Postoperative Complications in the Tube Versus Trabeculectomy (TVT) Study During Five Years of Follow-up

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• PURPOSE: **To describe postoperative complications encountered in the Tube Versus Trabeculectomy (TVT) Study during 5 years of follow-up.**

• DESIGN: **Multicenter randomized clinical trial.**

• METHODS: SETTINGS: **Seventeen clinical centers.** STUDY POPULATION: **Patients 18 to 85 years of age who had previous trabeculectomy and/or cataract extraction with intraocular lens implantation and uncontrolled glaucoma with intraocular pressure (IOP) ≥18 mm Hg and ≤40 mm Hg on maximum tolerated medical therapy.** INTERVENTIONS: **Tube shunt (350-mm^2 Baerveldt glaucoma implant) or trabeculectomy with mitomycin C (MMC 0.4 mg/mL for 4 minutes).** MAIN OUTCOME MEASURES: **Surgical complications, reoperations for complications, visual acuity, and cataract progression.**

• RESULTS: **Early postoperative complications occurred in 22 patients (21%) in the tube group and 39 patients (37%) in the trabeculectomy group (P = .012). Late postoperative complications developed in 36 patients (34%) in the tube group and 38 patients (36%) in the trabeculectomy group during 5 years of follow-up (P = .81). The rate of reoperation for complications was 22% in the tube group and 18% in the trabeculectomy group (P = .29). Cataract extraction was performed in 13 phakic eyes (54%) in the tube group and 9 phakic eyes (43%) in the trabeculectomy group (P = .43).**

• CONCLUSIONS: **A large number of surgical complications were observed in the TVT Study, but most were transient and self-limited. The incidence of early postoperative complications was higher following trabeculectomy with MMC than tube shunt surgery. The rates of late postoperative complications, reoperation for complications, and cataract extraction were similar with both surgical procedures after 5 years of follow-up. (Am J Ophthalmol 2012;xx:xxx. © 2012 by Elsevier Inc. All rights reserved.)**

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THE TUBE VERSUS TRABECULECTOMY (TVT) STUDY IS a multicenter randomized clinical trial comparing the safety and efficacy of tube shunt surgery and trabeculectomy with mitomycin C (MMC). Our companion article reviews the outcomes of treatment in the TVT Study during 5 years of follow-up.[1] Tube shunt surgery had a higher success rate than trabeculectomy with MMC during the first 5 years of the study. A higher rate of reoperation for glaucoma was observed after trabeculectomy with MMC compared with tube shunt surgery. Both surgical procedures had similar intraocular pressure (IOP) reduction and use of supplemental medical therapy at 5 years. Vision loss occurred at a similar rate following placement of a tube shunt and trabeculectomy with MMC.

A comparison of surgical procedures requires not only an assessment of efficacy, but also an evaluation of the incidence and severity of associated complications. Tube shunt surgery and trabeculectomy with MMC each has its own set of complications that may occur in the early or late postoperative periods. This article describes the postoperative complications encountered during 5 years of follow-up in the TVT Study and the management of these complications.

METHODS

• STUDY DESIGN: The study protocol is described in detail in a previous publication.[2] In brief, patients 18 to 85 years of age who had previous cataract extraction with intraocular lens implantation and/or trabeculectomy with IOP ≥18 mm Hg and ≤40 mm Hg on maximum tolerated medical therapy were enrolled in the study. Baseline demographic and clinical information were collected for each patient. One eye of each eligible patient was randomized to placement of a 350-mm^2 Baerveldt glaucoma implant (Abbott Medical Optics, Santa Ana, California, USA) or trabeculectomy with MMC (0.4 mg/mL for 4 minutes). Follow-up visits were scheduled at 1 day, 1 week, 1 month, 3 months, 6 months, 1 year, 18 months, 2 years, 3 years, 4 years, and 5 years postoperatively. Each examination included measurement of Snellen visual acuity (VA), IOP, slit-lamp biomicroscopy, Seidel testing, and

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ophthalmoscopy. Humphrey perimetry, Early Treatment Diabetic Retinopathy Study (ETDRS) VA, and quality of life using the National Eye Institute Visual Function Questionnaire were evaluated at baseline and at the annual follow-up visits. Investigators provided an explanation for loss of 2 or more lines of Snellen VA at follow-up visits after 3 months. Failure was prospectively defined as IOP >21 mm Hg or less than 20% reduction below baseline on 2 consecutive follow-up visits after 3 months, IOP ≤5 mm Hg on 2 consecutive follow-up visits after 3 months, additional glaucoma surgery, or loss of light perception vision. Patients who underwent additional glaucoma surgery were censored from analysis of complications after the reoperation for glaucoma. The study was monitored by an independent Safety and Data Monitoring Committee.

Investigators in the TVT Study recorded postoperative interventions and complications on standardized forms at each follow-up visit. The data forms listed several complications that were required to be designated as present or absent, and blank spaces were also included for recording complications that did not appear on the list. Investigators were asked to report any complications that were present at the scheduled follow-up visit or between study visits. The definition of a complication was not standardized, and documentation of a complication was left to the discretion of the surgeon. Early postoperative complications were defined as surgical complications developing within the first month after randomized surgical treatment, and late postoperative complications were complications that occurred at least 1 month following glaucoma surgery. Surgical complications that developed during the first postoperative month and persisted with longer follow-up were counted only as early postoperative complications. The date and type of surgical treatment for any complications were recorded. Reoperation for a complication was defined as additional surgery requiring a return to the operating room to manage a surgical complication, such as a pars plana vitrectomy or penetrating keratoplasty. A vitreous tap with injection of intravitreal antibiotics for endophthalmitis was also counted as a reoperation for a complication. Interventions performed at the slit lamp, such as bleb needling for an encapsulated bleb or reformation of a shallow anterior chamber, were not considered reoperations. Persistent diplopia, persistent corneal edema, and dysesthesia were defined as the postoperative development of these complications and their presence at the 6-month follow-up visit or thereafter. Eyes that were Seidel positive within the first month of follow-up were classified as having wound leaks, and those that were Seidel positive after 1 month were categorized as having bleb leaks. Serious complications were defined as surgical complications that produced loss of 2 or more lines of Snellen VA and/or required reoperation to manage the complication. Cataracts were considered to have progressed if there was loss of 2 or more Snellen lines that was attributed to cataract at the 6-month follow-up visit or thereafter, or if cataract surgery was performed.

TABLE 1. Postoperative Interventions in the Tube Versus Trabeculectomy Study

	Tube Group[a] (n = 107)	Trabeculectomy Group[a] (n = 105)
Laser suture lysis	6 (6)	58 (55)
Removal of rip cord	19 (18)	—
5-FU injection	1 (1)	26 (25)
Needling	3 (3)	14 (13)
Anterior chamber reformation	4 (4)	0 (0)
Injection of intracameral tPA	1 (1)	2 (2)
Suture wound leak	0	1 (1)
Autologous blood injection	0	1 (1)
Selective laser trabeculoplasty	0	1 (1)
YAG to internal ostium	—	1 (1)
YAG vitreolysis	0	1 (1)
Total number of patients with postoperative interventions[b]	27 (25)	74 (70)

5-FU = 5-fluorouracil; tPA = tissue plasminogen activator; YAG = yttrium-aluminum-garnet.
[a]Data are presented as number (percentage).
[b]$P < .001$ for the difference in total number of patients with postoperative interventions between treatment groups (χ^2 test).

• **STATISTICAL ANALYSIS:** Univariate comparisons between treatment groups were made using the 2-sided Student t test, χ^2 test, or Fisher exact test. The associations of surgical complications with treatment outcome, vision loss, and cataract progression were assessed for statistical significance with the χ^2 test or Fisher exact test. A P value of .05 or less was considered statistically significant.

RESULTS

• **RECRUITMENT AND SURGICAL TREATMENT:** A total of 212 eyes of 212 patients were enrolled in the TVT Study, including 107 patients who underwent placement of a tube shunt and 105 patients who had a trabeculectomy with MMC. All patients received their assigned treatment. Additional details on operative data and intraoperative complications were provided in a previous publication.[3]

• **POSTOPERATIVE INTERVENTIONS:** Table 1 lists postoperative interventions. Most interventions occurred in the early postoperative period and were previously reported.[3] The frequency of postoperative interventions was significantly higher in the trabeculectomy group than in the tube group. A total of 34 interventions were performed in 27 patients (25%) in the tube group, and 105 interven-

TABLE 2. Early Postoperative Complications[a] in the Tube Versus Trabeculectomy Study

	Tube Group[b] (n = 107)	Trabeculectomy Group[b] (n = 105)
Choroidal effusion	15 (14)	14 (13)
Shallow or flat anterior chamber	11 (10)	10 (10)
Wound leak	1 (1)	12 (11)
Hyphema	2 (2)	8 (8)
Aqueous misdirection	3 (3)	1 (1)
Suprachoroidal hemorrhage	2 (2)	3 (3)
Vitreous hemorrhage	1 (1)	1 (1)
Decompression retinopathy	0	1 (1)
Cystoid macular edema	0	1 (1)
Total number of patients with early postoperative complications[c,d]	22 (21)	39 (37)

[a]Onset ≤1 month.
[b]Data presented as number of patients (percentage).
[c]Some patients had more than 1 complication.
[d]$P = .012$ for the difference in total number of patients with early postoperative complications between treatment groups (χ^2 test).

TABLE 3. Late Postoperative Complications[a] in the Tube Versus Trabeculectomy Study

	Tube Group[b,c] (n = 107)	Trabeculectomy Group[b,c] (n = 105)
Persistent corneal edema	17 (16)	9 (9)
Dysesthesia	1 (1)	8 (8)
Persistent diplopia	6 (6)	2 (2)
Encapsulated bleb	2 (2)	6 (6)
Bleb leak	0	6 (6)
Choroidal effusion	2 (2)	4 (4)
Cystoid macular edema	5 (5)	2 (2)
Hypotony maculopathy	1 (1)	5 (5)
Tube erosion	5 (5)	—
Endophthalmitis/blebitis	1 (1)	5 (5)
Chronic or recurrent iritis	2 (2)	1 (1)
Tube obstruction	3 (3)	—
Retinal detachment	1 (1)	1 (1)
Corneal ulcer	0	1 (1)
Shallow or flat anterior chamber	1 (1)	0
Total number of patients with late postoperative complications[d,e]	36 (34)	38 (36)

[a]Onset >1 month.
[b]Data censored after a reoperation for glaucoma.
[c]Data presented as number of patients (percentage).
[d]Some patients had more than 1 complication.
[e]$P = .81$ for the difference in total number of patients with late postoperative complications between treatment groups (χ^2 test).

tions were made in 74 patients (70%) in the trabeculectomy group ($P < .001$, χ^2 test). The most common postoperative intervention was laser suture lysis in 58 patients (55%) in the trabeculectomy group and rip cord removal in 19 patients (18%) in the tube group.

Some interventions occurred in the late postoperative period. There were 2 patients in the tube group who had interventions at least 1 year after surgery, 1 requiring injection of intracameral tissue plasminogen activator for tube obstruction following a penetrating keratoplasty and 1 patient with elevated IOP requiring bleb needling. Interventions were performed after the first postoperative year in 11 patients in the trabeculectomy group; interventions included laser suture lysis in 1 patient for elevated IOP, an autologous blood injection in 1 patient for a late-onset bleb leak, yttrium-aluminum-garnet (YAG) vitreolysis in 1 patient with vitreous incarceration in the internal ostium, selective laser trabeculoplasty in 1 patient for elevated IOP, and YAG laser treatment to the internal ostium in 1 patient with a failing bleb. There were 6 additional patients who underwent needling procedures, including 1 patient for an encapsulated bleb and 5 patients for a flat bleb. A subconjunctival 5-fluorouracil (5-FU) injection was administered in conjunction with the needling procedure in 3 patients. In the trabeculectomy group, placement of a tube shunt was ultimately performed as a reoperation for glaucoma in 2 patients who had needling procedures and in the patient who underwent YAG laser treatment to the internal ostium. The patient who received an autologous blood injection subsequently had a bleb revision for a persistent bleb leak.

• **EARLY POSTOPERATIVE COMPLICATIONS:** Table 2 shows early postoperative complications developing within the first month after surgery. Early postoperative complications occurred with significantly greater frequency in the trabeculectomy group compared with the tube group. A total of 35 early postoperative complications were reported in 22 patients (21%) in the tube group, and 51 complications were noted in 39 patients (37%) in the trabeculectomy group ($P = .012$, χ^2 test). Among the 21 patients with a shallow or flat anterior chamber, 10 patients had associated choroidal effusions, 4 patients had aqueous misdirection, and 3 patients had suprachoroidal hemorrhages. There were 37 patients who had only 1 early postoperative complication. Several patients developed multiple early postoperative complications, including 23 patients with 2 complications and 1 patient with 3 complications.

Wound leak was the only early postoperative complication that was significantly more common in the trabeculectomy group compared with the tube group ($P = .004$, χ^2 test). No early postoperative complications occurred with significantly greater frequency in the tube group than in the trabeculectomy group. A tendency toward a higher incidence of hyphema in the trabeculectomy group relative

TABLE 4. Reoperations for Complications in the Tube Versus Trabeculectomy Study

	Tube Group[a] (n = 107)	Trabeculectomy Group[a] (n = 105)
Penetrating keratoplasty	6	
Pars plana vitrectomy	6	0
Tube shunt revision with patch graft	5	—
Bleb revision	0	5
Drainage of choroidal effusion	2	1
DSAEK	2	1
Vitreous tap with injection of intravitreal antibiotics	0	2
Penetrating keratoplasty and tube repositioning	1	—
Tube repositioning	1	—
Drainage of suprachoroidal hemorrhage	0	1
Lysis of iris adhesions to tube and cataract extraction	1	—
Tube revision with patch graft and cataract extraction	1	—
Removal of tube shunt	1	—
Trabeculectomy revision and tube shunt	0	1
Total number of patients (cumulative percentage) with reoperations for complications[b,c]	20 (22)	15 (18)

DSAEK = Descemet stripping automated endothelial keratoplasty.

[a]Data censored after a reoperation for glaucoma.

[b]Some patients had more than 1 type of reoperation for complications.

[c]P = .29 for the difference in 5-year cumulative reoperation rates for complications between treatment groups from Kaplan-Meier analysis (log-rank test adjusted for stratum).

TABLE 5. Serious Complications Associated With Reoperation and/or Vision Loss in the Tube Versus Trabeculectomy Study

	Tube Group[a] (n = 107)	Trabeculectomy Group[a] (n = 105)
Reoperation for complications, n (%)	20[b] (19)	15 (14)
Persistent corneal edema	9	6
Tube erosion	5	—
Bleb leak	0	4
Choroidal effusion	2	1
Endophthalmitis	1	2
Tube obstruction	3	—
Aqueous misdirection	2	0
Hypotony maculopathy	0	1
Suprachoroidal hemorrhage	0	1
Retinal detachment	1	0
Vision loss of ≥2 Snellen lines, n (%)	15[c] (14)	13[c] (12)
Persistent corneal edema	13	7
Suprachoroidal hemorrhage	1	2
Endophthalmitis	1	1
Hypotony maculopathy	0	2
Retinal detachment	1	1
Cystoid macular edema	0	1
Total number (%) of patients with serious complications[d,e]	24 (22)	21 (20)

[a]Data censored after a reoperation for glaucoma.

[b]Three patients had reoperations for 2 different complications.

[c]One patient had 2 different complications producing vision loss.

[d]Some patients had both a reoperation for a complication and vision loss.

[e]P = .79 for the difference in serious complication rates between treatment groups (χ^2 test).

to the tube group was observed, but the difference was not statistically significant (P = .058, Fisher exact test).

• **LATE POSTOPERATIVE COMPLICATIONS:** Table 3 reviews late postoperative complications occurring more than 1 month after surgery. The overall incidence of late postoperative complications was similar between treatment groups. A total of 47 late postoperative complications were seen in 36 patients (34%) in the tube group, and 50 complications were observed in 38 patients (36%) in the trabeculectomy group (P = .81, χ^2 test). A single late postoperative complication developed in 56 patients. Other patients experienced multiple late postoperative complications, including 14 patients with 2 complications, 3 patients with 3 complications, and 1 patient with 4 complications.

Several patients in each treatment group developed both early and late postoperative complications. The overall rate of postoperative complications was significantly higher in the trabeculectomy group compared with the tube group. During 5 years of follow-up, 46 patients (43%) in the tube group and 66 patients (63%) in the trabeculectomy group experienced 1 or more surgical complications postoperatively (P = .006, χ^2 test).

Bleb leak (P = .014, Fisher exact test) and dysesthesia (P = .018, Fisher exact test) were late postoperative complications that occurred with significantly greater frequency in the trabeculectomy group than in the tube group. No late postoperative complications were significantly more common in the tube group compared with the trabeculectomy group.

• **REOPERATION FOR COMPLICATIONS:** Table 4 presents the reoperations that were performed for complications. A

TABLE 6. Visual Acuity Results in the Tube Versus Trabeculectomy Study

	Patients With Complications			Patients Without Complications			
	Tube Group	Trabeculectomy Group	Overall Group	Tube Group	Trabeculectomy Group	Overall Group	*P* Value[a]
ETDRS VA, mean ± SD (n)							
Baseline	61 ± 24 (46)	65 ± 18 (66)	63 ± 21 (112)	64 ± 24 (61)	64 ± 22 (39)	64 ± 23 (100)	.89[b]
5 years	33 ± 31 (18)	56 ± 26 (30)	47 ± 30 (48)	46 ± 36 (19)	44 ± 30 (11)	46 ± 33 (30)	.80[b]
Snellen VA, logMAR mean ± SD (n)							
Baseline	.46 ± 54 (46)	.36 ± .36 (66)	.40 ± .44 (112)	.39 ± .55 (61)	.38 ± .41 (39)	.39 ± .50 (100)	.80[b]
5 years	.96 ± 1.00 (34)	.70 ± .79 (49)	.81 ± .88 (83)	.74 ± .94 (33)	.54 ± .61 (27)	.65 ± .81 (60)	.29[b]
Loss of ≥2 Snellen lines, n (%)	18[d] (51%)	22 (45%)	40 (48%)	13 (39%)	11 (41%)	24 (40%)	.46[c]

ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation; VA = visual acuity.

[a]*P* value comparing the overall groups with and without complications.

[b]Student *t* test.

[c]χ^2 test.

[d]One patient who did not have Snellen VA measured at 5 years was determined to have lost >2 Snellen lines based on change in ETDRS VA.

TABLE 7. Association of Surgical Complications With Treatment Outcome, Vision Loss, and Cataract Progression in the Tube Versus Trabeculectomy Study

	Treatment Outcome[a]			Vision Loss[b]			Cataract Progression[c]		
	Success[d] (n = 91)	Failure[d] (n = 66)	*P* Value	Stable Vision[d] (n = 80)	Loss of ≥2 Snellen Lines[d] (n = 64)	*P* Value	Stable[d] (n = 8)	Progressed[d] (n = 31)	*P* Value
Any postoperative complication									
No	39 (43)	28 (42)	>.99[e]	36 (45)	24 (38)	.46[e]	7 (88)	15 (48)	.11[g]
Yes	52 (57)	38 (58)		44 (55)	40 (63)		1 (13)	16 (52)	
Number of postoperative complications									
0	39 (43)	28 (42)	>.99[f]	36 (45)	24 (38)	.092[f]	7 (88)	15 (48)	.15[f]
1	29 (32)	19 (29)		27 (34)	20 (31)		0	8 (26)	
2	14 (15)	14 (21)		13 (16)	11 (17)		1 (13)	4 (13)	
3	5 (5)	4 (6)		3 (4)	6 (9)		0	1 (3)	
4	4 (4)	1 (2)		1 (1)	3 (5)		0	3 (10)	

[a]Analysis includes all patients who completed a 5-year follow-up visit and/or failed during the first 5 years of the study.

[b]Analysis includes all patients who had Snellen VA measured at the 5-year follow-up visit. One additional patient did not have Snellen VA assessed at 5 years, but was determined to have lost >2 Snellen lines based on change in Early Treatment Diabetic Retinopathy Study visual acuity.

[c]Analysis includes all phakic patients who completed a 5-year visit and/or had cataract progression during the first 5 years of the study.

[d]Data are presented as number (percentage).

[e]χ^2 test.

[f]Armitage exact test of trend in proportions.

[g]Fisher exact test.

total of 20 patients in the tube group and 15 patients in the trabeculectomy group underwent additional surgery to manage postoperative complications. The 5-year cumulative reoperation rate for complications from Kaplan-Meier survival analysis was 22% in the tube group and 18% in the trabeculectomy group, a difference that was not statistically significant ($P = .29$, log-rank test adjusted for stratum). There were 6 patients in the tube group and 5 patients in the trabeculectomy group who had persistent corneal edema requiring a penetrating keratoplasty. One of these patients in the tube group underwent a repeat penetrating keratoplasty and, later, a pars plana vitrectomy for vitreous obstruction of the tube in the study eye. An additional patient in the tube group had a penetrating keratoplasty in conjunction with repositioning of the tube. A pars plana vitrectomy was performed in 6 patients in the

TABLE 8. Comparison of Postoperative Complication Rates After Trabeculectomy in Multicenter Randomized Clinical Trials

	TVT Study[a] (n = 105)	CIGTS[b] (n = 465)	AGIS[c] (n = 509)	FFSS[a] (n = 213)
Shallow or flat anterior chamber	10%	13%	17.3%	NR
Wound leak	11%	6%	6.5%	20% without 5-FU 32% with 5-FU
Choroidal effusion	17%	11%	7.9%	NR
Anterior chamber bleeding	8%	10%	11.4%	NR
Encapsulated bleb	6%	12%	14.1%	NR
Bleb leak	6%	NR	NR	2% without 5-FU 9% with 5-FU
Suprachoroidal hemorrhage	3%	0.7%	NR	6.2% without 5-FU 6.2% with 5-FU
Endophthalmitis/blebitis	5%	0%	NR	.9% without 5-FU 1.9% with 5-FU
Cystoid macular edema	3%	.2%	NR	NR
Aqueous misdirection	1%	.4%	NR	NR
Overall rate[d]/follow-up	37%/1 month 63%/5 years	50%/1 month	53.6%/≥3 months	NR

AGIS = Advanced Glaucoma Intervention Study; CIGTS = Collaborative Initial Glaucoma Treatment Study; FFSS = Fluorouracil Filtering Surgery Study; 5-FU = 5-fluorouracil; NR = not reported; TVT = Tube Versus Trabeculectomy.

[a]Complication rates reported during 5 years of follow-up.

[b]Complication rates reported during 1 month of follow-up.

[c]Complication rates reported during ≥3 months of follow-up.

[d]Table does not list all complications, only those reported in more than 1 study.

tube group, including 2 patients for aqueous misdirection, 2 patients for tube obstruction by vitreous, 1 patient for endophthalmitis, and 1 patient for a retinal detachment. Revision of the tube shunt with placement of a new patch graft was performed in 5 patients in the tube group for tube erosion, which included 1 patient who initially had this procedure in conjunction with cataract extraction. The patient who had a tube shunt revision and cataract surgery developed a recurrent erosion requiring a second tube revision with patch graft. Another patient needed a repeat tube shunt revision, followed by removal of the tube shunt for repeated exposure. There were 5 patients in the trabeculectomy group who underwent a bleb revision, including 4 patients for bleb leaks and 1 patient for hypotony maculopathy. The patient with hypotony maculopathy subsequently had a trabeculectomy revision and placement of a 350-mm^2 Baerveldt glaucoma implant. Drainage of a choroidal effusion was performed in 2 patients in the tube group and 1 patient in the trabeculectomy group. The 2 patients in the tube group who had choroidal drainage later had additional surgery for other complications, including a penetrating keratoplasty for corneal edema in 1 patient and a pars plana vitrectomy to repair a retinal detachment in the other patient. There were 2 patients in the tube group and 1 patient in the trabeculectomy group who underwent a Descemet stripping automated endothelial keratoplasty (DSAEK) for persistent corneal edema. Tube repositioning was performed in 1 patient in the tube group for corneal edema, and a DSAEK was subsequently done for persistent corneal edema. Bleb-related endophthalmitis was treated with a vitreous tap with injection of intravitreal antibiotics in 2 patients in the trabeculectomy group. Drainage of a suprachoroidal hemorrhage was performed in 1 patient in the trabeculectomy group, and 1 patient in the tube group had lysis of iris adhesions obstructing the tube combined with cataract extraction.

• **SERIOUS COMPLICATIONS:** Table 5 shows serious complications resulting in reoperation and/or vision loss. The incidence of serious complications was similar between treatment groups. Serious complications were observed in 24 patients (22%) in the tube group and 21 patients (20%) in the trabeculectomy group ($P = .79$, χ^2 test). Persistent corneal edema was the most common cause for both reoperation for a complication and loss of 2 or more lines of Snellen VA in the tube and trabeculectomy groups. Reoperations for 2 different complications were performed in 3 patients in the tube group, including 1 patient who had a pars plana vitrectomy for tube obstruction by vitreous and a subsequent penetrating keratoplasty for corneal edema, 1 patient who underwent drainage of a choroidal effusion followed by a penetrating keratoplasty for corneal edema, and 1 patient who had drainage of a choroidal effusion and later a pars plana vitrectomy for a retinal detachment. One patient in each treatment group experienced loss of 2 or more Snellen lines from 2

postoperative complications, including a patient in the tube group who had a suprachoroidal hemorrhage and retinal detachment and a patient in the trabeculectomy group who had endophthalmitis and cystoid macular edema. A total of 11 patients in the tube group and 7 patients in the trabeculectomy group underwent a reoperation to manage a complication and also suffered vision loss.

• **VISION LOSS ASSOCIATED WITH POSTOPERATIVE COMPLICATIONS:** Table 6 shows visual acuity results in patients with and without postoperative complications. A significant decrease in Snellen and ETDRS VA was observed in patients who did and did not experience postoperative complications. ETDRS and Snellen VA were similar between patients with and without complications at 5 years, and no significant difference in the rate of loss of 2 or more Snellen lines was seen between these groups after 5 years of follow-up.

The relationship between postoperative complications and vision loss was explored, and the results are presented in Table 7. The presence of any postoperative complication did not significantly increase the rate of loss of 2 or more Snellen lines ($P = .46$, χ^2 test), and the number of complications was not significantly associated with vision loss. Examination of the individual complications listed in Tables 2 and 3 revealed that only persistent corneal edema significantly predicted vision loss in univariate ($P = .001$, χ^2 test) and multivariate ($P < .001$, logistic regression) analyses. Vision was reduced in 17 of 21 patients (81%) with corneal edema and in 47 of 123 patients (38%) without corneal edema.

• **CATARACT PROGRESSION:** The incidence of cataract progression during 5 years of follow-up was examined in the 24 eyes in the tube group and the 21 eyes in the trabeculectomy group that were phakic at the time of enrollment in the study. There were 4 patients in the tube group and 2 patients in the trabeculectomy group who were lost to follow-up before 5 years, and a determination as to whether cataract progression occurred could not be made in these patients. Worsening of cataract occurred in 16 patients (80%) in the tube group, including 13 patients who had cataract surgery and 3 patients who experienced loss of 2 or more lines of Snellen VA attributed to cataract. Cataract progression developed in 15 patients (79%) in the trabeculectomy group, including 9 patients who underwent cataract extraction and 6 patients who had loss of 2 or more Snellen lines from cataract. No significant difference in the rates of cataract surgery ($P = .43$, χ^2 test) or cataract progression ($P > .99$, Fisher exact test) were observed between treatment groups.

The risk of cataract progression relative to postoperative complications was assessed in Table 7. The presence of any postoperative complication ($P = .11$, Fisher exact test) and the number of postoperative complications ($P = .15$, Armitage exact test of trend) were not significantly associated with cataract progression. No postoperative complication significantly predicted progression of cataract in univariate and multivariate analyses.

TABLE 9. Comparison of Postoperative Complication Rates After Tube Shunt Surgery in Multicenter Randomized Clinical Trials

	TVT Study[a] (n = 107)	ABC Study[b,c] (n = 133)
Shallow or flat anterior chamber	11%	23%
Persistent corneal edema	16%	12%
Choroidal effusion	16%	11%
Hyphema	2%	18%
Tube obstruction	3%	14%
Persistent diplopia	6%	8%
Cystoid macular edema	5%	5%
Tube erosion	5%	1%
Chronic or recurrent iritis	2%	3%
Vitreous hemorrhage	1%	4%
Suprachoroidal hemorrhage	2%	2%
Hypotony maculopathy	1%	3%
Endophthalmitis	1%	2%
Retinal detachment	1%	0%
Overall rate[d]/follow-up	21%/1 month 43%/5 years	58%/3 months 69%/1 year

ABC = Ahmed Baerveldt Comparison; TVT = Tube Versus Trabeculectomy.

[a]Complication rates reported during 5 years of follow-up.

[b]Complication rates reported during 1 year of follow-up.

[c]Data are presented for patients randomized to receive a Baerveldt glaucoma implant.

[d]Table does not list all complications, only those reported in both studies.

• **EFFECT OF POSTOPERATIVE COMPLICATIONS ON TREATMENT OUTCOME:** The association of postoperative complications with treatment outcome was evaluated in Table 7. Treatment failures were pooled from both treatment groups for risk factor analyses. The risk of failure during 5 years of follow-up was not significantly increased by the presence of any postoperative complication ($P > .99$ χ^2 test) or the number of complications ($P > .99$ Armitage exact test of trend). No specific postoperative complication was significantly associated with treatment failure in univariate and multivariate analyses.

DISCUSSION

THE TVT STUDY IS A MULTICENTER RANDOMIZED CLINICAL trial comparing the safety and efficacy of tube shunt surgery to trabeculectomy with MMC in patients who had previous cataract and/or filtering surgery. Early postoperative complications occurred more frequently after trabeculec-

tomy with MMC than after tube shunt surgery. The rates of late postoperative complications and reoperation for complications were similar with both surgical procedures during 5 years of follow-up. However, all surgical complications are not equal in seriousness. We had considered trying to "weight" complications, but there is obvious difficulty in attempting to assign a relative value to individual complications because they have a broad range of severity. For example, diplopia may represent an infrequent symptom elicited in extreme gaze or a disabling problem that is always present, and a suprachoroidal hemorrhage may be visually devastating or limited and without sequelae. We instead chose to define serious complications as postoperative events that produced loss of 2 or more lines of Snellen VA and/or required reoperation to manage the complication. No significant difference in the frequency of serious complications was seen after tube shunt surgery and trabeculectomy with MMC.

The rates of postoperative complications in the TVT Study are similar to those of other multicenter randomized clinical trials involving trabeculectomy and tube shunt surgery, as shown in Tables 8 and 9. The incidence of early postoperative complications within the first month after trabeculectomy was 37% in TVT Study and 50% in the Collaborative Initial Glaucoma Treatment Study (CIGTS).[4] During the first year of follow-up, the overall rate of postoperative complications after Baerveldt implantation was 34% in the TVT Study and 69% in the Ahmed Baerveldt Comparison (ABC) Study.[5] The rates of specific postoperative complications are also remarkably consistent across these clinical trials, despite differences in study populations and length of follow-up. Many of the surgical complications observed in each of the clinical trials were transient and self-limited, such as anterior chamber shallowing and choroidal effusions. It is not unexpected that prospective studies generally report higher complication rates than retrospective case series. Complications may be overlooked unless attention is specifically directed toward their detection. Moreover, even when surgical complications are observed, they may not be documented in the medical record (especially if they are believed to be insignificant).

The incidences of most postoperative complications were similar between treatment groups. Wound leak was the only early postoperative complication that occurred with greater frequency in the trabeculectomy group compared with the tube group. While nonvalved tube shunt surgery produces a delayed drainage of aqueous humor to the equatorial region of the eye, trabeculectomy results in an immediate filtration of aqueous near the conjunctival incision with a greater tendency toward postoperative wound leaks. As noted in Table 8, the rate of would leak after trabeculectomy was slightly higher in the TVT Study (11%) than in the Advanced Glaucoma Intervention Study (AGIS) (6.5%)[6] or CIGTS (6%).[4] However, the Fluorouracil Filtering Surgery Study (FFSS) may be a more appropriate clinical trial for comparison with the TVT Study because both studies enrolled similar patient groups (ie, previous cataract or glaucoma surgery) and employed the same protocol of Seidel testing at each follow-up visit.[7,8] This method for meticulously detecting wound leaks was not used in AGIS or CIGTS. The rate of early postoperative wound leak was 20% in the standard treatment group and 32% in the 5-FU group in FFSS.[7] Bleb leak and dysesthesia were late complications that were observed more frequently in the trabeculectomy group compared with the tube group. In contrast to the thick-walled bleb overlying the end plate of a tube shunt, trabeculectomy with an adjunctive antifibrotic agent typically creates a thin-walled perilimbal bleb that is prone to bleb leaks and dysesthesia.

No postoperative complications were significantly more common in the tube group compared with the trabeculectomy group. There was a tendency for diplopia to be more common in the tube group than in the trabeculectomy group after 1 year and 3 years of follow-up. However, the addition of 1 patient in the tube group and 2 patients in the trabeculectomy group with late-onset diplopia made the difference in the rate of this complication even less significant at 5 years. Although many of the differences in complication rates were not statistically significant, they may be clinically relevant. For example, the occurrence of endophthalmitis or blebitis in 1 patient in the tube group and 5 patients in the trabeculectomy group is not statistically significant, but raises concern. The power of this study to detect differences in complications with low incidence rates was limited by the sample size.

A reduction in VA was observed in both the tube and trabeculectomy groups, but Snellen and ETDRS VA were similar between treatment groups at 5 years.[1] No significant difference in the rate of vision loss was seen between patients who did and did not develop postoperative complications. The presence of any postoperative complication and the number of complications did not increase the risk of vision loss. Most surgical complications were not significantly associated with loss of vision. Only patients with persistent corneal edema were more likely to experience a decline in vision. Almost twice as many patients in the tube group developed corneal edema relative to the trabeculectomy group, although the rates of persistent corneal edema and corneal transplantation were not statistically different between the 2 treatment groups. Corneal edema may develop after glaucoma surgery secondary to hypotony or endothelial cell loss. A greater number of patients in the TVT Study experienced persistent hypotony after trabeculectomy with MMC than after tube shunt surgery.[1] A reduction in corneal endothelial density has been described after tube shunt surgery[9–11] and trabeculectomy with MMC.[12–15] Some complications that commonly produce reduction in vision, such as cystoid macular edema and hypotony maculopathy, were not significantly associated with vision loss in risk factor analyses. This may

indicate successful treatment of these conditions, or inadequate power to identify them as risk factors because of their low rates of occurrence.

A total of 45 eyes (21%) were phakic at the time of enrollment in the TVT Study. Cataracts were considered to have progressed if there was loss of 2 or more lines of Snellen VA that was attributed to cataract, or if cataract surgery was performed. We did not use methods of grading lens opacities with standard lens photographs, such as the Lens Opacities Classification System II (LOCS II)[16] or the Wisconsin System.[17] Cataract progression was common during 5 years of follow-up, but occurred at a similar rate in the tube and trabeculectomy groups. No significant difference in the rate of cataract surgery was observed between treatment groups. Several studies have reported that glaucoma surgery is associated with a higher incidence and progression of cataract.[18–26] AGIS found that the risk of cataract formation was greater when there was at least 1 surgical complication, particularly marked inflammation and flat anterior chamber.[25] The presence of any postoperative complication and the number of complications were not associated with cataract progression during 5 years of follow-up in the TVT Study, and no specific postoperative complication predicted the progression of cataract.

Conflicting information is present about the effect of surgical complications on final outcome. Previous studies have reported no significant effect of postoperative complications on trabeculectomy failure.[19,27] However, AGIS determined that the presence of any postoperative complication doubled the risk of failure of trabeculectomy.[6] The TVT Study found that the presence of any postoperative complication and the number of complications did not increase the risk of treatment failure. Wound leak and hypotony maculopathy were associated with failure in our study after the first year of follow-up. However, no postoperative complication predicted treatment failure when additional failures were accrued during 5 years of the TVT Study.

Stein and associates recently evaluated the rates of postoperative complications after glaucoma surgery among Medicare beneficiaries.[28] The rates of adverse outcomes were higher after tube shunt surgery than primary trabeculectomy or trabeculectomy with scarring. The difference in study results between the TVT Study and the study by Stein and associates likely relates to differences in study populations and design. There are limitations of data derived from Medicare claims, including the possibility of misattributing adverse events from the fellow eye.[28,29] Tube shunts have historically been reserved for patients who are considered to be at high risk for failure of standard trabeculectomy with an adjunctive antifibrotic agent, and the results of Stein's study may be attributable to differences in case severity among the glaucoma procedures that were compared. In contrast, patients who underwent tube shunt surgery and trabeculectomy with MMC in the TVT Study had similar characteristics as a result of the randomization process, and included lower-risk patients than have traditionally had tube shunt surgery (eg, only prior clear cornea cataract extraction).

There are several weaknesses of this study. There were no standard definitions or quantification of complications. For example, a hyphema could have represented a small amount of blood layered in the inferior angle or complete filling of the anterior chamber with hemorrhage. Even though the presence of postoperative complications was recorded at study and nonstudy visits, it is possible that some complications may have developed and resolved between follow-up visits, resulting in an underestimation of the true incidence of postoperative complications. Patients were censored from analysis of complications after a reoperation for glaucoma, and this may have produced an underestimation of complication rates. Because the trabeculectomy group had a higher frequency of glaucoma reoperations, this effect was potentially greater in this treatment group. The large number of significance tests that were performed increases the probability of finding statistically significant results by chance alone. The low incidence of certain complications limits the power of the study to detect significant differences. The TVT Study enrolled patients who met specific inclusion and exclusion criteria, and all patients randomized to the tube group received a 350-mm^2 Baerveldt glaucoma implant. The study results cannot be generalized to other patient groups or different implant types. Many aspects of both surgical procedures were standardized, but some variation in surgical technique occurred between investigators. Limbus-based conjunctival flaps were used in the majority of patients who were randomized to trabeculectomy, and MMC (0.4 mg/mL for 4 minutes) was applied intraoperatively. Since the TVT Study was initiated, there has been a trend toward use of fornix-based conjunctival flaps with a more diffuse application of MMC at a lower dosage.[30] This modification in surgical technique may result in a lower rate of bleb-related complications following trabeculectomy.[31]

Several minimally invasive glaucoma procedures have been introduced in recent years. Lower rates of surgical complications have been reported with these procedures compared with trabeculectomy, but they are generally less effective in decreasing IOP.[32–34] With the expansion of surgical options for managing glaucoma, selecting the most appropriate glaucoma operation involves balancing the risks of adverse events and the benefit of IOP reduction for an individual patient. Comparative studies like the TVT Study are required to fully assess the relative efficacy and safety of the various glaucoma procedures available to surgeons. Long-term follow-up data are needed, as the cumulative risk of many surgical complications increases over time.

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TUBE VERSUS TRABECULECTOMY STUDY GROUP:
A complete list of the investigators in the TVT Study and their financial disclosures are provided in Gedde SJ, Schiffman JC, Feuer WJ, et al. Treatment outcomes in the Tube Versus Trabeculectomy (TVT) Study after five years of follow-up. Am J Ophthalmol 2012. Forthcoming.

REFERENCES

1. Gedde SJ, Schiffman JC, Feuer WJ, et al. Treatment outcomes in the Tube Versus Trabeculectomy Study after five years of follow-up. Am J Ophthalmol 2012. Forthcoming.
2. Gedde SJ, Schiffman JC, Feuer WJ, et al. The Tube Versus Trabeculectomy Study: Design and baseline characteristics of study patients. Am J Ophthalmol 2005;140(2):275–287.
3. Gedde SJ, Herndon LW, Brandt JD, et al. Surgical complications in the Tube Versus Trabeculectomy Study during the first year of follow-up. Am J Ophthalmol 2007;143(1):23–31.
4. Jampel HD, Musch DC, Gillespie BW, et al. Perioperative complications of trabeculectomy in the Collaborative Initial Glaucoma Treatment Study (CIGTS). Am J Ophthalmol 2005;140(1):16–22.
5. Budenz DL, Barton K, Feuer WJ, et al. Treatment outcomes in the Ahmed Baerveldt Comparison Study after 1 year of follow-up. Ophthalmology 2011;118(3):443–452.
6. AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 11. Risk factors for failure of trabeculectomy and argon laser trabeculoplasty. Am J Ophthalmol 2002; 134(4):481–498.
7. Parrish RK, Schiffman JC, Feuer WJ, Heuer DK, Fluorouracil Filtering Surgery Study Group. Prognosis and risk factors for early postoperative wound leaks after trabeculectomy with and without 5-fluorouracil. Am J Ophthalmol 2001;132(5): 633–640.
8. The Fluorouracil Filtering Surgery Study Group. Five-year follow-up of the fluorouracil filtering surgery study. Am J Ophthalmol 1996;121(4):349–366.
9. Kim CS, Yim JH, Lee EK, Lee NH. Changes in corneal endothelial cell density and morphology after Ahmed glaucoma valve implantation during the first year of follow up. Clin Experiment Ophthalmol 2008;36(2):142–147.
10. Mendrinos E, Dosso A, Sommerhalder J, Shaarawy T. Coupling of HRT II and AS-OCT to evaluate corneal endothelial cell loss and in vivo visualization of the Ahmed glaucoma valve implant. Eye 2009;23(9):1836–1844.
11. Lee EK, Yun YJ, Lee JE, Yim JH, Kim CS. Changes in corneal endothelial cells after Ahmed glaucoma valve implantation: 2-year follow-up. Am J Ophthalmol 2009;148(3): 361–367.
12. The Fluorouracil Filtering Surgery Study Group. Fluorouracil filtering surgery study one year follow-up. Am J Ophthalmol 1989;108(6):625–635.
13. Pastor SA, Williams R, Hetherington J, Hoskins HD, Goodman D. Corneal endothelial cell loss following trabeculectomy with mitomycin C. J Glaucoma 1993;2(2):112–113.
14. Arnavielle S, Lafontaine PO, Bidot S, Creuzot-Garcher C, D'Athis P, Bron AM. Corneal endothelial cell changes after trabeculectomy and deep sclerectomy. J Glaucoma 2007; 16(3):324–328.
15. Storr-Paulsen T, Norregaard JC, Ahmed S, Storr-Paulsen A. Corneal endothelial cell loss after mitomycin C-augmented trabeculectomy. J Glaucoma 2008;17(8):654–657.
16. Chylack LT, Leske MC, McCarthy D, Khu P, Kashiwagi T, Sperduto R. Lens Opacities Classification System II (LOCS II). Arch Ophthalmol 1989;107(7):991–997.
17. Klein BE, Klein R, Linton KL, Magli YL, Neider MW. Assessment of cataracts from photographs in the Beaver Dam Eye Study. Ophthalmology 1990;97(11):1428–1433.
18. Mills KB. Trabeculectomy: A retrospective long-term follow-up of 444 cases. Br J Ophthalmol 1981;65(11):790–795.
19. Watson PG, Jakeman C, Ozturk M, Barnett MF, Barnett F, Khaw KT. The complications of trabeculectomy (a 20-year follow-up). Eye 1990;4(3):425–438.
20. Costa VP, Smith M, Spaeth GL, Gandham S, Markovitz B. Loss of visual acuity after trabeculectomy. Ophthalmology 1993;100(5):599–612.
21. Cheung JC, Wright MM, Murali S, Pederson JE. Intermediate-term outcome of variable dose mitomycin C filtering surgery. Ophthalmology 1997;104(1):143–149.
22. Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol 1998;126(4):487–497.
23. The AGIS Investigators. The Advanced Glaucoma Intervention Study, 6: Effect of cataract on visual field and visual acuity. Arch Ophthalmol 2000;118(12):1639–1652.
24. Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. Ophthalmology 2001;108(11):1943–1953.
25. The AGIS Investigators. The Advanced Glaucoma Intervention Study: 8. Risk of cataract formation after trabeculectomy. Arch Ophthalmol 2001;119(12):1771–1779.
26. Hylton C, Congdon N, Friedman D, et al. Cataract after glaucoma filtration surgery. Am J Ophthalmol 2003;135(2): 231–232.
27. Lavin MJ, Wormald RPL, Migdal CS, Hitchings RA. The influence of prior therapy on the success of trabeculectomy. Arch Ophthalmol 1990;108(11):1543–1548.
28. Stein JD, Ruiz D, Belsky D, Lee PP, Sloan FA. Longitudinal rates of postoperative adverse outcomes after glaucoma surgery among medicare beneficiaries 1994 to 2005. Ophthalmology 2008;115(7):1109–1116.

29. Javitt JC. Trab vs. tube, a 15-year retrospective: What have we learned in 20 years? Ophthalmology 2008;115(7):1107–1108.
30. Jones E, Clarke J, Khaw PT. Recent advances in trabeculectomy technique. Curr Opin Ophthalmol 2005;16(2):107–113.
31. Wells AP, Cordeiro MF, Bunce C, Khaw PT. Cystic bleb formation and related complications in limbus- versus fornix-based conjunctival flaps in pediatric and young adult trabeculectomy with mitomycin C. Ophthalmology 2003; 110(11):2192–2197.
32. Minckler D, Mosaed S, Dustin L, Francis B, Trabectome Study Group. Trabectome (trabeculectomy-internal approach): Additional experience and extended follow-up. Trans Am Ophthalmol Soc 2008;106:149–159.
33. Lewis RA, von Wolff K, Tetz M, et al. Canaloplasty: Circumferential viscodilation and tensioning of Schlemm canal using a flexible microcatheter for the treatment of open-angle glaucoma in adults: Two year interim clinical study. J Cataract Refract Surg 2009;35(5):814–824.
34. Samuelson TW, Katz LJ, Wells JM, Duh YJ, Giamporcaro JE, US iStent Study Group. Randomized evaluation of the trabecular micro-bypass stent with phacoemulsification in patients with glaucoma and cataract. Ophthalmology 2011; 118(3):459–467.

Biosketch

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