Needle Revision With 5-fluorouracil for the Treatment of Ahmed Glaucoma Valve Filtering Blebs

5-Fluoruracil Needling Revision can be a Useful and Safe Tool in the Management of Failing Ahmed Glaucoma Valve Filtering Blebs

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Purpose: To determine the outcome of needling with adjunctive 5-fluorouracil (5-FU) in patients with a failing Ahmed glaucoma valve (AGV) implant, and to identify predictors of long-term intraocular pressure (IOP) control.

Methods: A prospective observational study was performed on consecutive patients with medically uncontrolled primary open-angle glaucoma (POAG) with AGV encapsulation or fibrosis and inadequate IOP control. Bleb needling with 5-FU injection (0.1 mL of 50 mg/mL) was performed at the slit-lamp. Patients were examined 1 week following the needling, and then at months 1, 3, and 6. Subsequent follow-up visits were scheduled at 6-month intervals for at least 2 years. Needling with 5-FU was repeated no more than twice during the first 3 months of the follow-up. Procedure outcome was determined on the basis of the recorded IOP levels.

Results: Thirty-six patients with an encapsulated or fibrotic AGV underwent 67procedures (mean 1.86 ± 0.83). Complete success, defined as IOP ≤ 18 mm Hg without medications, was obtained in 25% at 24 months of observation. The cumulative proportion of cases achieving either qualified (ie, IOP ≤ 18 mm Hg with medications) or complete success at 24 months of observation was 72.2%. In a univariate Cox proportional hazards model, age was the only variable that independently influenced the risk of failing 5-FU needling revision. Fourteen eyes (38.8%) had a documented complication.

Conclusions: Needling over the plate of an AGV supplemented with 5-FU is an effective and safe choice in a significant proportion of POAG patients with elevated IOP due to encapsulation or fibrosis.

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Glaucoma drainage implants have become a valuable tool in the surgical management of refractory glaucoma.[1,2] They are effective in reducing intraocular pressure (IOP) and are especially useful when there is high risk of failure for a filtering procedure.[3,4]

The Ahmed glaucoma valve (AGV) is a widely used glaucoma drainage implant. To reduce the occurrence of severe postoperative hypotony, this valve is equipped with internal resistance that reduces the need for intraoperative modifications.[5] However, fibrosis or encapsulation around the valve reservoir may occur, with formation of a Tenon's cyst. This early postoperative complication may increase distal outflow resistance and result in IOP elevation and subsequent valve failure.[6] An encapsulated bleb is one that has been walled-off by the Tenon's capsule, resulting in a rigid elevation of the mobile conjunctival tissue. Vice versa, a fibrotic bleb, which results from the adherence of the conjunctival and Tenon's tissues to the underlying episclera surrounding the valve plate, is characterized by a flat appearance. Fibrosis or encapsulation of the filtering bleb might compromise the outcome of trabeculectomy.

Needling revision of the filtering bleb, with or without adjunctive 5-fluorouracil (5-FU) or mitomycin C, is frequently used to improve flow through an encapsulated or fibrotic filtering bleb.[7,8] We have undertaken this prospective observational study to determine the outcome of needling with adjunctive 5-FU in patients with a failing AGV implant, and to identify predictors of long-term IOP control.

MATERIALS AND METHODS

The study included consecutive patients with medically uncontrolled primary open-angle glaucoma (POAG) with valve encapsulation and inadequate IOP control after a period of at least 6 months from uncomplicated AGV implantation (Model S2; New World Medical, Rancho Cucamonga, LA) in the superotemporal quadrant. All patients had at least 1 failed trabeculectomy with intraoperative use of mitomycin C before the insertion of the valve. Qualified patients showed a patent tube in the anterior chamber (AC) as determined by slit-lamp examination.

Patients were excluded if they had previous or current inflammatory ocular conditions, diabetes mellitus, or a history of previous ocular surgery, with the exception of uncomplicated cataract surgery or trabeculectomy at least 12 months before enrollment.

The study adhered to the tenets of the Helsinki Declaration. Written informed consent was obtained from all participants before any study procedures or examinations were performed. All AGV implantations and subsequent interventions were performed in a single academic center by an experienced glaucoma surgeon (L.Q.). The original technique has been described elsewhere.[9]

Bleb needling was performed at the slit-lamp using a standardized technique by the same surgeon (L.Q.). Patients were instructed to look to the direction opposite the quadrant where the AGV was located. Amethocaine 1.0%, phenylephrine 2.5%, chloramphenicol 0.5%, and povidone-iodine 5% drops were instilled before needling. A 28-G needle attached to a 1-mL syringe was used to enter the subconjunctival space adjacent to the reservoir on the temporal side. The needle was introduced underneath the conjunctiva near the reservoir and was advanced a short distance (approximately 5 to 6 mm). The tip of the needle was turned toward the surface of the AGV to penetrate the fibrous capsule or the Tenon's cyst, and several tears were made in the capsule. Due attention was given to avoid inadvertent perforation of the overlying conjunctiva and subconjunctival blood vessels. Reestablishment of aqueous flow was documented as an immediate increase in bleb size. If recovery of flow was not observed, or if a previous needling attempt had proven ineffective, a different entry site into the subconjunctival space was used. A subconjunctival injection of 0.1 mL of 50 mg/mL 5-FU solution was carried out at the needling site. Following a negative or minimally positive Seidel test, the eye was patched until the next morning with tobramycin antibiotic ointment. Patients were placed on topical dexamethasone 6 times daily for 1 month and then tapered as clinically indicated for 3 months. Topical chloramphenicol was given 4 times daily for a week.

Patients were examined 1 week following the needling procedure, and then at months 1, 3, and 6. Subsequent follow-up visits were scheduled at 6-month intervals for a minimum of 2 years. Additional visits were performed at the discretion of the surgeon. At each follow-up visit, Snellen best corrected visual acuity was determined and Goldmann sitting applanation tonometry was performed. A slit-lamp examination was performed and possible needling complications were documented. Bleb morphology was assessed and further needling and/or 5-FU injection was considered in case of active fibrosis, or failure to achieve the desired target IOP. Needling with 5-FU was repeated no more than twice during the first 3 months of follow-up.

Procedure outcome was determined on the basis of the recorded IOP levels. Study patients were classified as "nonresponders" if they had sustained (≥ 2 visits) IOP of >18 mm Hg, "qualified success" if IOP was ≤ 18 mm Hg with glaucoma medication, and "complete success" if IOP was ≤ 18 mm Hg without glaucoma medications. A univariate Cox proportional hazard model was used to test the association between demographic characteristics and clinical features and procedure outcome. Results are expressed as hazard ratios with 95% confidence intervals. Paired t test was used to compare IOP levels at each timepoint and baseline. The statistical significance was set at 0.05 for a bilateral test. Analyses were carried out using the SAS Software, version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Thirty-six consecutive adult POAG patients with an encapsulated AGV implant were enrolled. All patients completed the study procedures and were eligible for analysis. Table 1 summarizes patient and intervention characteristics. Sixty-seven needling procedures were performed (mean number ± SD = 1.86 ± 0.83 needlings/eye). Fifteen patients underwent a single needling, 11 and 10 patients had 2 and 3 procedures, respectively. Four (11.1%), 25 (69.4%), and 7 (19.4%) patients underwent 1, 2, and 3 previous surgeries, respectively. All patients were pseudophakic.

Treatment Outcome

The criterion of complete success (ie, IOP ≤ 18 mm Hg without medications) was met in all patients at the first week postneedling visit. Complete success was maintained in 63.9%, 33.3%, 27.8%, 25.0%, 25.0%, and 25.0% at 1, 3, 6, 12, 18, and 24 months of observation, respectively. Glaucoma medications had to be reinstated for adequate IOP control in 23 patients (63.9%) within 3 months of the needling revision procedure. After this initial phase, the proportion of patients with complete success appeared to stabilize at 27.8% after 6 months, and 25% from month 12 onward. The cumulative proportion of cases achieving either qualified or complete success at 1, 3, 6, 12, 18, and 24 months of observation was 100%, 97.8%, 86.1%, 75.0%, 75.0%, and 72.2%, respectively. Figure 1 presents the proportion of patients with no response and qualified success/no response over the study period.

IOP Over Time

IOP levels significantly increased in the early period following needling, from 10 (SD = 3.4) mm Hg at 1 week to 16.9 (SD = 4.5) mm Hg at month 6. After this period, the tendency of IOP to increase subsided (Table 2).

Factors Influencing Treatment Efficacy

In a univariate Cox proportional hazards model, age was the only variable that independently influenced the risk of failing needling revision and 5-FU treatment, with a 10 times greater risk of failure (hazard ratio = 10.4; 95% confidence interval, 1.8-60.1; $P = 0.009$) for each 10-year age increase (Table 3). It should be stressed, however, that

TABLE 1. Patient and Intervention Characteristics

Age (y)	
Mean (SD)	58.3 (5.7)
Min-max	45-66
Sex [N (%)]	
Male	18 (50)
Female	18 (50)
Bleb type [N (%)]	
Encapsulated	14 (38.9)
Fibrous	22 (61.1)
Months from AGV intervention	
Mean (SD)	20.1 (12.9)
Min-max	6-60
IOP (mm Hg)	
Mean (SD)	29.5 (3.8)
Min-max	24-37

AGV indicates Ahmed glaucoma valve; min-max, minimum and maximum values.

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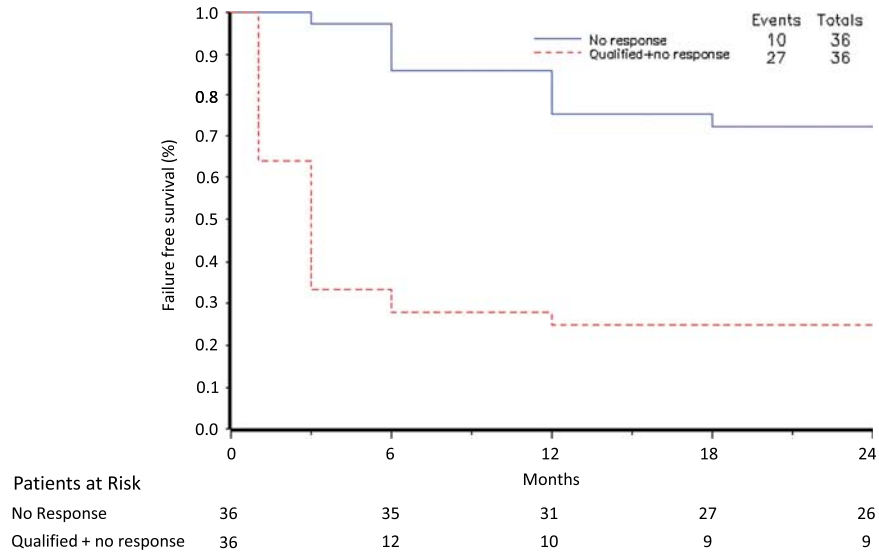

FIGURE 1. Failure-free survival in 36 patients undergoing 5-fluorouracil needling revision of encapsulated blebs over a 48-month follow-up period.

"nonresponders" represent a subgroup of participants who failed both needling with 5-FU and medical treatment.

Male sex was found to be a risk factor of borderline significance ($P = 0.05$) for not achieving complete success.

Needling Revision Complications

After a total of 67 needling procedures performed, 14 eyes (38.8%) had a documented complication (Table 4). Of these, 12 were minor and resolved spontaneously. The most frequent complication was subconjunctival hemorrhage (8 cases), and aqueous leakage from the needling site, which was present in 4 cases after 2 to 3 needling revisions. In 2 cases, aqueous leakage was associated with choroidal detachment and/or significant AC shallowing. The interventions to address these complications included administration of aqueous suppressants, compressive bandages, and curtailing topical steroids until the leak stopped. Conjunctival sutures and AC reformation with viscoelastic were required in these 2 cases after 1 week of conservative treatment.

DISCUSSION

Implantation of an AGV has been proven an effective method for treating refractory glaucoma, with long-term success rates ranging from 49% to 83.6%.[10–12] The long-term success of glaucoma drainage devices depends on the characteristics of the fibrotic reaction surrounding the valve reservoir in the episcleral space. Previous reports have shown that plate size, configuration, and composition can have an impact on long-term outcome.[6]

Encapsulation is one of the main reasons for glaucoma valve failure.[13] An encapsulated cyst (also called Tenon's cyst) develops when Tenon's capsule adheres to the episclera forming a high, domed, smooth, 2-layered bleb.[14–16] The encapsulated bleb is impervious to aqueous humor outflow and leads to IOP elevation. The proliferation of fibrous tissue around the implant plates is another block to aqueous humor diffusion.[17] It is widely agreed that distal resistance is the primary mechanism for IOP elevation.[6] There is also evidence to suggest that proinflammatory cytokines are found at higher levels in the aqueous of eyes with encapsulated blebs and elevated IOP.[18] Therefore, wound modulation and adequate anti-inflammatory treatment may help control the fibrotic changes that jeopardize the success of bleb-dependent glaucoma operations.

Needling revision of the filtering bleb, with or without antimetabolites, is frequently used to restore flow through encapsulated or fibrotic blebs.[7,8] Nonetheless, evidence of

TABLE 2. Intraocular Pressure and Topical Antiglaucoma Medication Use Over Time

		IOP (mm Hg)			No. Antiglaucoma Medications		
Timepoint	**No. Patients**	**Mean (SD)**	**Min-Max**	***P****	**N†**	**Mean (SD)**	**Min-Max**
Baseline	36	29.5 (3.7)	24-37	—	0	0	0
1 wk	36	10.0 (3.4)	4-16	< 0.0001	0	0	0
1 mo	36	14.2 (2.8)	10-22	< 0.0001	13	1.3 (0.6)	1-3
3 mo	36	16.0 (3.8)	10-24	< 0.0001	24	2.0 (1.0)	1-4
6 mo	35	16.9 (4.5)	10-26	< 0.0001	25	2.2 (1.0)	1-4
12 mo	31	16.4 (4.5)	10-26	< 0.0001	22	2.2 (0.9)	1-4
18 mo	27	15.4 (2.8)	11-24	< 0.0001	22	2.0 (1.0)	1-4
24 mo	26	15.4 (2.4)	10-18	< 0.0001	17	1.9 (0.6)	1-3

*The *t* test for the comparison of each timepoint versus baseline.
†Number of patients using topical antiglaucoma medications.
IOP indicates intraocular pressure; min-max, minimum and maximum values.

TABLE 3. Factors Influencing the Risk of Needling and 5-Floruouracil Treatment Failure

	No Response		Qualified Success or No Response	
Characteristics	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Bleb				
Encapsulated (reference)	1	—	1	—
Fibrous	7.1 (0.9-56.1)	0.063	2.0 (0.9-4.6)	0.084
Time from AGV intervention (for each 5 mo increase)	0.9 (0.6-1.2)	0.366	1.0 (0.8-1.1)	0.557
IOP pre-5FU needling (for each 5 mm Hg increase)	0.9 (0.38-2.2)	0.822	0.7 (0.4-1.2)	0.259
Age (for each 10 y increase)	10.4 (1.8-60.1)	0.009	1.5 (0.7-3.4)	0.930
Sex				
Female (reference)	1	—	1	—
Male	1.6 (0.4-5.7)	0.466	2.2 (1.0-4.8)	0.050
Previous surgeries				
1 (reference)	1	—	1	—
2	0.4 (0.1-2.1)	0.293	1.1 (0.3-3.7)	0.904
3	0.92 (0.18-6.57)	0.924	0.8 (0.2-3.8)	0.808

AGV indicates Ahmed glaucoma valve; CI, confidence interval; HR, hazard ratio.

the efficacy of this procedure is contradictory. Depending on classification criteria and length of follow-up, the reported success rate of needling revision of a filtering trabeculectomy bleb varies between 49% and 96%.[19] Long-term success can be influenced by numerous factors such as previous surgeries, ethnicity, etiology of glaucoma, and surgical technique.[19–21] Moreover, Costa et al[22] showed in a randomized trial that treatment with aqueous suppressants and digital massage is superior to needling without antimetabolites in patients with encapsulated trabeculectomy blebs after a follow-up of 9.6 months. Hence, there is yet no consensus on the effectiveness of needling revisions of glaucoma drainage implants, with or without adjunctive antimetabolites. Few case series have been published so far,[23,24] but information from controlled trials is not available.

Our prospective observational study evaluated 36 patients showing the maintenance of either complete or qualified success in 72% of cases over a 48-month follow-up period. The findings of the present study suggest that the use of 5-FU during needling revision favorably influences the outcome of IOP control after AGV implantation. In our study, 5-FU needling in eyes with AGV implants was able to reestablish control of IOP, with or without additional medications, in 76% of eyes over a 24-month follow-up period.

TABLE 4. Complications Encountered in the Study

Complications	**No. Eyes**	**Intervention**
Subconjunctival hemorrhage	8	Nil
Needling site leak		
Without hypotony/ choroidal shallow AC	2	Nil (resolved in 1 wk)
With hypotony/ choroidal shallow AC	2	Conjunctival suture and AC reformation with viscoelastic
Small hyphema (< 1 mm)	2	Nil (resolved in 1-2 wk)

AC indicates anterior chamber.

Our clinical impression was that needling was most likely to succeed if an immediate increase in bleb size was noticed during the needling procedure. Our data suggest that the procedure was equally effective for encapsulated and fibrous blebs. Moreover, no long-term side effects of antimetabolites were observed in either the conjunctiva or the cornea.

Older age was identified as a risk factor for failure of the needling procedure. One potential explanation may be the fact that older age is a surrogate for longer disease duration, and thus greater cumulative exposure to antiglaucoma drugs and preservatives. There is evidence that exposure to antiglaucoma medications correlates with poorer long-term survival of glaucoma filtering procedures.[25] Our data indicate that male sex may be a risk factor for not achieving complete success. However, this result was of marginal significance ($P = 0.05$) and larger studies are needed to confirm this finding.

Our study has some limitations. Neither a control group of patients receiving only medical therapy nor a control group undergoing needling without adjunctive 5-FU injection was employed. Therefore, the exact efficacy of needling with adjunctive 5-FU per se cannot be determined. This limitation of design was difficult to avoid, as clinical judgement and routine practice mandated the use of medication and needling with 5-FU. It is clear, however, that our procedure is efficacious in a significant proportion of patients (25%) who achieved medication-free IOP control over a 2-year period. Another limitation of our study is that these results may not be entirely applicable to patients implanted with other glaucoma drainage devices or even different versions of the AGV.

In conclusion, this study demonstrates that needling over the plate of an AGV supplemented with 5-FU is an effective choice in a proportion of POAG patients with elevated IOP due to encapsulation or fibrosis. The procedure, performed as many times as deemed necessary, can lessen the fibrotic changes that threaten the long-term success of an AGV. Performed at the slit-lamp, needling revision is a relatively simple and safe procedure that reinstates aqueous flow in a significant proportion of POAG patients. More information from controlled studies is needed in the future to elucidate the success of this procedure in other glaucoma types with worse prognosis.

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