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Effect of Early Treatment with Aqueous Suppressants on Ahmed Glaucoma Valve Implantation Outcomes

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Objective: To evaluate the effect of early aqueous suppressant treatment on Ahmed glaucoma valve (AGV) surgery outcomes.

Design: Randomized clinical trial.

Participants: Ninety-four eyes of 94 patients with refractory glaucoma.

Methods: After AGV implantation, 47 cases (group 1) received topical timolol-dorzolamide fixed-combination drops twice daily when intraocular pressure (IOP) exceeded 10 mmHg, whereas 47 controls (group 2) received conventional stepwise treatment when IOP exceeded target pressure.

Main Outcome Measures: Main outcome measures included IOP and success rate (6 mmHg $<$ IOP $<$ 15 mmHg and IOP reduction of at least 30% from baseline). Other outcome measures included best-corrected visual acuity, complications, and hypertensive phase frequency.

Results: Groups 1 and 2 were both followed up for a mean of 45$\pm$11.6 and 47.2$\pm$7.4 weeks, respectively ($P = 0.74$). Mixed model analysis revealed a significantly greater IOP reduction in group 1 at all intervals ($P<0.001$). At 1 year, the cases exhibited a significantly higher success rate (63.2% vs. 33.3%; $P = 0.008$) and reduced hypertensive phase frequency (23.4% vs. 66.0%; $P<0.001$).

Conclusions: Early aqueous suppressant treatment may improve AGV implantation outcomes in terms of IOP reduction, success rate, and hypertensive phase frequency. *Ophthalmology 2014;121:1693-1698 © 2014 by the American Academy of Ophthalmology.*

Glaucoma drainage devices (GDD) have been used for decades for the management of refractory glaucomas.[1] After GDD implantation, intraocular pressure (IOP) normally goes through 2 phases: the hypotensive phase that occurs immediately after surgery and lasts for at least 1 week, followed by the hypertensive phase, which usually occurs 1 to 6 weeks after surgery, when congestion of the bleb wall is intense, and can last as long as 6 months.[2–5]

The Ahmed glaucoma valve (AGV) has a 1-way valve mechanism designed to open when IOP exceeds 8 to 10 mmHg; this arrangement tends to decrease the likelihood of early postoperative hypotony. However, the hypertensive phase seems to occur more frequently with AGVs (40%–80% of cases) when compared with nonvalved implants.[6–9]

A thicker and more congested capsule surrounding the AGV plate may contribute to the increased likelihood of the hypertensive phase, which may be the result of early contact of aqueous inflammatory mediators with overlying tissues.[2] Another possibility may be higher aqueous hydrostatic pressure within the bleb, which could compress, compact, and stiffen the capsule.

We speculated that the early initiation of aqueous suppressant treatment after AGV implantation may improve treatment outcomes by reducing the levels of aqueous humor inflammatory mediators surrounding the plate and diminishing hydrostatic pressure within the capsule. Both of these effects may lead to a thinner and more delicate capsular wall, and thus, better percolation of the aqueous and lower IOP levels. The current study was designed to assess the efficiency of this hypothesis.

Methods

This prospective, randomized clinical trial included 94 eyes of 94 patients with refractory glaucoma who underwent AGV implantation from December 2010 through October 2012. The study adhered to the Declaration of Helsinki, was approved by the ethics committee (equivalent to an institutional review board) of the Ophthalmic Research Center at Shahid Beheshti University of Medical Sciences, and was registered at http://www.clinicaltrials.gov (no. NCT01814514) on March 19, 2013, according to the standards set by the International Committee of Medical Journal Editors and the World Health Organization. After providing adequate explanations about the procedure, written informed consent was obtained from all patients before enrollment.

Patients with refractory glaucoma requiring AGV implantation were included. The exclusion criteria were age younger than 18 years, mental illness or dementia, history of glaucoma implants, known allergies to glaucoma medications, and known contraindications to the use of β-blockers. Eyes with fewer than 3 months of follow-up also were excluded from the analysis, but cases in which implantation was not successful were included.

All procedures were performed with use of the same technique by 1 of 2 glaucoma specialists (M.P. and S.Y.) or by a glaucoma fellow under their direct supervision. The procedures were performed as follows: a conjunctival incision was made 4 mm posterior to the

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Table 1. Demographic Characteristics of the Study Population

Parameter	Overall	Group 1	Group 2	P Value
Age (yrs), mean ± SD	44±19	47±18	41±19	0.195*
BCVA (logMAR), mean ± SD	1.2±0.77	1.32±0.8	1.1±0.74	0193†
VCDR, mean ± SD	0.83±0.19	0.82±0.21	0.84±0.17	0.559†
IOP (mmHg), mean ± SD	31.4±9.3	30.9±9.3	31.8±9.3	0.691*
Mean glaucoma medications ± SD	3.6±0.6	3.7±0.6	3.6±0.6	0.650*
History of intraocular surgery, no. (%)				
No surgery	34 (36.2)	16 (34.0)	18 (38.3)	0.688‡
Cataract	38 (40.4)	20 (42.6)	18 (38.3)	0.674‡
Trabeculectomy	21 (22.3)	10 (21.3)	11 (23.4)	0.804‡
Vitrectomy	3 (3.2)	2 (4.3)	1 (2.1)	>0.99§
Penetrating keratoplasty	2 (2.1)	2 (4.3)	0 (0.0)	0.495§
Glaucoma type, no. (%)				0.996§
Combined mechanism	17 (18.1)	9 (19.1)	8 (17.0)	
Aphakic	17 (18.1)	8 (17.0)	9 (19.1)	
NVG	14 (14.9)	8 (17.0)	6 (12.8)	
Pseudophakic	10 (10.6)	4 (8.5)	6 (12.8)	
Developmental	8 (8.5)	3 (6.4)	5 (10.6)	
PCG	7 (7.4)	4 (8.5)	3 (6.4)	
Inflammatory	6 (6.4)	3 (6.4)	3 (6.4)	
PACG	4 (4.3)	3 (6.4)	1 (2.1)	
Post traumatic	2 (2.1)	1 (2.1)	1 (2.1)	
JOAG	2 (2.1)	1 (2.1)	1 (2.1)	
POAG	2 (2.1)	1 (2.1)	1 (2.1)	
PXG	2 (2.1)	1 (2.1)	1 (2.1)	
Steroid-induced	1 (1.1)	0 (0.0)	1 (2.1)	
Ghost cell	1 (1.1)	0 (0.0)	1 (2.1)	

BCVA = best-corrected visual acuity; IOP = intraocular pressure; JOAG = juvenile open-angle glaucoma; logMAR = logarithm of the minimum angle of resolution; NVG = neovascular glaucoma; PACG = primary angle-closure glaucoma; PCG = primary congenital glaucoma; POAG = primary open-angle glaucoma; PXG = pseudoexfoliative glaucoma; SD = standard deviation; VCDR = vertical cup-to-disc ratio.
Group 1 comprised those who received early treatment with timolol plus dorzolamide. Group 2 comprised the controls.
*Mann–Whitney *U* test.
†Based on *t* test.
‡Chi-square test.
§Fisher exact test.

limbus at the superior temporal quadrant followed by adequate dissection. The AGV was primed, and its plate was secured to the sclera 8 to 10 mm posterior to the surgical limbus using 2 interrupted 7-0 silk sutures. After trimming the tube with the bevel facing anteriorly, it was inserted into the anterior chamber through a corneoscleral tract created using a 23-guage needle. A rectangular donor scleral patch graft (4×7 mm) was fashioned and secured over the tube using 8-0 Vicryl sutures (Ethicon, Inc., Bridgewater, NJ). The conjunctiva and Tenon capsule were repaired using 10-0 nylon sutures in a running fashion. Betamethasone (4 mg) and cefazolin (50 mg) were injected subconjunctivally upon completion of the surgery.

The postoperative regimen included application of topical chloramphenicol 0.5% eye drops (Sina Darou Laboratories Co., Tehran, Iran) 4 times daily for 1 week and topical betamethasone 0.1% eye drops (Sina Darou Laboratories Co.) 6 times daily to be tapered gradually over 8 to 12 weeks depending on the degree of inflammation. Postoperative follow-up visits were scheduled on day 1 and weeks 1, 2, 3, 4, 6, 8, 12, 16, 24, and 54 after the operation and every 6 months thereafter. Considering the 30% or more reduction in IOP that can be achieved by dorzolamide hydrochloride plus timolol maleate fixed combination drops (Zilomole; Sina Darou Laboratories Co.) twice daily, and to prevent the risk of hypotony, we chose to initiate therapy when IOP reached 10 mmHg at any point during the follow-up point in group 1. After 3 months, the decision to continue or modify the treatment regimen of dorzolamide hydrochloride plus timolol maleate was made based on the target pressure. Group 2 (controls) received stepwise glaucoma treatment when IOP exceeded target pressure. The stepwise regimen included timolol maleate 0.5% (Sina Darou Laboratories Co.) twice daily, dorzolamide hydrochloride 2% (Sina Darou Laboratories Co.) twice daily, brimonidine tartrate 0.2% (Sina Darou Laboratories Co.) 3 times daily, and latanoprost 0.005% (Sina Darou Laboratories Co.) once daily.

The clinical data collected included age, sex, best-corrected visual acuity, and the type of glaucoma. The main outcome measures included IOP and success rate, which was defined as 6 mmHg < IOP < 15 mmHg and an IOP reduction of 30% or more from baseline. Because of the advanced glaucomatous damage in our patients, we considered a target pressure of 15 mmHg for all cases. Complete success was said to have been achieved when these criteria were met without medications and qualified when the same goals were met with maximum tolerated glaucoma medication. Other outcome measures included complications and the frequency of hypertensive phases (defined as an IOP increase to more than 21 mmHg in the first 3 months after surgery).

Based on our experience with the initial pilot study of 20 cases, we achieved standard deviations of 4 mmHg for IOP in both groups and estimated the required sample size to be able to detect a 3-mmHg difference in IOP with study power of 95% to be at least 47 patients in each study group. All data are represented as mean ± standard deviation, median (range), and frequency (percentage) values. To compare differences between the study groups we used the *t* test, the Mann–Whitney *U* test, the chi-square test, and the Fisher exact test. To adjust for baseline values, we used the analysis of covariance and ordinal logistic methods. To evaluate differences throughout the course of the study, we used linear and generalized mixed models. All statistical analyses were performed using SPSS software version 21.0 (IBM Corp., Armonk, NY). *P* values of less than 0.05 were considered to be statistically significant.

Results

This randomized clinical trial included 94 eyes of 94 patients with a mean age of 44±19 years; an equal number of eyes (47 cases) were assigned randomly to study groups 1 and 2 and were followed up for a mean of 45±11.6 and 47.2±7.4 weeks, respectively ($P = 0.74$). Table 1 summarizes the baseline and demographic characteristics of the study groups. No significant differences were observed between the 2 groups with regard to patient's age, best-corrected visual acuity, IOP, vertical cup-to-disc ratio, number of glaucoma medications, type of glaucoma, or history of intraocular surgeries.

Mixed-model analysis revealed that the IOP was reduced significantly from baseline values during the study period in both groups ($P<0.001$). IOP was consistently and significantly lower in group 1 at all follow-up intervals except on postoperative day 1 ($P<0.05$; Table 2; Fig 1).

Considering the timolol plus dorzolamide fixed combination as 2 drugs for generalized linear mixed-model analysis, the mean number of glaucoma medications was higher in group 1 from 2 to 12 weeks after the operation. However, the study groups were

Table 2. Intraocular Pressure Changes during the Study Period

Time	Group 1		Group 2		P Value*
	Mean ± Standard Deviation	*Range*	*Mean ± Standard Deviation*	*Range*	
Baseline	30.9±9.3	16–56	31.8±9.3	13–56	0.691
Day 1	11.1±8.0	2–50	12.2±6.0	0–34	0.063
Week 1	10.2±6.5	0–38	13.1±7.2	0–46	0.003
Week 2	10.6±6.0	2–24	14.3±7.6	0–46	0.005
Week 3	10.8±5.3	2–23	16.3±7.7	0–46	<0.001
Week 4	12.8±5.3	6–32	17.0±4.9	7–28	0.001
Week 6	14.6±6.1	3–29	18.0±4.2	9–28	0.001
Week 12	14.2±5.4	4–22	18.3±5.1	6–30	<0.001
Week 24	13.1±3.8	2–24	16.9±4.1	8–28	<0.001
Week 54	14.0±4.5	0–22	16.8±4.4	9–28	0.012

Group 1 comprised patients receiving early treatment with timolol plus dorzolamide. Group 2 comprised the controls.
*Mann–Whitney *U* test for baseline and analysis of covariance for follow-up visits.

comparable in this regard at weeks 24 and 54 (Table 3; Fig 2). According to the generalized linear mixed model, the overall success rate was significantly higher in group 1 ($P<0.001$; Table 4).

Binary logistic regression analysis showed no statistically significant interaction between the lens status and study group regarding the odds of complete, qualified, or overall success at any interval (all $P>0.05$). A similar analysis regarding prior intraocular surgery also showed no significant difference between the study groups (all $P>0.05$). Therefore, neither the lens status nor prior intraocular surgery affected treatment success in this study.

Baseline best-corrected visual acuity in logarithm of the minimum angle of resolution notation was comparable between the study groups (1.42±0.79 and 1.30±0.49; $P = 0.385$) and remained similar throughout the follow-up period ($P = 0.478$).

Table 5 details the complications in each group; the overall number of complications did not differ between the study groups. Hypertensive phase frequency was significantly lower in the early treatment group (23.4% vs. 66.0%; $P<0.001$), but its duration was comparable between the groups (11.2±13.3 vs. 11.7±12.4 weeks in groups 1 and 2, respectively; $P = 0.954$).

Discussion

This study evaluated the early initiation of aqueous suppressant treatment with respect to the effects on outcomes after AGV implantation. We observed significantly lower IOP, a higher success rate, and less frequent hypertensive phases in eyes receiving aqueous suppressants in the early postoperative period before IOP elevation occurred compared with eyes treated with the conventional approach.

The so-called hypertensive phase has been reported after the implantation of GDDs, including single- and double-plate Molteno implants, Krupin valves, and AGVs.[5,9–15] The hypertensive phase usually occurs in the early postoperative period when bleb wall congestion around the device plate is most intense.[2–5] After a short-lived hypotensive phase lasting 7 to 10 days, IOP increases gradually because of the formation of a well-circumscribed bleb. During the first few weeks after the hypertensive phase, intense congestion of the bleb is noted, with untreated IOPs increasing to 30 to 50 mmHg. When bleb congestion and inflammation are reduced over the ensuing months, the capsule becomes less dense and IOP stabilizes.[2–5] Epstein[16] showed that when aqueous inflammatory mediators come into contact with the conjunctiva and Tenon's capsule, the contents of the glaucomatous aqueous trigger an inflammatory reaction. Prostaglandins and various eicosanoids, as well as tissue growth factor β, have been shown to be present at a higher concentration in the glaucomatous aqueous.[17]

These mediators induce an inflammatory reaction that, if excessive, results in fibrosis and poor functioning of the filtering bleb. The hypertensive phase is more common after AGV implantation, perhaps because of the early contact of glaucomatous aqueous with tissues overlying the device plate.[2] Another possible explanation for the higher prevalence

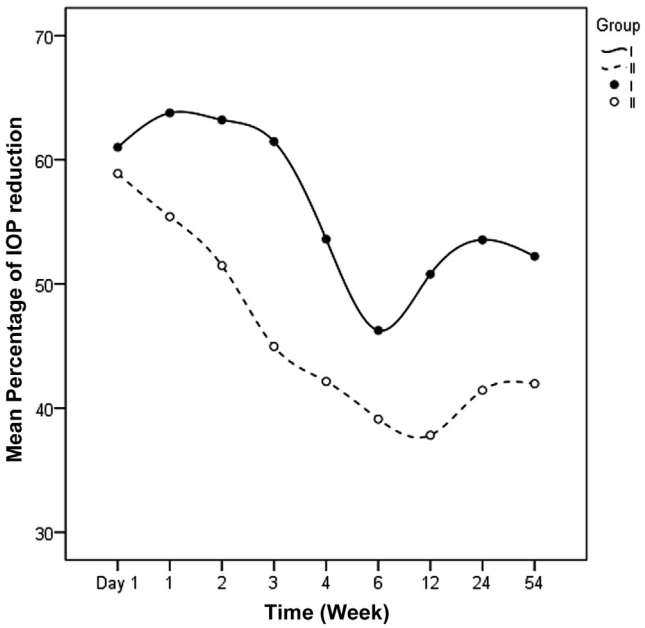

Figure 1. The percentage of intraocular pressure (IOP) reduction during the study in each study group. Group 1 = early treatment with timolol plus dorzolamide; group 2 = controls.

Table 3. Number of Glaucoma Medications* Administered during the Study

Time	Overall		Group 1		Group 2		P Value†
	Mean ± Standard Deviation	Range	Mean ± Standard Deviation	Range	Mean ± Standard Deviation	Range	
Baseline	3.6±0.6	3–5	3.7±0.6	3–5	3.6±0.6	3–5	0.650
Day 1	0±0	0–0	0±0	0–0	0±0	0–0	>0.99
Week 1	0±0	0–0	0±0	0–0	0±0	0–0	>0.99
Week 2	0.5±0.8	0–3	0.8±1.0	0–3	0.2±0.5	0–2	<0.001
Week 3	0.6±0.9	0–3	1.2±1.1	0–3	0.3±0.6	0–2	<0.001
Week 4	0.9±1.0	0–3	1.5±1.0	0–3	0.4±0.6	0–2	<0.001
Week 6	1.2±0.9	0–3	1.9±0.8	0–3	0.7±0.7	0–2	<0.001
Week 12	1.4±0.9	0–4	1.8±0.8	0–3	1.1±0.9	0–4	<0.001
Week 24	1.6±1.0	0–4	1.7±1.0	0–3	1.5±1.0	0–4	0.158
Week 54	1.7±1.0	0–4	1.8±1.1	0–4	1.6±1.0	0–4	0.184

Group 1 comprised those who received early treatment with timolol plus dorzolamide. Group 2 comprised the controls.
*We considered the timolol-dorzolamide fixed combination as two medications.
†Mann–Whitney *U* test for baseline and ordinal logistic test for follow-up visits.

of hypertensive phases after AGVs may be the plate material (silicone in flexible plate [FP] models), which could induce more inflammation because of lower rigidity and the micromovement of the plate.[6]

With the early initiation of aqueous suppressants in group 1, the number of glaucoma medications during the early postoperative period was higher, but there was no significant difference in the number of medications at 6 or 12 months. The incidence of hypertensive phases was significantly lower in group 1, which is an important advantage for such vulnerable optic nerves with advanced glaucomatous damage. In group 1, IOP was consistently and significantly lower at all intervals except at week 54; even at this time, IOP was still clinically lower (2.8 mmHg) than group 2. All of these differences summed up to a higher overall rate of success in group 1 (63.2% vs. 33.3%; $P = 0.008$) at the final follow-up visit. Souza et al[18] and Topouzis et al[19] reported overall success rates of 80% and 87%, respectively, for AGV implantation at 1 year. These figures are higher than the success rates in the current series, which may be because of our definition of success was based on a target pressure of 15 mmHg (because of more advanced glaucomatous damage) compared with 21 mmHg in the above-mentioned studies. Although the stricter success criteria of 15 mmHg may be considered one of the strengths of our study, one also could consider it a drawback because of our use of the same target IOP for all eyes.

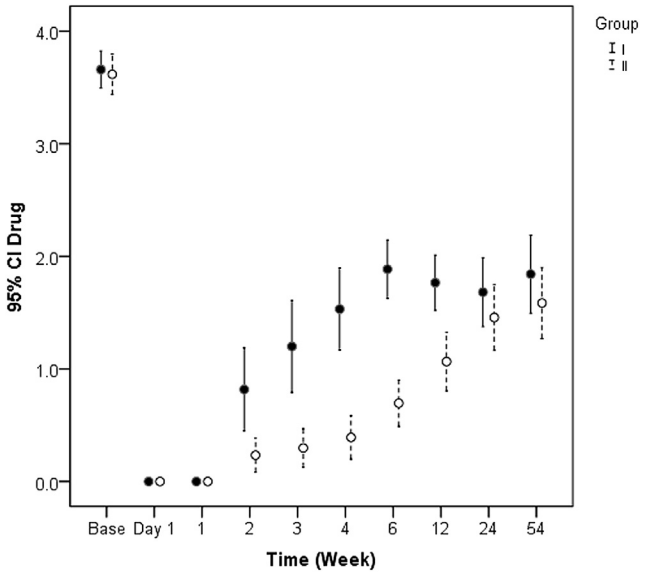

Figure 2. The mean number of glaucoma medications during the study course. CI = confidence interval; group 1 = early treatment with timolol plus dorzolamide; group 2 = controls.

We believe that if aqueous suppressants are initiated early in the postoperative course, a lower concentration of inflammatory mediators may reach tissues surrounding the AGV plate. At the same time, less hydrostatic pressure is exerted on the fibrous capsule; both of these factors may lead to a thinner and looser Tenon's capsule, leading to better aqueous filtration over the long term. High pressures within the bleb have been noted (Freedman J, Goddard D, Greenidge K. [1997] Mechanisms of inflammatory fibrosis: a role for transforming growth factor β. Poster presented at ARVO Meeting, Fort Lauderdale, Florida) to induce secretion of tissue growth factor β by the bleb lining. The higher the pressure within the bleb, the greater the amount of tissue growth factor β production, resulting in more severe inflammation, greater fibrosis, and poor bleb function. This matter may be of greater significance when dealing with the hypertensive stage, which typically occurs 4 to 6 weeks after implantation.

Molteno et al[20] described the histopathologic features of capsules surrounding Molteno implants in eyes with primary and secondary glaucoma. They concluded that without aqueous flow, the episcleral plate of the implant stimulates encapsulation by a thin avascular collagenous layer. With aqueous flow, an immediate inflammatory reaction that includes both collagenous and vascular components develops in episcleral connective tissues.[11,13]

In the current study, early treatment with aqueous suppressants resulted in lower hypertensive phase rates (23% vs. 66.0%). Nouri-Mahdavi et al[2] reported a hypertensive

Table 4. Complete, Qualified, and Overall Success Rates in Group 1 and 2

Time	Complete Success			Qualified Success			Overall Success		
	Group 1	*Group 2*	P *Value**	*Group 1*	*Group 2*	P *Value**	*Group 1*	*Group 2*	P *Value**
Week 12	5 (10.6)	4 (8.7)	0.751	18 (40.0)	7 (15.2)	0.008	23 (51.1)	11 (23.9)	0.007
Week 24	9 (20.5)	4 (8.7)	0.113	22 (50.0)	11 (23.9)	0.010	31 (70.5)	15 (32.6)	<0.001
Week 54	6 (15.8)	2 (4.8)	0.101	18 (47.4)	12 (28.6)	0.083	24 (63.2)	14 (33.3)	0.008

Group 1 comprised those receiving early treatment with timolol plus dorzolamide. Group 2 comprised the controls. Data are no. (%) unless otherwise indicated.
*Chi-square test.

phase rate of 56%, much higher than that in our treatment group and slightly less than our controls; Ayyla et al[9] reported a hypertensive phase rate of 82%. Considering the advanced nature of glaucomatous damage in most GDD candidates, the low likelihood of a hypertensive phase can be considered an advantage of this protocol.

The number of medications was significantly higher in the early treatment group from weeks 2 to 24 because aqueous suppressant treatment had been started before the IOP increase; however, at later intervals, no significant difference was observed between the study groups with respect to the number of medications. In the first 3 months after surgery, cases in group 1 actually were overtreated based on our protocol, which may have led to the IOP reduction observed. However, after this period, lower IOP in the treated group may have been the result of a thinner and less dense capsule, which should be explored further.

We observed 3 cases of choroidal effusion in group 1, which can be attributed to early IOP reduction. All cases were managed conservatively without any consequences. We did not detect any adverse local or systemic reaction in the early treatment group and also did not observe any significant difference between the study groups in terms of overall postoperative complications.

Table 5. Postoperative Complications and Rate of Hypertensive Phase

	Overall	Group 1	Group 2	*P* Value
No. of eyes	63 (67.0)	30 (63.8)	33 (70.2)	0.514*
Wound leakage	1 (1.1)	0 (0.0)	1 (2.1)	>0.99†
Conjunctiva melting/ dehiscence	2 (2.1)	1 (2.1)	1 (2.1)	1†
Implant/tube exposure	1 (1.1)	1 (2.1)	0 (0.0)	>0.99†
Implant extrusion	1 (1.1)	1 (2.1)	0 (0.0)	>0.99†
Tube malposition	1 (1.1)	1 (2.1)	0 (0.0)	>0.99†
Tube block	4 (4.3)	2 (4.3)	2 (4.3)	1†
Choroidal effusion	5 (5.3)	3 (6.4)	2 (4.3)	>0.99†
Hyphema	7 (7.4)	3 (6.4)	4 (8.5)	>0.99†
Vitreous hemorrhage	1 (1.1)	0 (0.0)	1 (2.1)	>0.99†
Infectious scleritis	1 (1.1)	0 (0.0)	1 (2.1)	>0.99†
Malignant glaucoma	3 (3.2)	1 (2.1)	2 (4.3)	>0.99†
Hypertensive phase	42 (44.7)	11 (23.4)	31 (66.0)	<0.001*

Group 1 comprised those who received early treatment with timolol plus dorzolamide. Group 2 comprised the controls. Data are no. (%) unless otherwise indicated.
*Chi-square test.
†Fisher exact test.

One may need to consider some limitations when generalizing from the findings of the current study to other populations. One important fact is that subjects enrolled in the present series were relatively young, with mean ages in the mid- to high forties. The postoperative healing response may be more intense in a relatively young patient group. Therefore, the results could have been different if an older age group were enrolled.

In summary, we demonstrated that early initiation of aqueous suppressant treatment after AGV implantation improves the success rate of the procedure, provides better IOP control, and reduces the likelihood of a hypertensive phase. Therefore, such an approach may be recommended for routine postoperative management of patients who have undergone this procedure.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
AGV = Ahmed glaucoma valve; **GDD** = glaucoma drainage device; **IOP** = intraocular pressure.

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