Fuchs Heterochromic Iridocyclitis-Associated Glaucoma: A Retrospective Comparison of Primary Ahmed Glaucoma Valve implantation and Trabeculectomy with MMC

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Purpose: To compare the safety and efficacy of a primary trabeculectomy with mitomycin C (T) and an Ahmed glaucoma valve (AGV) implantation in patients with Fuchs heterochromic iridocyclitis (FHIC) related glaucoma, a rare complication of an uncommon form of uveitis.

Design: Retrospective comparative case series.

Method: Twenty-six patients with uncontrolled FHIC-associated glaucoma received T (n=12) or an AGV (n=14). Primary outcome measures were the surgical success defined as IOP ≤ 21 mmHg and decreased ≥ 20% from the baseline and no secondary glaucoma surgery. Secondary outcome measures were the number of glaucoma medications, complications, best corrected visual acuity (BCVA), and intraocular pressure.

Results: The follow-up (mean±SD) was 34.0±17.7 in T and 33.4±18.6 months in AGV (p = 0.837). The cumulative probability of success rate at the final follow-up at three years was 41.7% for T and 85.7% for AGV. There was no significant difference in complications between the two groups (P>0.05).

The mean preoperative IOP in T was 23.4±3.3 mmHg and 21.6±5.2 mmHg at the final visit (P= 0.041). In AGV, the preoperative IOP was 24±7.8 and 17.1±2.6 mmHg at the final visit (P= 0.003), respectively. AGV had a significantly lower average IOP at the final follow-up visit compared to T (P= 0.018).

The number of glaucoma medications at baseline was 3.3±0.5 in T and 3±0.6 in AGV (P= 0.233). This decreased significantly to 2.4±1.0 and 1.7±0.6 at the final follow-up (P= 0.008 and 0.002, respectively). Patients in AGV needed fewer glaucoma medications (P= 0.041). BCVA was equal in both groups and did not change (p>0.05).

Conclusion: Primary AGV had a higher success rate than T in the management of FHIC-associated glaucoma. The risk of cataract formation and progression was significantly higher following T in these patients.

Keywords: Fuchs heterochromic iridocyclitis; primary AGV; trabeculectomy with MMC; uveitic glaucoma.

Introduction

Fuchs heterochromic iridocyclitis (FHIC) is a rare form of uveitis. While the incidence of all forms of uveitis is approximately 0.035% of the population,[1] the incidence of FHIC is only about 0.00105% (3% of all uveitis cases)[2,3] and occurs in both eyes in 10% of patients.[4] It is characterized by a low-grade intraocular inflammation, small stellate keratic precipitates, and iris stromal atrophy.[5] Recent evidence points towards an association between rubella and FHIC[6,7] but an association between FHIC and toxoplasmosis and toxocariasis has also been reported.[8,9] Affected patients are often asymptomatic for years and mostly present with symptoms of a cataract or floaters during the third or fourth decade of life. Because the presentation is often variable, FHIC is among the most underdiagnosed conditions in ophthalmology.[10] Since there is an average of 3.7 years delay in diagnosing FHIC, it should be considered as a differential diagnosis for any young patient with unilateral low-grade uveitis and good visual acuity.[5] Although FHIC is frequently complicated by cataract formation in two-thirds of patients, the outcome of phacoemulsification and intraocular lens implantation is excellent and comparable to normal eyes.[11] Older age and a cataract can put patients with FHIC at risk for glaucoma[12] which occurs in 15 to 59%.[13,14]

Since anterior and posterior synechiae are uncommon in this condition, angle-closure mechanisms do not play an important role in the development of glaucoma. Abnormal angle vessels, physical obstruction of trabecular meshwork by inflammatory cells, disruption of uveal and juxtacanalicular structures, trabecular meshwork fibrosis and steroid-induced ocular hypertension are all contributing causes.[13,15]

FHIC often responds poorly to medical management requiring a surgical intervention to control IOP.[11,13,14,16] There is a paucity of literature regarding the best initial surgical approach in the management of FHIC-associated glaucoma. The purpose of this study was to compare the outcomes of the two most common surgical interventions, a glaucoma drainage device implantation and trabeculectomy, for glaucoma caused by FHIC. We hypothesized that Ahmed glaucoma drainage devices, a valved implant, would have a lower failure rate but at the expense of a higher average pressure as seen in other glaucomas with these modalities.[17]

Methods

This study was approved by the ethics committee and the institutional review board at the Ophthalmic Research Center and followed the tenets of the Declaration of Helsinki. A retrospective chart review of medical records at the Labbafinejad Medical Center,Tehran, Iran, from 2001 through 2017 yielded 26 patients with FHIC-associated glaucoma that either had MMC-augmented trabeculectomy (T) or a primary Ahmed Glaucoma Valve (AGV) implantation. FHIC-associated glaucoma was defined as cases of previously known FHIC or diagnosed as Fuchs at the time of presentation accompanied by uncontrolled IOP and progressive glaucomatous optic neuropathy.

Demographic data including age, gender, baseline best corrected visual acuity (BCVA), baseline IOP, number of medications, type of surgery, and surgical details were recorded. In all cases, surgery was only performed when the eyes were not inflamed.[18] Primary outcome measures were surgical success defined as IOP ≤ 21 mmHg and decreased ≥ 20% from the baseline, no secondary glaucoma surgery, and no loss of light perception.

Secondary outcome measures were the rate of complications, cataract development, numbers of medications, and IOP reduction. Hypotony was defined as IOP less than 6 mmHg at any postoperative visit, and hypertensive phase following AGV implantation was defined as an intraocular pressure more than 21 mmHg during the first three months after the surgery (with or without medications).[19] All postoperative data for each surgery were documented until the last follow-up visit or when a secondary glaucoma surgery was performed.

Surgical technique

Trabeculectomy: A 7-0 silk traction suture was passed through the superior cornea. A conjunctival peritomy was performed at the supranasal quadrant followed by Tenon's dissection. Wet field cautery was used to stop episcleral vessels bleeding. A 4 by 3 mm trapezoidal half thickness scleral flap was created followed by lamellar dissection to peripheral cornea. Sponges soaked in 0.04% MMC were applied for 3 minutes. After creating a sideport, a keratome was used to enter the anterior chamber underneath the flap, and a block of clear cornea was removed by Kelly punch. The scleral flap was closed relatively tightly with two releasable sutures so that spontaneous drainage was minimal. The conjunctiva was closed with 10-0 nylon sutures. At the conclusion of surgery betamethasone and cefazolin were injected into the subtenon space away from the site of operation. The postoperative regimen consisted of chloramphenicol 0.5% eye drops (Sina Darou Lab. Co., Tehran, Iran) four times a day for one week and betamethasone 0.1% eye drops (Sina Darou Lab. Co., Tehran, Iran) six times a day, which was tapered over 10 weeks.

Ahmed glaucoma valve implantation: A 7-0 silk traction suture was placed through the superior clear cornea. The conjunctiva was opened 4 mm posterior to the limbus in the supratemporal quadrant, and a blunt dissection of Tenon was performed using Westcott scissors to provide space for the plate insertion. The device (Ahmed glaucoma drainage implant, model FP7, New World Medical, Rancho Cucamonga, California) was primed with 2 ml of buffered saline solution (BSS) and gently pushed into the subtenon space. The plate was secured to the sclera 10 mm posterior to the limbus using 7-0 silk sutures. The tube was trimmed bevel up with an estimated intracameral length of 2 mm. A 23-gauge needle was inserted into the anterior chamber bevel up, parallel to the iris and 1 mm posterior to the limbus. The tube was passed through the tunnel into the anterior chamber and secured to the sclera with a 10-0 nylon suture. A 5x8 mm scleral patch graft was placed over the tube. Tenon's capsule and the conjunctiva were closed using a running 10-0 nylon mattress suture. At the end of the surgery, 0.5 mL of subtenon triamcinolone (40 mg/mL) was injected next to the plate in four patients. Betamethasone (4 mg) and cefazolin (50 mg) were injected into inferior subconjunctival space upon conclusion of the surgery. The postoperative regimen comprised chloramphenicol 0.5% eye drops four times daily for one week and betamethasone 0.1% drops six times daily to be tapered gradually over six weeks.

Statistics

To test for a difference between the two groups at baseline, we used the t-test, Mann-Whitney, Chi-Square and Fisher exact test. We used a General linear model and Ordinal logistic regression to compare the groups adjusted for the baseline. Changes within groups were evaluated using paired t-test and Wilcoxon signed rank test. A P - value less than 0.05 was considered statistically significant. All statistical analyses were performed with SPSS software (IBM Corp. Released 2016. IBM SPSS

Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) Data was described as frequency (percent), mean±standard deviation, median and range.

Results

Twenty-six patients were included for the final analysis. Fourteen patients were male (53.8%). There were 12 trabeculectomies and 14 AGV surgeries. All cases were primary surgeries with no history of glaucoma surgery. There was no significant difference regarding sex, age, IOP, BCVA, and numbers of glaucoma medications at baseline (Table 1). The mean age at the time of surgery for T was 47.5±6.1 years and for AGV was 45.9±9.3 years (P= 0.608). Ten patients (83.3%) in T were phakic and 14 patients (100%) in AGV were phakic (P=0.203). Preoperatively, the angle was open in all patients upon gonioscopy. Two patients in T had a phacoemulsification and lens implantation in the same session. The mean follow-up was 34±17.7 months in T and 33.4±18.6 months in AGV (P= 0.837).

Surgical success at the final follow-up was 41.7% for T surgery and 85.7% in AGV (P= 0.025). IOP decreased significantly from 24±7.8 mmHg at baseline to 17.14±2.6 mmHg at the final follow-up in AGV (P= 0.003). The corresponding numbers for T were 23.4±3.3 and 21.58±5.2 mmHg, respectively (P= 0.041, Table 2). AGV had a significantly lower average IOP at the final follow-up visit compared to T (P= 0.018). Three patients in T and one in AGV needed a surgical revision specifically to control high intraocular pressure. AGV was used as a secondary glaucoma surgery in all these cases. The number of glaucoma medications decreased significantly from 3±0.6 at baseline to 1.71±0.6 at the final follow-up visit in AGV (P= 0.002). The medications in T were 3.3±0.5 at baseline and 2.41±1.01 at the conclusion of the study, respectively (P= 0.008).

Patients in AGV needed fewer glaucoma medications at the final follow-up (P= 0.041). Kaplan–Meier survival curves for the two groups are shown in Figure 1. The estimated mean survival time was 20.8 months for AGV and only 12.7 months for T (P= 0.002). The reason for failure in T was bleb fibrosis. Five patients (37.5%) in AGV experienced an early hypertensive phase.

Triamcinolone had no impact on IOP (P= 0.320). The most frequent complication in both groups was hyphema (Table 3). Five patients (41.6%) in T and three patients in AGV (21.4%) developed hyphema (P= 0.292) which could be managed conservatively. One patient in AGV and three in T established choroidal effusions and had to be drained in one AGV patient. One patient in each group developed endophthalmitis. The endophthalmitis in AGV was preceded by tube exposure. The patient underwent vitrectomy, and the device was removed. A new AGV was implanted in the infranasal location in the same session. Although the endophthalmitis in T could be controlled by an injection of intravitreal antibiotics and a corticosteroid (vancomycin (25 mg in 0.5 ml), ceftazidime (100 mg in 0.5 ml) and dexamethasone (6 mg in 0.25 ml) injected as a bolus), a glaucoma drainage device was needed. Two AGV patients experienced endothelial touch, and one of them underwent tube shortening due to early corneal decompensation. Hypotony was observed in 2 cases in T in the early postoperative period, which resolved without a surgical intervention within one month. There was no significant difference between the rate of complications between the two groups (Table 3). None of the listed complications were significant factors for surgical failure in AGV or T. A cataract extraction was indicated in five patients in T and in only one patient in AGV. The mean time between trabeculectomy and cataract surgery was 9.1±4.3 months.

Discussion

In this retrospective study, we evaluated the outcome of two common surgeries for FHIC-associated glaucoma, a valved tube shunt (AGV) and trabeculectomy with mitomycin C (T). Although FHIC is rare, occurring only in about 0.00105% of the population,[2,3] and the course typically mild, almost 50% of patients with FHIC develop glaucoma[12–14,20] and require aggressive management. We found that AGV had a significantly higher success rate compared to trabeculectomy, confirming our hypothesis. Patients also needed fewer glaucoma medications in AGV while the complication rate was similar.

Most glaucoma patients have an open angle on gonioscopy. Decreased outflow is instead caused by inflammatory cells, fibrotic changes of the trabecular meshwork, and long-term steroid use [13–15]. The management of FHIC-associated glaucoma is challenging.[21] In a study by Liesegang et al. 66% of patients with FHIC-associated glaucoma needed a surgical intervention and did so earlier in life than individuals with primary open angle glaucoma.[16] Laser trabeculoplasty is relatively contraindicated because it can exacerbate the inflammation, cause bleeding from neovascularization of the angle and induce peripheral anterior synechiae.[22]

When the uveitis is only mildly active, trabeculectomy can be performed to quickly lower IOP, including in FHIC,[23] despite the risk of bleb failure[24] but the success rate is less than 30% at five years,[25,26] far worse than in primary open angle glaucoma.[27] Although FHIC is not typically characterized by severe inflammation, trabeculectomy outcomes have been reported to be worse.[13,14] The high rate of hyphema in our series likely contributed to this because blood can reduce the bleb size in trabeculectomy[28,29] but not in tube shunts. Hyphema commonly occurs in FHIC because of the angle neovascularization in FHIC[30] and rupture of these fragile vessels following IOP reduction.[5] Cataract is another common occurrence in FHIC and has an increased incidence after trabeculectomy. In our study, five out of ten patients required cataract surgery. The high rate of cataract formation after trabeculectomy appears to be an under-reported risk of failure of trabeculectomy in FHIC-associated glaucoma. For this reason, same session cataract removal should be considered because modern phacoemulsification at the time of glaucoma surgery may have only a negligible impact on IOP outcomes.[31]

The reported intermediate success rate for glaucoma drainage devices in uveitic glaucoma is between 66% to 85%.[32–34] In a study by Tan et al., the short and long-term success rate of non-valved Baerveldt implants in uveitic glaucoma was 89% and 75%, respectively.[35] In another study, Satana et al. used valved Ahmed implants in 14 patients with uveitic glaucoma secondary to Behcet disease and reported the cumulative probability of surgical success rate of 90.9% at 18 months follow-up.[33] Kwon et al. examined the outcome of AGV implantation in 28 patients with uveitic glaucoma including FHIC and reported a success rate of 75% during two years follow-up.[36] Voykov and colleagues assessed the short and intermediate-term success rate of AGV implantation in 17 patients with FHIC- associated glaucoma.[37] Qualified success defined as 6 mmHg ≤ IOP ≤21 mmHg was achieved in 58.3% of patients after one year and only 38.4% after three years but 88% of patients had conjunctival scarring from prior procedures, a known risk factor.[38] This may also explain the rate of complications (23% tube exposure, 23% device exposure, 6% endophthalmitis, 6% diplopia, 11.7% hypotony) in the mentioned study.

Our results indicate that primary AGV has a higher cumulative probability of success in FHIC. Regardless, consistent with prior studies [34,39] our complication rate was high. This highlights how challenging and unpredictable uveitis is even though FHIC is a relatively mild form of uveitis. Given the high rate of complications and the patients' middle age, microincisional procedures should be

considered for FHIC that have been proven to be safe and effective in other mild-to-moderate forms of uveitic glaucoma,[40,41] and appropriate for a range of glaucoma severity.[42] The occurrence of a hypertensive phase in the current study is lower than the 47% incidence rate reported by Voykov et al.[37] The lower rate could partially be explained by modulating of encapsidation and inflammation by triamcinolone used in several patients here although contradictory results have been reported.[43,44] Bleb vascularity is a recently identified risk factor for bleb failure[27] that we did not examine here. An intensified treatment for this problem can include bevacizumab that can be used subconjunctivally[45] instead of intravitreally.[46] Another explanation for the lower incidence of early hypertension may be the start of aqueous suppressant to reduce fibroblast stimulation from stretch and cytokines.[47]

Limitations of this study are the relatively small patient number dictated by the overall rareness of FHIC, a retrospective design and use of triamcinolone in some patients. Although the anterior chamber cell reaction in FHIC is not as prominent as in other uveitic glaucomas, we could have systematically measured the anterior chamber cell reaction to see whether it correlated with survival.

In conclusion, this study shows that Ahmed glaucoma drainage devices are superior to trabeculectomy in FHIC-associated glaucoma. The relatively high complication rate is consistent with prior reports and highlights the considerable risk associated with this relatively mild form of uveitis.

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Tables and Figures

Table 1: Baseline clinical characteristics of patients in T and AGV.

		All	T	AGV	p
Age	Mean ± SD	46.6 ± 7.9	47.5 ± 6.1	45.9 ± 9.3	0.608†
	Median (range)	48 (32 to 60)	48.5 (36 to 56)	47 (32 to 60)	
Gender	Male	14 (53.8%)	8 (66.7%)	6 (42.9%)	0.267*
	Female	12 (46.2%)	4 (33.3%)	8 (57.1%)	
Lens status	Phakic	24 (92.3%)	10 (83.3%)	14 (100.0%)	0.203**
	Pseudophakic	2 (7.7%)	2 (16.7%)	0 (0.0%)	
BCVA	Mean ± SD	0.29 ± 0.3	0.3 ± 0.34	0.27 ± 0.27	0.835‡
	Median (range)	0.15 (0.05 to 1.1)	0.15 (0.05 to 1)	0.19 (0.05 to 1.1)	
IOP	Mean ± SD	23.7 ± 6	23.4 ± 3.3	24 ± 7.8	0.801†
	Median (range)	22 (14 to 42)	23 (18 to 28)	21 (14 to 42)	
Medications	Mean ± SD	3.1 ± 0.5	3.3 ± 0.5	3 ± 0.6	0.233‡
	Median (range)	3 (2 to 4)	3 (3 to 4)	3 (2 to 4)	
Follow-up	Mean ± SD	33.7 ± 17.8	34 ± 17.7	33.4 ± 18.6	0.837‡
	Median (range)	29.5 (11 to 89)	30 (11 to 80)	29.5 (13 to 89)	

BCVA: best corrected visual acuity. IOP: intraocular pressure. † Based on t-test. ‡ Based on Mann-Whitney test. * Based on Chi-Square test.
** Based on Fisher exact test.

Table 2: Change of examined variables during the course of the study.

Parameter		Group		Diff	95% CI		P
		T	AGV		Lower	Upper	
BCVA	Baseline	0.3 ± 0.34	0.27 ± 0.27	0.03	-0.21	0.28	0.835‡
	Final visit	0.34 ± 0.35	0.44 ± 0.67	-0.1	-0.55	0.34	0.417§
	Change	-0.03 ± 0.08	-0.17 ± 0.57	0.14	-0.21	0.48	
	Within P	0.006	0.004				
IOP	Baseline	23.4 ± 3.3	24 ± 7.8	-0.6	-5.6	4.4	0.801†
	Final visit	21.58 ± 5.2	17.14 ± 2.6	0.6	-2.4	3.6	0.018§
	Within P$	0.041	0.003				
Medication	Baseline	3.3 ± 0.5	3 ± 0.6	0.3	-0.2	0.7	0.233‡
	Final visit	2.41 ± 1.01	1.71 ± 0.6	0.2	-0.5	1	0.041¥
	Within P	0.008	0.002				
Baseline lens status	Phakic	10 (83.3%)	14 (100.0%)	16.70%	10.4%	-4.7%	0.203**
	Pseudophakic	2 (16.7%)	0 (0.0%)				
Final visit lens status	Phakic	3 (25.0%)	13 (92.9%)	67.90%	14.3%	38.3%	0.001**
	Pseudophakic	9 (75.0%)	1 (7.1%)				
Success rate at final visit		5 (41.7%)	12 (85.7%)	-22.60%	19.9%	-63.7%	0.025**

† Based on t-test. ‡ Based on Mann-Whitney test. * Based on Chi-Square test. ** Based on Fisher exact test. § Adjusted for the baseline, based on General linear model. ¥ Adjusted for the baseline, based on Ordinal logistic regression. Based on Wilcoxon signed rank test. $ Based on paired sample t-test. Diff

Table 3: Postoperative complications in T and AGV.

	T	AGV	P value
Early hypotony (within 3 months postoperatively)	2	none	0.31
Late hypotony (after 3 months postoperatively)	none	none	
Hyphema	5	3	0.292
Choroidal effusion	3	1	0.246
Corneal decompensation	0	1	0.213
Endophthalmitis	1	1	
Tube exposure (AGV only)	N/A	2	N/A
Tube-cornea touch (AGV only)	N/A	2	N/A
Bleb leakage (T only)	3	N/A	N/A
Diplopia	0	0	

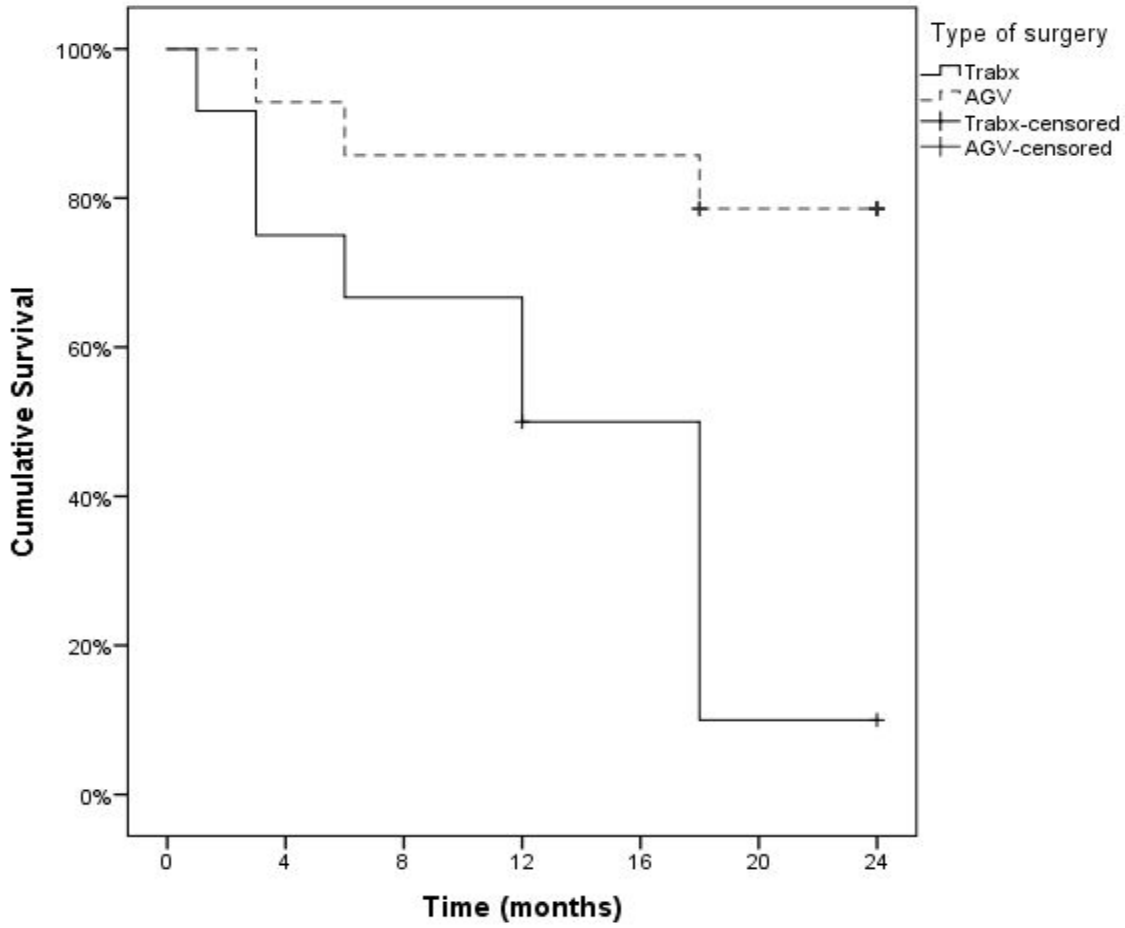

Figure 1: Kaplan–Meier survival curve for trabeculectomy (Trab) (solid line) and Ahmed Glaucoma Valve (AGV) (dotted line) surgeries for FHIC-associated glaucoma in this study. Log-rank P = 0.002. Estimated mean survival time for Trab is 12.7 months with 95% confidence interval (8.5 to 16.9). Estimated mean survival time for GDI surgery is 20.8 months with 95% confidence interval (17.2 to 24.4).