Ahmed Valve Implantation with Adjunctive Mitomycin C and 5-Fluorouracil: Long-term Outcomes

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• PURPOSE: **To evaluate long-term outcomes after Ahmed valve implantation in patients with glaucoma when using adjunctive intraoperative mitomycin C (MMC) and postoperative 5-fluorouracil (5-FU).**

• DESIGN: **Retrospective, interventional, consecutive case series.**

• METHODS: **A consecutive series of eyes undergoing Ahmed valve implantation, either alone (AHMED eyes) or in combination with cataract surgery (AHMED+PHACO), using both intraoperative MMC and postoperative 5-FU were evaluated. Failure was defined as the first occurrence of any of the following: 1) the first of three consecutive visits where intraocular pressure (IOP) was >18 mm Hg or <20% IOP reduction from baseline and the final number of topical medications was not reduced by at least two from baseline, 2) the need for additional surgery, or 3) the development of serious complications.**

• RESULTS: **A total of 130 eyes underwent Ahmed valve implantation with intraoperative exposure to 0.5 mg/ml MMC (median time: eight minutes; range, four to 10) and postoperative subconjunctival injections of 5 mg of 5-FU (median: five injections; range, zero to nine). Kaplan-Meier estimates of the cumulative probability of valve success and confidence interval (CI) at the sixth follow-up year were 0.72 (95% CI, 0.59 to 0.82) for AHMED eyes (n = 88), 0.84 (95% CI, 0.65 to 0.93) for AHMED+PHACO eyes (n = 42). A median of two fewer medications were required relative to baseline for both AHMED and AHMED+PHACO eyes.**

• CONCLUSIONS: **The adjunctive use of both intraoperative MMC and postoperative 5-FU with Ahmed valve implantation results in high success rates. IOP was well controlled in the majority of patients within the six-year postoperative period. (Am J Ophthalmol 2008;xx:xxx.**
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GLAUCOMA DRAINAGE DEVICES (GDD) PROVIDE AN alternative to conventional filtration surgery for the treatment of glaucomas recalcitrant to medical therapy. Introduced in 1993, the Ahmed implant is a GDD equipped with a unique valve mechanism,[1–3] which Coleman and associates have shown to be safe and efficacious in lowering intraocular pressure (IOP) for the treatment of glaucoma.[4–7] More recently, Wilson and associates directly compared the outcomes of Ahmed valve implantation with those of trabeculectomy in a prospective, randomized trial.[8] While trabeculectomy yielded lower IOPs during the first postoperative year, by the second year of the study the success and IOP control was found to be comparable between the Ahmed valve and trabeculectomy.[8] The efficacy of GDDs has also been demonstrated in a recent study comparing the Baerveldt drainage device with trabeculectomy.[9] Such positive outcomes, in conjunction with concerns over bleb-related complications, have led to a rapid rise in the number of GDDs implanted in recent years.[8,9]

The Ahmed drainage device permits aqueous to flow freely through a silicone tube, placed typically in the anterior chamber (AC), toward a polypropylene plate sutured to the sclera in the sub-Tenon space. The plate houses a trapezoidal chamber containing two Silastic elastomer membranes that function as a valve mechanism to decrease the risk of hypotony in the early postoperative period.[1–3] In the first few months following implantation, the healing repair process induces the formation of a connective tissue capsule, which may restrict the flow of aqueous around the plate.[7,10] Theoretically, the use of antimetabolites may inhibit excessive fibrosis and allow for the formation of thinner capsules, thereby facilitating the more rapid egress of aqueous and potentially a greater and more prolonged IOP reduction.

The beneficial effects of antimetabolites such as mitomycin C (MMC) and 5-fluorouracil (5-FU), used in conjunction with standard filtration surgery, have been demonstrated in multiple reports.[11–13] By contrast, several studies have failed to observe any significant improvement in long-term success rates with GDD implantation in conjunction with the use of antimetabolites.[14–17] In a randomized prospective study evaluating the intraoperative use of MMC for eyes receiving the Ahmed valve, Costa and associates observed lower IOPs only during the early postoperative period for MMC-treated eyes.[15] The authors concluded that the plastic plate acts as a foreign body and induces a vigorous wound-healing response that ultimately overwhelms any antifibrotic effects associated with the use of MMC.[15]

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Success post Ahmed valve implantation may be dependent upon a more prolonged inhibition of fibroblastic proliferation provided by both intraoperative and postoperative wound-healing retardants relative to the use of a single intraoperative agent. In this series, we report the long-term outcomes of Ahmed valve implantation using two wound-healing retardants, both intraoperative exposure to MMC and postoperative subconjunctival 5-FU injections. In addition, we describe a modified surgical technique for Ahmed valve implantation specifically designed to minimize corneal complications in pseudophakic and aphakic cases.

METHODS

WE EXAMINED THE CHARTS FROM A CONSECUTIVE SERIES of eyes of adult patients that underwent Ahmed valve implantation by a single surgeon (J.A.A.) between May 1996 and March 2001. Prior to beginning this surgical series, several GDDs purporting to function as a valve, including the Ahmed, Krupin, and the OptiMed devices, were tested in order to select a GDD that behaved as a "true valve," capable of regulating pressure within a desired range by varying resistance as a function of flow.[2] We learned that the Ahmed GDD does have an efficient valve mechanism[2] and thus this device was selected for implantation in this series. Our finding that the Ahmed functions as a valve has been substantiated by two subsequent reports.[1–3]

For the current study, inclusion criteria required that eyes undergoing Ahmed valve implantation also be treated with adjunctive intraoperative MMC. All eyes were eligible for the use of postoperative subconjunctival 5-FU injections. The number of 5-FU injections was initially determined empirically in children in whom we noted that the intraoperative use of MMC alone was insufficient in some cases. Since an examination under anesthesia was required to administer 5-FU injections in children, it seemed to us that five weekly injections was reasonable. Only eyes with at least six months of follow-up were included. Two clinical types of eyes were studied: 1) eyes with elevated IOP that received an Ahmed implant alone (AHMED) and 2) eyes with elevated IOP and a visually significant cataract that received an Ahmed valve in conjunction with cataract extraction (AHMED+PHACO). The decision to do combination surgery was not based on any prior experience evaluating combination surgery but rather simply on the presence or absence of cataract. Each eye type was analyzed separately. In patients with bilateral Ahmed valves, only the first operated eye that met the above criteria for each type was included.

• **SURGICAL TECHNIQUE:** The S2 model of the Ahmed valve (New World Medical Inc, Rancho Cucamonga, California, USA) was used exclusively for this study. The AHMED+PHACO eyes underwent a temporal clear corneal incision phacoemulsification procedure prior to Ahmed valve implantation. Following intraocular lens implantation, the corneal incision was closed with a 10-0 nylon suture.

In both the AHMED and AHMED+PHACO eyes, a fornix-based peritomy was performed in the superotemporal quadrant. The conjunctiva and Tenon capsule were dissected separately. Using Vannas scissors, the conjunctiva was cut at its insertion from the peripheral cornea. Next, the insertion of a Tenon capsule at the limboscleral junction was cauterized and separated with micro-Westcott scissors. Relaxing incisions were made on each side of the peritomy, which required prior cauterization along the incision planes. With blunt dissection, the superior and lateral rectus tendon insertions were identified and marked with cautery, and the dissection was extended posteriorly between the rectus muscles.

The valve was primed by injecting balanced salt solution [BSS] (Alcon Laboratories Inc, Fort Worth, Texas, USA) through the drainage tube and the valve housing. Then, the polypropylene plate was sutured with 9-0 nylon at each of the previously marked tendon insertion sites. Weck-cell sponges (Medtronics, Minneapolis, Minnesota, USA), soaked in a 0.5-mg/ml MMC solution, were placed over the plate in the sub-Tenon space for approximately five to eight minutes. The Weck-cell sponges were removed and the area was irrigated copiously with BSS. During MMC application, a partial-thickness quadrangular scleral flap, measuring 6 mm in the posterior-anterior dimension and 4 mm in width, was dissected using a #69 Beaver blade (BD Ophthalmics, Franklin Lakes, New Jersey, USA). Since the plate of the Ahmed device is anchored at the point of insertion of the superior and lateral rectus tendons, there is sufficient space (~1.5 mm in width) to dissect a "scleral bridge." This bridge was fashioned by making a partial scleral incision approximately 1.5 mm posterior to the edge of the scleral flap. A BD pocket knife (BD Ophthalmic Systems, Waltham, Massachusetts, USA) was then placed at the edge of the flap and directed posteriorly beneath the scleral tissues towards the previously made scleral incision. This bridge ensures placement of the entire length of the drainage tube intrasclerally, preventing contact of the tube with the Tenon capsule and potentially minimizing the development of erosions. Also, by keeping the tube closely applied to the scleral surface during its insertion, the bridge prevents the tube from deviating from its path along a preformed channel.

While mounting of the plate was carried out using a common technique for both AHMED and AHMED+PHACO eyes, insertion of the drainage tube into the eye was carried out using a different approach for phakic compared to pseudophakic/aphakic eyes. For phakic AHMED eyes, the tube was inserted using a 23-gauge needle connected to a syringe filled with viscoelastic material, as is the standard practice today.[6] The needle was

TABLE 1. Baseline Sample Characteristics for AHMED and AHMED+PHACO Eyes

	AHMED Eyes (n = 88)	AHMED+PHACO Eyes (n = 42)
Gender		
Female	51 (58.0%)	25 (59.5%)
Race		
Asian	12 (13.6%)	7 (16.7%)
Black	14 (15.9%)	4 (9.5%)
Hispanic	10 (11.4%)	10 (23.8%)
White	52 (59.1%)	21 (50.0%)
Primary diagnosis		
POAG	44 (50.0%)	22 (52.4%)
Uveitic	15 (17.1%)	2 (4.8%)
SOAG	10 (11.4%)	6 (14.3%)
NVG	9 (10.2%)	3 (7.1%)
ACG	6 (6.8%)	9 (21.4%)
Trauma	4 (4.6%)	0
Lens status		
Aphakic	10 (11.4%)	0
Phakic	20 (22.7%)	42 (100%)
Pseudophakic	58 (65.9%)	0
Previous glaucoma surgery		
Yes	47 (53.4%)	11 (26.2%)
Preoperative PKP		
Yes	10 (11.4%)	0
Age (years)		
Mean (SD)	65.1 (19.1)	72.3 (10.7)
Median (range)	71.0 (14 to 92)	74.0 (38 to 89)
Preoperative IOP (mm Hg)		
Mean (SD)	29.2 (10.2)	23.7 (9.1)
Median (range)	28.0 (15 to 56)	21.0 (13 to 52)
No. of preoperative medications		
Mean (SD)	2.9 (1.2)	3.4 (1.4)
Median (range)	4.0 (1 to 6)	3.0 (1 to 6)
MMC time (minutes)		
Mean (SD)	7.3 (1.2)	7.4 (1.0)
Median (range)	8.0 (4 to 10)	8.0 (4.5 to 8)
No. of 5-FU injections		
Mean (SD)	4.4 (2.0)	4.3 (2.02)
Median (range)	5.0 (0 to 9)	4.5 (0 to 9)

5-FU = 5-fluorouracil; ACG = angle-closure glaucoma; IOP = intraocular pressure; MMC = mitomycin C; NVG = neovascular glaucoma; PKP = penetrating keratoplasty; POAG = primary open-angle glaucoma; SD = standard deviation; SOAG = secondary open-angle glaucoma.

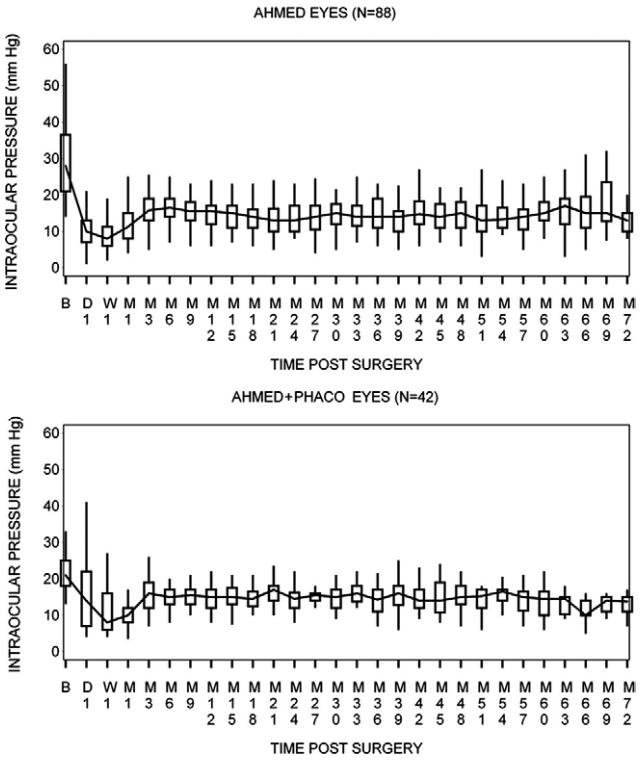

FIGURE 1. Intraocular pressure (IOP) following Ahmed valve implantation with adjunctive intraoperative mitomycin C (MMC) and postoperative 5-fluorouracil (5-FU). (Top) Box and whisker plots are shown of IOP at baseline (B) and during the postsurgical period for 88 AHMED eyes. (Bottom) Box and whisker plots are shown of IOP at baseline (B) and during the postsurgical period for 42 AHMED+PHACO eyes. D = day; W = week; M = month.

passed under the scleral flap starting at a point located ~3 mm posterior to the limbus and directed towards the sulcus of the AC. Upon withdrawal of the needle, the tract formed was filled with viscoelastic material to facilitate tube insertion.

In pseudophakic and aphakic eyes, which comprised all of the AHMED+PHACO eyes and some AHMED eyes, tube insertion was carried out using a different approach. Instead of inserting the tube directly into the AC, the tube was passed into the posterior chamber (PC) sulcus and then directed through a peripheral iridectomy (PI) across the iris and into the AC. This approach required making a PI prior to tube insertion. An incision at the base of the scleral flap was made with a #69 Beaver blade (BD Ophthalmics), and the peripheral iris was grasped and cut with Vannas scissors. Constriction of the pupil using a miotic agent usually brings the PI into view for the subsequent steps. A 20-gauge MVR blade (BD Ophthalmics) was placed ~4 mm posterior to the limbus within the exposed scleral flap. While aiming in the direction of the visible PI, the blade was passed through the ciliary body at the pars plicata and into the PC sulcus (the space posterior to the iris root and anterior to the ciliary processes). From the PC sulcus, the blade was directed through the PI and into the AC. The tract made by the MVR blade was immediately filled with a viscoelastic substance using a 27-gauge blunt cannula. The tube was trimmed to the appropriate length and passed sequentially beneath the scleral bridge and the primary 4 × 6 quadrangular scleral flap such that scleral tissue covered a majority

TABLE 2. Yearly Postoperative Intraocular Pressure (mm Hg) for AHMED and AHMED+PHACO Eyes

	AHMED		AHMED+PHACO	
Year Postoperative	Mean IOP (mm Hg) (SD)	Median IOP (mm Hg) (25^{th}, 75^{th} Percentile)	Mean IOP (mm Hg) (SD)	Median IOP (mm Hg) (25^{th}, 75^{th} Percentile)
Baseline	29.2 (10.3)	28.0 (21, 36.5)	23.7 (9.1)	21.0 (18, 25.0)
1	15.3 (5.0)	15.5 (12, 17.0)	14.4 (3.6)	15.0 (12, 16.3)
2	13.7 (4.4)	13.0 (10, 17.0)	14.4 (3.3)	14.5 (12, 16.3)
3	15.2 (5.7)	14.0 (11, 19.0)	14.2 (3.7)	14.3 (11, 17.0)
4	15.0 (4.8)	15.0 (11, 18.0)	15.4 (4.1)	15.0 (13, 18.0)
5	16.4 (5.8)	15.0 (13, 18.0)	13.6 (4.3)	14.5 (10, 16.5)
6	13.0 (3.8)	13.0 (10, 15.0)	12.9 (3.5)	13.8 (11, 15.0)

IOP = intraocular pressure; SD = standard deviation.

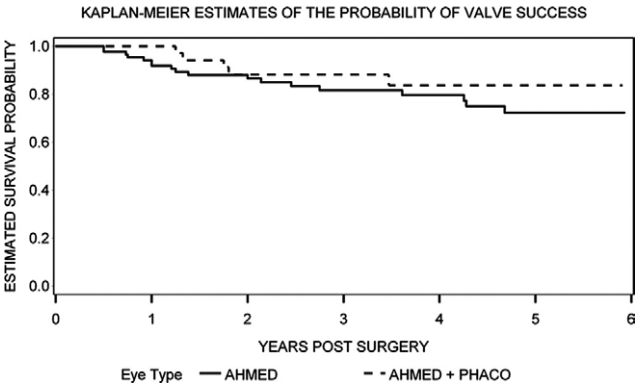

FIGURE 2. Kaplan-Meier estimates of the cumulative probability of valve success for AHMED and AHMED+PHACO eyes. Failure was defined as the first occurrence following an initial postoperative period of any of the following events: 1) IOP >18 mm Hg for three consecutive visits or <20% IOP reduction from baseline and the final number of topical medications was not reduced by at least two from baseline, 2) need for additional surgery to repair a malfunctioning Ahmed valve, or 3) serious postoperative complication.

of the tube. The iridectomy incision was closed with a single interrupted 10-0 nylon suture.

In all cases, the scleral flap was closed tightly with at least five interrupted 10-0 nylon sutures, one at each corner and along each side of the flap, as well as one suture between the flap and bridge. The conjunctiva and Tenon capsule were brought down over the plate and secured with 8-0 Vicryl sutures (Ethicon Inc, San Angelo, Texas, USA), and subconjunctival antibiotics were injected (see Supplemental Video and Figure available at AJO.com).

• **POSTOPERATIVE CARE:** Postoperatively, topical antibiotics and cycloplegic agents were given for one week, and topical steroids (1% prednisolone acetate; Allergan Inc, Irvine, California, USA) were given four times daily for four weeks, twice daily for one week, and then once daily for a final week. The 5-FU injections began at the first postoperative week. At each visit, 5-FU was applied subconjunctivally in the general location of the implant plate. The conjunctiva was anesthetized first by applying a topical anesthetic, and then by injecting 0.1 ml of 1% lidocaine subconjunctivally, which usually results in formation of a "blister." Using a 30-gauge needle, another 0.1 ml containing 5 mg of 5-FU was injected within the previously formed "blister" into a space below the conjunctiva and above the Tenon capsule. The plan was to give 5-FU injections for four consecutive weeks, with a fifth injection at week six. Follow-up was at one day, one week, two weeks, three weeks, one month, and every three months thereafter. Immediately postoperatively, all topical glaucoma medications were stopped. Glaucoma medications were restarted one at a time based on IOP and the patient's glaucomatous condition.

• **AHMED VALVE FAILURE:** The primary objective was to evaluate long-term outcomes after Ahmed valve implantation in AHMED and AHMED+PHACO eyes. The reintroduction of glaucoma medications was permitted postoperatively. Based largely on the criteria proposed by Fontana and associates,[12] failure was defined as the first occurrence of any of the following events subsequent to the visit in which the final adjustment in topical medications was made to the treatment regimen: 1) IOP >18 mm Hg for three consecutive visits or <20% IOP reduction from baseline and the final number of topical medications was not reduced by at least two from baseline, 2) need for additional surgery to repair a malfunctioning Ahmed valve, or 3) serious postoperative complication.

• **STATISTICAL ANALYSIS:** Eyes were analyzed separately based on their classification as AHMED or AHMED+PHACO. We estimated the Kaplan-Meier cumulative survival function for each type of eye using criteria for failure as described above. Cox proportional hazard regressions were used to evaluate the effects of baseline clinical characteristics on survival. In order to provide a readily

TABLE 3. Kaplan-Meier Estimates of Probability of Success in AHMED and AHMED+PHACO Eyes

Year Postoperative	Occurrence of Corneal Complication Not Included in Failure Criteria (95% Confidence Interval)		Occurrence of Corneal Complication Included in Failure Criteria (95% Confidence Interval)
	AHMED	AHMED+PHACO	AHMED
1	0.92 (0.84 to 0.96)	1.00 (1.00 to 1.00)	0.92 (0.84 to 0.96)
2	0.87 (0.77 to 0.92)	0.88 (0.71 to 0.95)	0.85 (0.75 to 0.91)
3	0.82 (0.71 to 0.89)	0.88 (0.71 to 0.95)	0.80 (0.69 to 0.88)
4	0.80 (0.68 to 0.87)	0.84 (0.65 to 0.93)	0.76 (0.64 to 0.85)
5	0.72 (0.68 to 0.87)	0.84 (0.65 to 0.93)	0.69 (0.55 to 0.79)
6	0.72 (0.59 to 0.82)	0.84 (0.65 to 0.93)	0.69 (0.55 to 0.79)

TABLE 4. Postoperative Characteristics of AHMED and AHMED+PHACO Eyes

Condition/Medications	AHMED Eyes (n = 88)	AHMED+PHACO Eyes (n = 42)
Severe corneal complication		
Yes	3.0 (3.4%)	0
Hypertensive phase		
Yes	25.0 (28.4%)	6.0 (14.3%)
Postoperative no. of medications		
Mean (SD)	1.4 (1.5)	1.2 (1.2)
Median (range)	1.0 (0 to 6)	1.0 (0 to 5)
Change in no. of medications from baseline		
Mean (SD)	−2.5 (1.8)	−2.2 (1.6)
Median (range)	−2.0 (−6 to 1)	−2.0 (−5 to 1)
No. of eyes with change in glaucoma medications relative to baseline		
Lower no. of medications	73.0 (83.0%)	36.0 (85.7%)
Same no. of medications	11.0 (12.5%)	5.0 (11.9%)
Greater no. of medications	4.0 (4.6%)	1.0 (2.4%)

SD = standard deviation.

apparent characterization of IOP control, box and whisker plots were constructed to show how postoperative IOP varied as a function of time. All analyses were conducted using SAS 9.1.3 (SAS Institute, Cary, North Carolina, USA).

RESULTS

• **SAMPLE CHARACTERISTICS:** Based on the inclusion criteria, two eyes of the same patient could be included in the study if the two eyes were separately analyzed within the two categories. Three patients contributed one eye to both categories and no patient contributed more than one eye to a single eye category. A total of 130 eyes met our sample inclusion criteria. Table 1 presents demographic and baseline characteristics for 88 AHMED eyes and 42 AHMED+PHACO eyes. At least one postoperative injection of 5-FU was administered in 82/88 of AHMED eyes and in 37/42 of AHMED+PHACO eyes. The omission of any 5-FU injection was inadvertent and not based on any specific postoperative findings or particular patient characteristics.

• **INTRAOCULAR CONTROL:** The median postsurgical follow-up time for all 130 eyes was 50.4 months, with a minimum of six months and a maximum of 90.3 months. Box and whisker plots of postsurgical IOP for the AHMED and AHMED+PHACO eyes are shown separately in Figure 1. Table 2 provides a yearly summary for the two types of eyes. Both the means and medians range from ~13 mm Hg to ~16 mm Hg during the entire six-year postoperative period. Further, the interquartile ranges (middle 50% of the distributions) demonstrate that IOP control was highly predictable and tight.

• **VALVE SUCCESS:** Kaplan-Meier estimates of the cumulative probability of valve success for the AHMED and

TABLE 5. Transient Postoperative Complications for AHMED and AHMED+PHACO Eyes

Complication	Frequency (%)
Hyphema	14.6
Blocked tube	9.2
Choroidal effusion	3.8
Conjunctival dehiscence	2.3
Tube-corneal contact	2.3
Flat chamber/transient hypotony	2.3
Tube/implant exposure	1.5
Retraction of tube from anterior chamber	1.5

AHMED+PHACO eyes are plotted in Figure 2. The "failure event" for these estimates is defined as the first failure of the valve postoperatively, where failure is defined according to the criteria provided in the METHODS SECTION. A yearly summary of the Kaplan-Meier estimates and their associated 95% confidence intervals (CI) is found in Table 3. When corneal complications are not included in the definition of valve failure, the cumulative probability that the valve did not fail after six years is estimated to be 0.72 (95% CI, 0.59 to 0.82) for AHMED eyes, and 0.84 (95% CI, 0.65 to 0.93) for AHMED+PHACO eyes. No eyes failed as a result of serious complications as defined in the METHODS SECTION. With one exception among the AHMED eyes, in which additional surgery was required, all failures were secondary to elevated IOP. No failures were because of loss of vision, ocular infection, persistent hypotony, or recurrent hyphema.

Only three eyes, all of which were AHMED eyes (3.4% of 88 AHMED eyes), developed serious postoperative corneal complications (Table 4). Each of the three eyes had undergone prior penetrating keratoplasty (PKP). Two of the three eyes required repeat PKP for corneal decompensation, and the third developed an acute graft rejection successfully treated with topical corticosteroids. When corneal complications are included in the definition of valve failure, the cumulative probability that the valve did not fail after six years is now estimated to be 0.69 (95% CI, 0.55 to 0.79) for the AHMED eyes, instead of 0.72 when corneal complications are not included in the failure criteria.

Cox regression to evaluate the effects of baseline clinical and demographic variables on valve success was carried out only for the 88 AHMED eyes since there were so few failures among the AHMED+PHACO eyes (five of 42). None of the variables evaluated in this analysis (age, gender, race, primary diagnosis, lens status, previous glaucoma surgery, preoperative PKP, number of preoperative medications, MMC exposure, or number of 5-FU injections) was found to have a statistically discernible effect ($P < .05$) on valve success.

• **TRANSIENT AND LONG-TERM POSTOPERATIVE COMPLICATIONS:** The complications that occurred in the early postoperative period and typically resolved without further intervention are presented in Table 5. Intraocular bleeding–related events were the most common transient complications and included the formation of hyphema and blockage of the drainage tube. All hyphemas resolved spontaneously without requiring any intraocular surgical intervention. In one case, the neodymium-doped yttrium aluminium garnet (Nd:YAG) laser was required to resolve tube blockage.

Only three serious corneal complications developed, as described in the previous section. No cases of persistent corneal epithelial abnormalities, ulceration, or infectious keratitis were observed. In addition, there were no cases of diplopia, infection around the plate, or endophthalmitis. A single case of cystoid macular edema developed that resolved with topical nonsteroidals and corticosteroids.

• **PREOPERATIVE AND POSTOPERATIVE MEDICATIONS:** For each eye category, the change in the number of glaucoma medications required postoperatively relative to baseline is presented in Table 4. For both the AHMED and AHMED+PHACO eyes, there was a median of two fewer medications required postoperatively than preoperatively. No postoperative medications were required in 42% (37/88) of the AHMED eyes and 36% (15/42) of the AHMED+PHACO eyes. Of the 78 eyes that required postoperative medications, 76% (59) received all necessary glaucoma drops within eight months of the Ahmed placement. In 24% (19) of cases, additional topical medications were added as late as 66 months postoperatively.

DISCUSSION

THIS STUDY INTRODUCES THE CONCEPT OF USING BOTH intraoperative and postoperative antimetabolites in association with Ahmed valve implantation in order to improve surgical outcomes. In addition, the study also reports a consecutive series of eyes in which a modified surgical technique was employed in pseudophakic and aphakic eyes in order to potentially provide greater tube separation from the corneal endothelium and minimize corneal complications. We did not employ the approach through the posterior chamber in the phakic eyes in this series, as instruments may inadvertently damage the crystalline lens. Our use of intraoperative antimetabolites is based on our original rabbit studies in which we demonstrated that the encapsulation process that follows Ahmed valve implantation can be delayed more than four-fold with a five-minute application of 0.5 mg/ml MMC (Butler P, et al. IOVS 1993;34:816).

TABLE 6. Estimated Probability* of Valve Success from Selected Studies of AHMED Implantation Alone and Combined with Cataract Extraction

	Postoperative Year	
	2nd Year	4th Year
AHMED eyes		
Alvarado and associates (present study)	0.88	0.84
Topouzis and associates[7]	0.82	0.76
Nouri-Mahdavi and associates[10]	0.55	0.46
Wilson and associates[8]	0.81	0.70
Souza and associates[20]	0.75	0.55
Tsai and associates[21]	0.75	0.62
Yalvac and associates[22]	0.56	0.38
Ayyala and associates[24]	0.45	
Lima and associates[19]	0.71	—
Das and associates[18]	0.83	—
AHMED + PHACO eyes		
Alvarado and associates (present study)	0.88	0.80
Chung and associates[23]	0.75	—

*Probability based on Coleman[6] criteria of Intraocular pressure > 21 mm Hg for two consecutive visits.

• COMPARISON OF OUTCOMES WITH OTHER AHMED VALVE STUDIES: Although the current series was based on clinical data and we did not directly compare the effects of wound-healing retardants to untreated controls, we have conducted several analyses comparing our outcomes with those reported in other studies in which antimetabolites were not employed. These analyses suggest that there is a potential benefit associated with the use of MMC and 5-FU in combination during the intraoperative and early postoperative period. In order to compare the results for valve success for both our AHMED and AHMED+PHACO eyes with those described by others either with implants alone[7,8,10,18–22] or in combined cases,[23] respectively, we modified our failure criteria, as described in METHODS SECTION, by using an IOP threshold of 21 mm Hg and requiring that the IOP failure criteria be met for two instead of three consecutive visits. Kaplan-Meier estimates of the probability of valve success for the second and fourth postoperative years for both the AHMED and AHMED+PHACO eyes were calculated and compared to the results of prior series of Ahmed implants alone and in combination with cataract surgery (Table 6). For our AHMED eyes, the estimated probabilities of valve success, for both the second (0.88) and the fourth postoperative years (0.84), exceeded those found in each of the other studies, where the probability of success ranged from 0.45 to 0.82 for the second year and from 0.46 to 0.76 for the fourth year. Similarly, the estimates at the second (0.88) and fourth postoperative years (0.80) in our AHMED+PHACO eyes both exceeded prior estimates.[23] While these comparisons cannot definitively attribute the favorable estimates of valve success to the application of MMC and 5-FU, they do suggest that the use of wound-healing retardants is beneficial to achieving a desirable outcome.

• THE HYPERTENSIVE PHASE AND FACTORS PREDICTIVE OF SUCCESS/FAILURE: The IOP manifest following Ahmed valve implantation is likely related to numerous factors, including patient characteristics, prior medications, and ocular surgeries. However, we believe that differences in pressure regulation are unlikely the result of valve dysfunction. In vitro studies of the Ahmed valve have demonstrated similar pressure-regulating characteristics among Ahmed valves tested by three different groups of investigators.[1–3] Using our in vitro perfusion apparatus,[2] we have tested several Ahmed valves, which were suspected clinically to be dysfunctional and were removed, and we have concluded that the valve functioned normally in each case.

Simple inspection of the measured IOP graphs using the data from our study eyes reveals some subtle differences from prior reports.[6–8,23–26] One difference is related to the initial IOP rise, often observed during the first three to six postoperative months. In our series, this rise in IOP is very small relative to the rise that has been reported in several other studies in which adjunctive antimetabolites were either not employed[8,15,24–26] or only used intraoperatively,[15] suggesting that the use of both intraoperative and postoperative antimetabolites may modify the early pressure rise.

In evaluating their Ahmed valve eyes, Nouri-Mahdavi and Caprioli describe an early "hypertensive phase" that occurs when the IOP increases above 21 mm Hg after an initial postoperative IOP reduction to 21 mm Hg or less.[10] Using this criterion, 28.4% (25/88) of our AHMED eyes and 14.3% (six/42) of our AHMED+PHACO eyes exhibited a hypertensive phase during the first six months postoperatively. This is a markedly lower rate than what was reported by either Nouri-Mahdavi and Caprioli (56%)[10] or Ayyala and associates (82%),[24] which may be related to the as-yet-undetermined effects on capsule formation in eyes that receive intraoperative and postoperative antimetabolites.

Preimplantation factors that may contribute to the onset of a hypertensive phase were examined using multivariate logistic regression analysis. This analysis was performed only on the AHMED eyes, as only six AHMED+PHACO eyes underwent a hypertensive phase. For AHMED eyes, preoperative IOP was the only variable that significantly increased the risk for developing a hypertensive phase at the 0.05 level ($P = .018$; odds ratio, 1.06; 95% CI, 1.01 to 1.11). Of note, valve failure eventually developed in 36% (nine/25) of the hypertensive AHMED eyes and in only 14.3% (nine/63) of nonhypertensive AHMED eyes. Kaplan-Meier analyses of the Ahmed eyes, with stratification by hypertensive phase occurrence, showed that exhibiting a hypertensive phase significantly increased the likelihood of valve failure (log-rank P value = .004). Of note, we have treated several patients demonstrating a hypertensive phase with up to nine 5-FU injections postoperatively. Our early experience suggests that

additional injections may allow for successful outcomes despite the onset of a hypertensive phase.

• **CORNEAL COMPLICATIONS:** Corneal edema and graft failure are well-known complications associated with GDDs.[4,5,7] Explanations for corneal complications include endothelial decompensation secondary to tube-corneal contact, progressive endothelial loss following multiple intraocular surgeries, and changes in the immunologic status of the AC.[26,27] The most critical factor for us was designing a surgery in which the tube could be maintained at a sufficient distance from the corneal endothelium to minimize mechanical trauma. Our relatively low rate of corneal complications suggests that the location and placement of the tube based on our surgical methodology may reduce corneal complications. Unlike other reports in which the inclusion or exclusion of corneal complications leads to profound changes in overall success, only a small difference was observed in our study when corneal failures were included (Table 3).

• **TRANSIENT POSTOPERATIVE COMPLICATIONS:** There are several well-described complications associated with placement of GDDs, which typically resolve spontaneously within several weeks.[4,5,7,8,10,24,28] Our study demonstrated that the relative frequencies of these transient complications, such as hyphema, are similar to those previously described.[8,10] A key difference between our study and those of others was the surgical technique employed, in particular in aphakic and pseudophakic eyes. The creation of a tract with an MVR knife through the ciliary body into the PC, and through the PI into the AC, may result in a small degree of both intraoperative and early postoperative bleeding, which led to hyphema in 15% of our cases. To reduce the frequency of bleeding, it is necessary to maintain the AC filled with a viscoelastic material throughout the operation. The hyphema typically breaks down in several days, and none of our patients required AC washout secondary to hyphema.

The use of wound-healing retardants in this study of the S2-Ahmed valve did not result in any chronic, delayed, or significant ocular surface abnormalities involving the corneal epithelium or healing of the incisions made during valve implantation. However, we have implanted the FP-7 Ahmed valve (Ahmed New World Medical Inc, Rancho Cucamonga, California, USA), which is made entirely of silicone and has a flatter profile than the S2 model, in three consecutive eyes using intraoperative and postoperative antimetabolites. In each case, the wounds failed to close and chronic leaks developed, requiring explantation. At a later time, we implanted the S2-Ahmed valve in each of these eyes, also using intraoperative and postoperative antimetabolites, and we did not experience any wound-healing problems. We suspect that the different materials, and perhaps even the valve design, of the two models may impact the effects of antimetabolites.

The findings of the present study strongly suggest that the use of MMC and 5-FU, meticulous surgical technique, and topical anti-inflammatory agents favorably influence outcomes of Ahmed valve implantation, and that the use of antimetabolites in combination may reduce the likelihood of developing a postoperative hypertensive phase. We postulate that when a hypertensive phase is observed, even while using antimetabolites, such eyes may benefit from a greater number of 5-FU injections over a longer postoperative period.

In this study, no long-term untoward effects from the use of antimetabolites were observed in either the conjunctiva or the cornea.

In addition, the placement of the tube as described in this study may limit the onset of corneal complications. These results lend further support to the favorable prognosis after the implantation of Ahmed valves as either a primary or secondary surgical option in glaucomas refractory to medical therapy.

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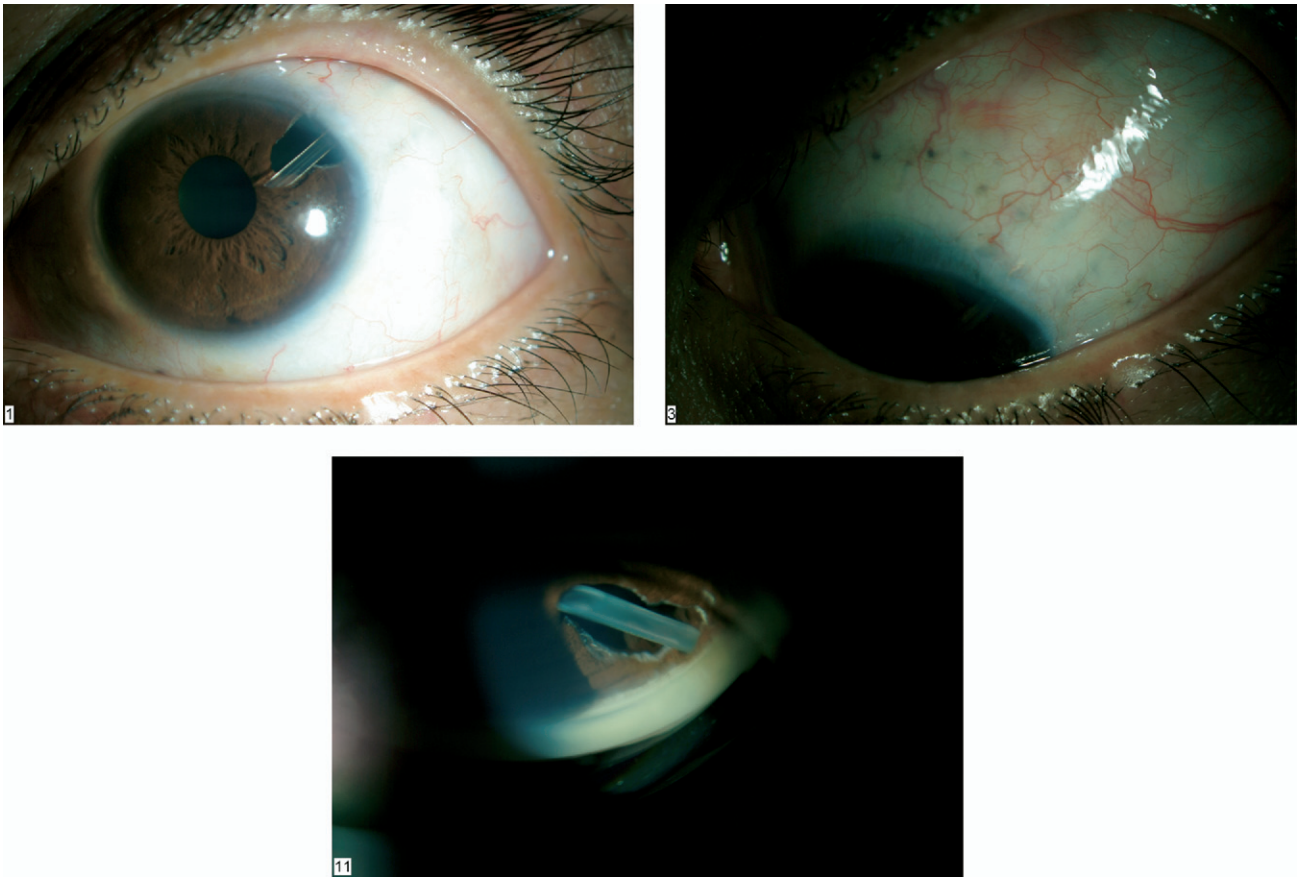
REFERENCES

1. Eisenberg DL, Koo EY, Hafner G, Schuman JS. In vitro flow properties of glaucoma implant devices. Ophthalmic Surg Lasers 1999;30:662–667.
2. Francis BA, Cortes A, Chen J, Alvarado JA. Characteristics of glaucoma drainage implants during dynamic and steady-state flow conditions. Ophthalmology 1998;105:1708–1714.
3. Stay MS, Pan T, Brown JD, Barocas V. Thin-film coupled fluid-solid analysis of flow through the Ahmed glaucoma drainage device. J Biomech Eng 2005;127:776–781.
4. Coleman AL, Hill R, Wilson MR, et al. Initial clinical experience with the Ahmed glaucoma valve implant. Am J Ophthalmol 1995;120:23–31.
5. Coleman AL, Smyth RJ, Wilson MR, Tam M. Initial clinical experience with the Ahmed glaucoma valve implant in pediatric patients. Arch Ophthalmol 1997;115:186–191.
6. Huang MC, Netland PA, Coleman AL, Siegner SW, Moster MR, Hill RA. Intermediate-term clinical experience with the Ahmed Glaucoma Valve implant. Am J Ophthalmol 1999;127:27–33.

7. Topouzis F, Coleman AL, Choplin N, et al. Follow-up of the original cohort with the Ahmed glaucoma valve implant. Am J Ophthalmol 1999;128:198–204.
8. Wilson MR, Mendis U, Paliwal A, Haynatzka V. Long-term follow-up of primary glaucoma surgery with Ahmed glaucoma valve implant versus trabeculectomy. Am J Ophthalmol 2003;136:464–470.
9. Gedde SJ, Schiffman JC, Feuer WJ, Herndon LW, Brandt JD, Budenz DL. Treatment outcomes in the tube versus trabeculectomy study after one year of follow-up. Am J Ophthalmol 2007;143:9–22.
10. Nouri-Mahdavi K, Caprioli J. Evaluation of the hypertensive phase after insertion of the Ahmed glaucoma valve. Am J Ophthalmol 2003;136:1001–1008.
11. The Fluorouracil Filtering Surgery Study Group. Five-year follow-up of the Fluorouracil Filtering Surgery Study. Am J Ophthalmol 1996;121:349–366.
12. Fontana H, Nouri-Mahdavi K, Caprioli J. Trabeculectomy with mitomycin C in pseudophakic patients with open-angle glaucoma: outcomes and risk factors for failure. Am J Ophthalmol 2006;141:652–659.
13. Lamping KA, Belkin JK. 5-Fluorouracil and mitomycin C in pseudophakic patients. Ophthalmology 1995;102:70–75.
14. Cantor L, Burgoyne J, Sanders S, Bhavanani V, Hoop J, Brizendine E. The effect of mitomycin C on Molteno implant surgery: a 1-year randomized, masked, prospective study. J Glaucoma 1998;7:240–246.
15. Costa VP, Azuara-Blanco A, Netland PA, Lesk MR, Arcieri ES. Efficacy and safety of adjunctive mitomycin C during Ahmed glaucoma valve implantation: a prospective randomized clinical trial. Ophthalmology 2004;111:1071–1076.
16. Lee D, Shin DH, Birt CM, et al. The effect of adjunctive mitomycin C in Molteno implant surgery. Ophthalmology 1997;104:2126–2135.
17. Trible JR, Brown DB. Occlusive ligature and standardized fenestration of a Baerveldt tube with and without antimetabolites for early postoperative intraocular pressure control. Ophthalmology 1998;105:2243–2250.
18. Das JC, Chaudhuri Z, Sharma P, Bhoma S. The Ahmed glaucoma valve in refractory glaucoma: experiences in Indian eyes. Eye 2005;19:183–190.
19. Lima FE, Magacho L, Carvalho DM, Susanna R, Avila M. A prospective, comparative study between endoscopic cyclophotocoagulation and the Ahmed drainage implant in refractory glaucoma. J Glaucoma 2004;13:233–237.
20. Souza C, Tran DH, Loman J, Law SK, Coleman AL, Caprioli J. Long-term outcomes of Ahmed glaucoma valve implantation in refractory glaucomas. Am J Ophthalmol 2007;144:893–900.
21. Tsai JC, Johnson CC, Kammer JA, Dietrich MS. The Ahmed shunt versus the Baerveldt shunt for refractory glaucoma II: longer-term outcomes from a single surgeon. Ophthalmology 2006;113:913–917.
22. Yalvac IS, Eksioglu U, Satana B, Duman S. Long-term results of Ahmed glaucoma valve and Molteno implant in neovascular glaucoma. Eye 2007;21:65–70.
23. Chung AN, Aung T, Wang JC, Chew PT. Surgical outcomes of combined phacoemulsification and glaucoma drainage implant surgery for Asian patients with refractory glaucoma with cataract. Am J Ophthalmol 2004;137:294–300.
24. Ayyala RS, Zurakowski D, Smith JA, et al. A clinical study of the Ahmed glaucoma valve implant in advanced glaucoma. Ophthalmology 1998;105:1968–1976.
25. Minckler DS, Heuer DK, Hasty B, Baerveldt G, Cutting RC, Barlow WE. Clinical experience with the single-plate Molteno implant in complicated glaucomas. Ophthalmology 1988;95:1181–1188.
26. Alvarenga LS, Mannis MJ, Brandt JD, Lee WB, Schwab IR, Lim MC. The long-term results of keratoplasty in eyes with a glaucoma drainage device. Am J Ophthalmol 2004;138:200–205.
27. Kirkness CM. Penetrating keratoplasty, glaucoma and silicone drainage tubing. Dev Ophthalmol 1987;14:161–165.
28. Gil-Carrasco F, Salinas-VanOrman E, Recillas-Gispert C, Paczka JA, Gilbert ME, Arellanes-Garcia L. Ahmed valve implant for uncontrolled uveitic glaucoma. Ocul Immunol Inflamm 1998;6:27–37.

Biosketch

Jorge A. Alvarado, MD, received his undergraduate, medical school, specialty, and sub-specialty training at the University of California, in Berkeley and San Francisco, California. Over 30 years ago, he became the first full-time glaucoma specialist at the University of California, San Francisco. Most recently, he has uncovered a cell-to-cell signaling and the cellular and molecular basis for the regulation of aqueous outflow in the eye. This cell signaling mechanism is of great potential for the development of novel glaucoma therapies.



SUPPLEMENTAL FIGURE. Slit-lamp photographs taken one month postimplantation of an Ahmed valve with adjunctive antimetabolites and modified technique technique in which the tube was placed through the ciliary body into posterior chamber (PC) sulcus and across a peripheral iridectomy (PI) into the anterior chamber (AC). (Top left) Slit-lamp photograph is shown demonstrating tube extending through a PI into the AC. (Top right) Photograph showing the superotemporal quadrant demonstrating the intrascleral passage of the tube and the absence of any "bleb." (Bottom) Higher-magnification photograph showing the tube from the Ahmed valve, demonstrating the tube extending from the ciliary body across the PI into the AC.