraocular pressure.

The mean IOPs of the low-IOP and moderate-IOP initiation groups were similar except at postoperative day 1 and week 3. On postoperative day 1, mean IOP of the moderate group was significantly lower (8.9 ± 3.2 vs. 11.1 ± 4.3 mm Hg, respectively; $P = 0.040$), and in postoperative week 3, it was significantly higher (20.6 ± 8.9 vs. 15.7 ± 3.6, respectively; $P = 0.012$) than the mean IOP of the lower-IOP initiation group (Table 5, Fig. 1). However, the differences did not remain significant with Bonferroni correction. Eyes in the low-IOP initiation group were placed on a higher number of glaucoma medications in the early postoperative period, as expected, but the differences after 4 months were no longer significant. The differences in number of glaucoma medications at postoperative weeks 1, 2, and 3 remained significant after Bonferroni correction (Fig. 2).

TABLE 4. Preoperative and Postoperative Intraocular Pressure of Eyes That Developed HP and Those That did not Develop HP After Silicone Ahmed Valve Implantation

Mean Intraocular pressure (mm Hg)	Eyes That did not Developed HP (n = 31)	Eyes That Developed HP (n = 21)	*P*
Preoperative	27.5 ± 8.6	24.7 ± 8.7	0.238*
Postoperative 1 d	10.1 ± 3.9	9.9 ± 4.0	0.858*
Postoperative 1 wk	10.8 ± 7.7	10.4 ± 3.5	0.808*
Postoperative 2 wk	14.3 ± 5.5	16.2 ± 5.9	0.235*
Postoperative 3 wk	17.0 ± 6.3	19.9 ± 8.1	0.667*
Postoperative 4 wk	15.3 ± 4.5	17.4 ± 4.6	0.109*
Postoperative 2 mo	14.6 ± 4.9	18.2 ± 5.5	0.019*
Postoperative 3 mo	15.3 ± 3.9	15.4 ± 5.7	0.942*
Postoperative 4 mo	16.3 ± 8.5	14.5 ± 4.1	0.396*
Postoperative 5 mo	13.5 ± 6.0	12.1 ± 5.0	0.433*
Postoperative 6 mo	12.9 ± 4.3	16.8 ± 8.5	0.044*
Postoperative 12 mo	11.4 ± 4.3	15.1 ± 5.2	0.021*
Postoperative 18 mo	12.4 ± 3.9	14.3 ± 5.2	0.201*
Postoperative 24 mo	12.0 ± 3.3	13.3 ± 3.8	0.290*
Mean interval of starting aqueous suppressant therapy postoperatively (d)	13.5 ± 15.4	19.2 ± 27.0	0.353*
Additional glaucoma surgery required [n (%)]	1 (3.2)	6 (28.6)	0.013†

Mean values are presented with SDs (± SD).

*Student *t* test.

†Fisher exact test.

HP indicates hypertensive phase.

There was no significant difference between the low-IOP initiation group and moderate-IOP initiation group with regard to complication rates and additional glaucoma surgery required (Table 2). Hypotony complications, such as choroidal effusion or maculopathy, were not seen in either group despite the initiation of aqueous suppressant therapy in the immediate postoperative period. Visual outcomes between the 2 groups were also similar. The visual acuities of the low-IOP and moderate-IOP initiation groups were 0.66 ± 0.68 and 0.66 ± 0.66, respectively, at 12-month follow-up and 0.69 ± 0.73 and 0.77 ± 0.87, respectively, at 24-month follow-up ($P > 0.05$).

Comparison Between Eyes That had Aqueous Suppressant Therapy Started Before or After HP Onset

Aqueous suppressant therapy could not be initiated before the onset of HP in all cases despite the prospective design of our study and frequent postoperative monitoring of the IOP. Twelve eyes (23.1%) had onset of HP before initiation of aqueous suppressant therapy. Eleven of the 12 eyes were from the moderate-IOP initiation group and 1 eye was from the low-IOP initiation group ($P = 0.001$).

Table 6 summarizes the characteristics of eyes in which aqueous suppressant therapy was initiated after the onset of HP (n = 12) compared with those in which it was initiated before HP when IOP was ≤ 21 mm Hg (n = 40). The

TABLE 5. Preoperative and Postoperative IOP of Eyes in the Low-IOP Initiation Group and the Moderate-IOP Initiation Group

Mean IOP (mm Hg)	Low-IOP Initiation Group	Moderate-IOP Initiation Group	*P* (Student *t* Test)
Preoperative	24.3 ± 6.6 (26 eyes)	28.4 ± 10.1 (26 eyes)	0.092*
Postoperative 1 d	11.1 ± 4.3 (26 eyes)	8.9 ± 3.2 (26 eyes)	0.040*
Postoperative 1 wk	11.5 ± 7.9 (26 eyes)	9.7 ± 4.0 (26 eyes)	0.298*
Postoperative 2 wk	15.3 ± 7.0 (26 eyes)	14.9 ± 4.3 (26 eyes)	0.811*
Postoperative 3 wk	15.7 ± 3.6 (26 eyes)	20.6 ± 8.9 (26 eyes)	0.012*
Postoperative 4 wk	16.7 ± 4.4 (26 eyes)	15.6 ± 4.8 (26 eyes)	0.404*
Postoperative 2 mo	15.7 ± 5.1 (26 eyes)	16.6 ± 5.8 (26 eyes)	0.577*
Postoperative 3 mo	15.1 ± 4.3 (26 eyes)	15.5 ± 5.2 (26 eyes)	0.729*
Postoperative 4 mo	15.0 ± 4.1 (25 eyes)	16.2 ± 9.4 (23 eyes)	0.543*
Postoperative 5 mo	13.3 ± 4.4 (24 eyes)	12.7 ± 6.7 (23 eyes)	0.734*
Postoperative 6 mo	14.9 ± 7.4 (24 eyes)	14.1 ± 5.8 (23 eyes)	0.682*
Postoperative 12 mo	13.0 ± 4.6 (21 eyes)	13.2 ± 5.6 (18 eyes)	0.919*
Postoperative 18 mo	14.4 ± 5.1 (20 eyes)	12.1 ± 3.8 (18 eyes)	0.129*
Postoperative 24 mo	12.3 ± 3.1 (17 eyes)	12.8 ± 4.0 (17 eyes)	0.722*
Maximum within first 6 mo	21.1 ± 6.1	24.5 ± 8.8	0.109*
No. eyes with IOP > 21 mm Hg within 6 mo postoperatively [n (%)]	9 (34.6)	12 (46.2)	0.286†
Mean interval of starting aqueous suppressant therapy postoperatively (d)	5.2 ± 6.6	29.7 ± 24.8	< 0.0001*

Mean values are presented with SDs (± SD), and absolute numbers are presented with percentages (%).
*Student *t* test.
†Fisher exact test.
IOP indicates intraocular pressure.

demographic and preoperative characteristics between the 2 groups were similar except for a significantly higher mean preoperative IOP in the group of eyes with therapy started after HP onset (30.7 ± 8.9 vs. 25.1 ± 8.3 mm Hg in the rest of eyes, $P = 0.048$). Postoperative IOP differences between the 2 groups were statistically significant at 3 weeks, 2, 3, and 4 months, and the difference at 3 weeks remained significant with Bonferroni correction (25.4 ± 10.9, 16.0 ± 3.5 mm Hg, $P < 0.001$) (Fig. 3). Aqueous suppressant therapy was started significantly later in eyes that had HP onset before therapy was initiated (30.3 ± 31.4 vs. 11.4 ± 14.3 d in eyes with therapy started when IOP was ≤21 mm Hg, $P = 0.006$) and at a significantly higher IOP level (31.3 ± 8.7 vs. 15.3 ± 3.4 mm Hg, respectively; $P < 0.001$). A higher proportion of additional glaucoma surgery was required in the eyes that developed HP before aqueous suppressant therapy initiation than in those eyes where initiation occurred at postoperative IOP ≤21 mm Hg (25% or 3 of 12 eyes vs. 10.0% or 4 of 40 eyes, respectively; $P = 0.013$).

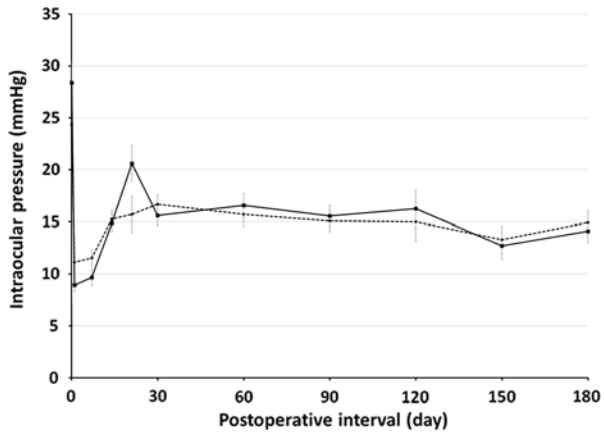

FIGURE 1. Intraocular pressure (IOP) courses of eyes with aqueous suppressant therapy initiated when postoperative IOP reached a level >17 mm Hg in the moderate-IOP initiation group (solid line) or >10 mm Hg in the low-IOP initiation group (broken line). Error bars displayed represent SEs [Differences of IOP between groups at postoperative day 1 and postoperative week 3 (day 21) were statistically significant ($P < 0.05$), but did not remain significant with Bonferroni correction.]

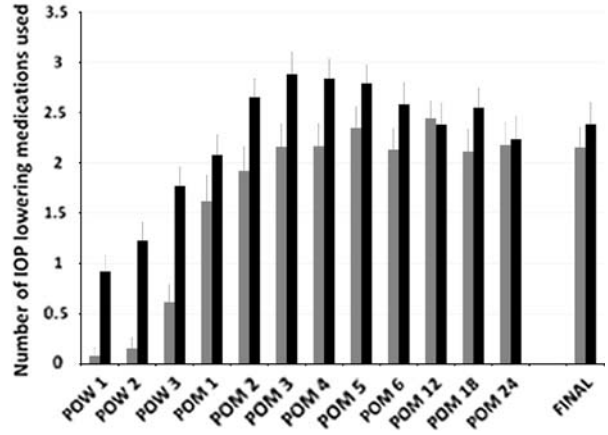

FIGURE 2. Postoperative number of glaucoma medications required in the low-intraocular pressure (IOP) initiation group (black bar) and moderate-IOP initiation group (gray bar). Error bars displayed represent SEs. [Differences between the 2 groups were statistically significant at postoperative weeks 1, 2, 3, and months 2, 3, and 4 ($P < 0.05$), and the difference at postoperative weeks 1, 2, and 3 remained significant after Bonferroni correction.]

TABLE 6. Characteristics of Eyes in Which the HP Started Before Aqueous Suppressant Therapy Could be Initiated Versus in Eyes in Which Aqueous Suppressant Therapy was Initiated While IOP was ≤21 mm Hg

	HP Occurred Before Medical Therapy was Started (n = 12)	Medical Therapy was Started When IOP was ≤21 mm Hg (n = 40)	*P*
Mean age (y)	61.6 ± 13.0	65.1 ± 14.1	0.452*
Sex			0.752†
Male	7	21	
Female	5	19	
Race			0.750‡
White	7	19	
Black	1	2	
Hispanic	2	6	
Asian	2	13	
Glaucoma subtype			0.620‡
Primary open-angle glaucoma	2	10	
Primary angle closure glaucoma	0	3	
Uveitic glaucoma	3	7	
Neovascular glaucoma	3	3	
Pseudoexfoliation glaucoma	1	2	
Congenital glaucoma	1	1	
Angle recession glaucoma	0	2	
Secondary open-angle glaucoma	1	4	
Secondary angle closure glaucoma	1	8	
Lens status			0.275‡
Phakia	2	9	
Posterior chamber intraocular lens	8	23	
Anterior chamber intraocular lens	0	5	
Aphakia	1	3	
Ophtec	1	0	
Preoperative characteristics			
Mean no. previous intraocular surgery	1.9 ± 1.3	1.8 ± 1.3	0.829*
Mean preoperative visual acuity (LogMAR)	1.08 ± 0.89	0.84 ± 0.84	0.404*
Mean preoperative IOP (mm Hg)	30.7 ± 8.9	25.1 ± 8.3	0.048*
Mean no. preoperative glaucoma medications	3.8 ± 1.1	3.6 ± 1.1	0.729*
Mean IOP before aqueous suppressant therapy was started postoperatively (mm Hg)	31.3 ± 8.7	15.3 ± 3.4	< 0.001*
Mean interval of starting aqueous suppressant therapy postoperatively (d)	30.3 ± 31.4	11.4 ± 14.3	0.006*

Mean values are presented with SDs (± SD).
*Student *t* test.
†Fisher exact test.
‡χ^2 test.
HP indicates hypertensive phase; IOP, intraocular pressure.

DISCUSSION

The HP describes a period of IOP rise occurring approximately 1 month after implantation of a GDD, after a short period of relatively low IOPs. Over time, IOP of the HP tends to improve and stabilize with medical therapy.[16,19] Among different GDDs, polypropylene AGV was reported to have a higher rate and more prolonged course of HP.[5,9] However, HP characteristics after silicone AGV have not been studied thoroughly. During the HP, IOP may rise to a level higher than preoperative pressures. This IOP increase may result in potentially irreversible damage to visual function in eyes with advanced glaucomatous optic neuropathy if medical therapy is not reinitiated soon after its start, especially if the IOP increase is prolonged.

In this prospective evaluation of HP with early initiation of aqueous suppressant therapy after silicone AGV (model FP-7) implantation, HP occurred at a rate of 40% with an average onset at approximately 1 month (32 ± 30 d) and an average duration of about 2 weeks (15 ± 32 d). In 90% of the eyes with HP IOP returned to ≤21 mm Hg within 1 month. The IOP of HP peaked at an average of 30 ± 8 mm Hg (range, 22 to 49 mm Hg, Table 3). At 1-year follow-up, the IOP of eyes that had HP was significantly higher than the IOP in those eyes that did not develop HP (Table 4). A significantly greater proportion of eyes with HP required additional glaucoma surgery compared with those eyes that did not experience HP (29% vs. 3%, respectively). Early initiation of aqueous suppressant therapy was able to maintain a significantly lower postoperative IOP at 3 weeks, when HP usually occurs,[5,12,16] without increasing the complication rate (Table 5, Fig. 1). Postoperative IOP was better controlled in the first 4 months if aqueous suppressant therapy was initiated before the onset of HP (Fig. 3).

The published literature on AGV reports an HP rate between 43% and 84%, with a lower rate reported in silicone AGV (43%) compared with polypropylene AGV (53% to 84%).[5,9,20] In a study comparing the effect of topical nonsteroid anti-inflammatory drugs (NSAID) versus topical steroids on HP in silicone AGV, Yuen et al[20]

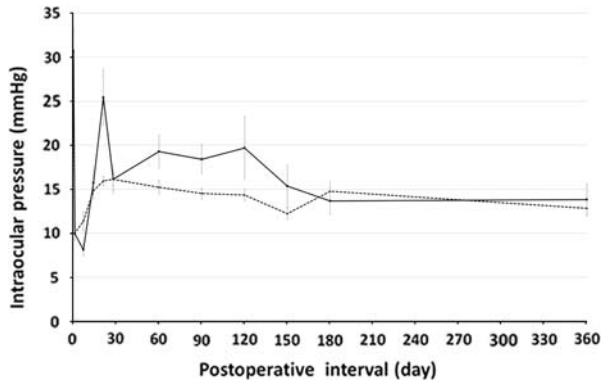

FIGURE 3. Intraocular pressure (IOP) courses of eyes with aqueous suppressant therapy initiated after the hypertensive phase had already developed (solid line) and eyes with therapy initiated when the postoperative IOP was still ≤21 mm Hg (broken line). Error bars displayed represent SEs. [Differences of IOP between groups at preoperative visit (day 0) and at postoperative week 3 (day 21), month 2 (day 60), month 3 (day 90), and month 4 (day 120) were statistically significant ($P < 0.05$), and the difference at postoperative week 3 remained significant after Bonferroni correction.]

reported a HP rate of 31% with NSAID use after silicone AGV. A similar rate of HP (35%) was observed in the low-IOP initiation group of our study, in which aqueous suppressant therapy was started when IOP first reached a level >10 mm Hg postoperatively. Although the HP rate was lower than in the moderate-IOP initiation group (46%), the difference was not statistically significant. Lack of significance is likely due to sample size not being large enough to detect a significant difference, despite our power calculation. Another explanation may be that the criteria for starting aqueous suppression, >10 versus >17 mm Hg, may not be large enough to observe a difference in the effect of the aqueous suppressant therapy on the HP rate.

HP onset in our study using silicone AGV (average, 32 ± 30 d) is similar to that reported for other GDDs.[5,12,16] The mean HP onset reported in the literature was 3 to 4 after GDD weeks implantation. However, the range of HP duration reported in the literature is rather large with studies reporting HP duration of up to 6 months.[12] Clinically, it may be difficult to differentiate a long duration of HP from poor pressure control, and additional surgical intervention may be necessary if the IOP elevation is prolonged.[5,12] Thus, some researchers have argued that HP is an inappropriate term that generalizes all IOP increases in the early postoperative period when in many cases the IOP elevation is not transient but rather represents a surgical failure.[5] In our study, we prospectively demonstrated that with early medical therapy after silicone AGV, a great majority (90%) of eyes with HP had a return of IOP to ≤21 mm Hg within 1 month (Table 3).

Previous studies suggested that final postoperative IOP tends to be higher in eyes with HP compared with those without HP in short-term follow-up (6 to 12 mo).[5,20] Our results also indicate a higher IOP at 12 months postoperatively in eyes that experienced a HP (Table 4). In addition, for eyes in which aqueous suppressant therapy was not started until after HP onset (ie, IOP already increased to >21 mm Hg), IOP was significantly higher from 1 to 4 months postoperatively than in eyes where aqueous suppression was started before IOP reached 21 mm Hg (Fig. 2). The IOP differences were no longer statistically significant at 2-year follow-up, when data from 65% of the sample remained available for analysis. Although long-term IOP outcomes might not be affected by the occurrence of HP, we observed that significantly more eyes experiencing HP required additional glaucoma surgeries (28.6%) compared with eyes that did not develop HP (3.2%) (Table 4). Eyes with HP tended to have poorer overall IOP control than those without HP.

As the HP onset coincides with the timing of a steroid-induced IOP increase, it has been postulated that postoperative topical steroids may initiate or worsen the HP.[20] In our series, all eyes received a tapering dose of topical steroid (prednisolone acetate 1%) starting 4 times daily and tapering over 4 to 6 weeks to minimize the IOP effect of steroid while providing the necessary control of postoperative inflammation. Although topical NSAID was associated with a lower HP rate and a lower IOP at 4 weeks postoperatively, we did not find it to be practical for postoperative management in our series that also included uveitic glaucoma, neovascular glaucoma, and pseudoexfoliation glaucoma. In addition, postoperative topical NSAID use was associated with greater wound-healing problems (wound leaks), whereas the early initiation of aqueous suppressant therapy in our series was not associated with an increased complication rate.[20]

The exact mechanism of HP is uncertain. The IOP rise of HP seems to overlap with the formation of a well-circumscribed capsule and intense vascular congestion around the GDD plate. Histologically, the encapsulation is a fibrous tissue formation surrounding the end-plate.[16,21] In contrast to nonvalved implants with tube ligation, the AGV allows for immediate filtration of aqueous humor postoperatively. It has been postulated that early exposure to aqueous humor with a higher concentration of inflammatory mediators is one of the factors that stimulate the formation of fibrous encapsulation.[9] However, the IOP rise tends to subside overtime in most patients, which suggests that a dynamic healing process in ongoing. Molteno and colleagues postulated that the filtration resistance of the encapsulation is determined by the fibroproliferative process and the fibrodegenerative process. The final thickness and permeability of the encapsulation was suggested to be dependent on the relative intensity and timing of these opposing processes.[16] Although IOP tends to improve overtime, medical IOP control during the HP is clinically important, especially in patients with advanced stages of glaucoma. Early initiation of aqueous suppressant therapy as soon as postoperative IOP reached ≥10 mm Hg was able to blunt the IOP rise at 3 weeks postoperatively. This therapy was more effective if it was initiated before the onset of HP (or before IOP > 21 mm Hg) (Fig. 3).

The postoperative IOP characteristics of eyes with aqueous suppressant therapy started after HP onset is worth mentioning. Twelve eyes in this series had HP developed before the initiation of aqueous suppressant therapy with 11 of the 12 eyes from the moderate-IOP initiation group. The postoperative IOP of the 11 eyes was ≤17 mm Hg (below the IOP criterion for starting aqueous suppressant therapy in the moderate-IOP initiation arm) at one visit and then subsequently doubled by the next visit (Fig. 3). The postoperative IOP of these eyes increased to a significantly higher level compared with the rest of the eyes before therapy was started (31.3 ± 8.7 vs. 15.3 ± 3.4 mm Hg, respectively, Table 6), and a greater proportion required additional glaucoma surgery (25% vs. 10%,

respectively). Comparing the demographic and preoperative characteristics of this group of eyes to the rest of the eyes, the only significant difference was that this group of eyes had a higher starting preoperative IOP (30.7 ± 8.9, 25.1 ± 8.3 mm Hg, $P = 0.048$). Those eyes with higher preoperative IOP might have worse natural aqueous outflow and/or a different aqueous humor composition and were more affected by the fibrous encapsulation resistance. Maximizing IOP control with early initiation of aqueous suppressant medical therapy may be particularly important in these eyes.

Despite the prospective design of the study, this study has some limitations, which are primarily a consequence of the inability to initiate aqueous suppressant therapy before onset of HP in all cases. It may have been prudent to follow the moderate-IOP initiation group on a weekly basis for at least 2 months, but this design would also have been impractical for patients coming from a long distance. Another study design that may better answer the questions posed by this study, is to compare immediate aqueous suppression, regardless of IOP level, to a group followed closely with initiation of therapy only after HP is established (IOP > 21 mm Hg). However, this study design may not have been ethical. Hypotony early after a GDD procedure has been associated with increased postoperative complications.[14,22] Without any prior data on the safety of early aqueous suppressant therapy following a tube shunt procedure, we were obliged to avoid lowering IOP too much too soon after surgery. With the demonstrated safety of early aqueous suppressant use in this study, future studies may initiate therapy even if IOP is < 10 mm Hg. Although we were able to evaluate the IOP course of those eyes in which aqueous suppressant therapy was initiated after HP onset, we cannot speculate on the effects of the therapy if it had been started earlier. We also acknowledge that because postoperative IOP after GDD placement can be highly variable, some eyes might have been unnecessarily started on aqueous suppressant therapy. However, early aqueous suppressant therapy was not associated with a greater complication rate. In addition, medical therapy that was initiated in both groups may have been continued longer than necessary due to the tendency to maximize pressure control in this sample of patients with advanced glaucomatous optic neuropathy. We have observed that the number of glaucoma medications was reduced in approximately one third of the sample after the early postoperative phase. Some subjects of the sample had nonglaucoma ocular diagnosis that progressed during the follow-up period. Although those progressions were unrelated to glaucoma or the GDD procedure, it is uncertain how they would have affected the long-term outcomes comparison. In addition, even with our vigorous attempts to encourage the subjects to keep their follow-up appointments in our clinic and obtain the postoperative data from referring physicians, the rate of loss to follow-up may be significant (25% at 12 mo and 35% at 24 mo), and could have weakened the conclusion of this study. With the drop-off in numbers to 39 total (21 eyes in low-IOP initiation group and 18 eyes in moderate-IOP initiation group), the power of comparison was reduced to 70% (0.70). Finally, the characteristics of HP observed in this study and the effects of the aqueous suppressant therapy cannot be generalized to other GDDs or different surgical techniques.

In summary, this study demonstrated that HP occurred in about 40% of eyes after silicone AGV placement despite the early initiation of aqueous suppressant therapy. The majority of eyes with HP had IOP return to ≤21 mm Hg within 1 month. Early initiation of aqueous suppressants was not associated with hypotony or associated complications, and it was able to suppress the IOP rise seen with the HP. To protect eyes with advanced glaucomatous optic neuropathy from IOP spike, aqueous suppressant therapy should be initiated early after silicone AGV placement before the onset of HP.

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