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Risk Factors and Long-Term Outcomes in Patients with Low Intraocular Pressure after Trabeculectomy

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Purpose: To examine risk factors for low intraocular pressure (IOP) after trabeculectomy and to describe long-term outcomes in these eyes.

Design: Retrospective case-control study.

Participants: Cases with low IOP included all patients with IOP ≤5 mmHg on 3 or more consecutive visits 3 months or later after trabeculectomy. Control patients without low IOP after trabeculectomy were randomly selected at a 1:2 case-to-control ratio.

Methods: A case-control study was performed of patients undergoing trabeculectomy at the Stein Eye Institute. Covariates included demographics, history of cataract surgery, refractive error, number of glaucoma medications, family history of glaucoma, diabetes, hypertension, visual acuity (VA), IOP, number of sutures in the scleral flap, laser suture lysis, surgeon, and laterality of surgery. Logistic regression modeling was used to examine associations between each covariate and low IOP. Postoperative outcomes that were examined included reoperation, vision loss, and surgical failure. The time between trabeculectomy and each outcome was compared between cases and controls with Cox proportional hazards regression modeling.

Main Outcome Measures: Low IOP after trabeculectomy, reoperation, vision loss, and surgical failure.

Results: Of 3659 total trabeculectomies performed by 5 surgeons between 1990 and 2013, 64 eyes had low IOP (1.7%), which were compared with 130 control eyes. Fifteen of the 64 eyes with low IOP had hypotony maculopathy (23.4%). After accounting for differences in baseline IOP, laser suture lysis was negatively correlated with low IOP after trabeculectomy (odds ratio [OR], 0.33; 95% confidence interval [CI], 0.13–0.87); surgeon was correlated with high vs. low IOP after trabeculectomy (OR, 5.32; 95% CI, 1.53–18.52). There were no statistically significant associations between low IOP and time to reoperation (hazard ratio [HR], 0.73; 95% CI, 0.32–1.68), vision loss (HR, 1.77; 95% CI, 0.81–3.88) or surgical failure (HR, 1.14; 95% CI, 0.62–2.11). In patients with low IOP, there was a higher unadjusted incidence of bleb revision in patients who had maculopathy (7.6 vs. 1.9 revisions/100 person-years; for maculopathy versus no maculopathy $P = 0.008$).

Conclusions: The absence of laser suture lysis and surgeon are factors potentially associated with low IOP after trabeculectomy. Numeric hypotony does not necessarily represent clinical failure after trabeculectomy. *Ophthalmology 2017;124:1457-1465 © 2017 by the American Academy of Ophthalmology*

Trabeculectomy is commonly performed in patients with medically uncontrolled glaucoma.[1] Antifibrotic agents such as mitomycin-C and 5-fluorouracil were introduced in the early 1990s as adjuncts to trabeculectomy to decrease bleb scarring and to improve surgical success.[2,3] Since the introduction of these agents, increased rates of ocular hypotony have been observed after trabeculectomy.[4] Although ocular hypotony is suggested by the presence of characteristic structural changes in the eye, such as hypotony maculopathy, choroidal effusion, and corneal decompensation,[3–7] it has been defined as intraocular pressure (IOP) <6.5 mmHg (which is <3 standard deviations below the mean[8]) or as IOP ≤5 mmHg 3 months or later postoperatively.[9] The characteristic structural changes typically have not been included in the definition.

Rates of low IOP after trabeculectomy range from 1.6% to 12.4% in clinical trials[9–11] and 7.2% to 42.2% in observational studies.[7,12–14] Proposed risk factors for postoperative ocular hypotony have included young age, myopia, preoperative glaucoma medication use, surgeon, laterality of surgery, and laser suture lysis.[13–15] These rates have been inconsistent across studies, and it remains unclear why certain eyes may be more predisposed to ocular hypotony after surgery than others. In addition, existing studies have mainly used a numeric definition to examine the incidence of ocular hypotony, but whether these numeric

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thresholds necessarily correspond to poor clinical outcomes is unknown. The purpose of this study was to examine risk factors and long-term surgical outcomes in eyes with ocular hypotony after trabeculectomy at the University of California, Los Angeles (UCLA) Stein Eye Institute.

Methods

A case-control study was conducted on eyes with primary trabeculectomy performed at the UCLA Stein Eye Institute between 1990 and 2013. Cases included all eyes with ocular hypotony after trabeculectomy, which was defined as eyes without a bleb leak and IOP ≤5 mmHg on 3 or more consecutive visits 3 months or later after surgery. Among the cases, those with hypotony maculopathy were defined as patients who met the definition for ocular hypotony and had macular folds or macular edema present on clinical examination or optical coherence tomography. Controls were identified with a cumulative sampling strategy and included a random sample of eyes with trabeculectomy and no ocular hypotony, selected at a 1:2 case-to-control ratio with the cases. Eyes with early vision loss or surgical failure, as defined next, before 3 months postoperatively were excluded. The UCLA Institutional Review Board approved the study.

Preoperative covariates that were collected for the study population included age at time of trabeculectomy, gender, ethnicity, glaucoma subtype, history of diabetes, history of hypertension, history of cataract surgery, family history of glaucoma, refractive error, number of glaucoma medications at the last visit before trabeculectomy, IOP at the last visit before trabeculectomy, visual acuity (VA) at the last visit before trabeculectomy, and central corneal thickness (CCT). Intraoperative and early postoperative covariates that were collected included laterality, surgeon, number of sutures placed in the scleral flap, performance of laser suture lysis, and postoperative IOP within the first 30 days after trabeculectomy.

Long-term outcomes that were examined included (1) reoperation, defined as the need for bleb revision or additional glaucoma surgery 3 months or later after the initial trabeculectomy and after the date of low IOP for patients in the ocular hypotony group; (2) vision loss, defined as the loss of 2 or more lines of Snellen VA on at least 2 postoperative visits 3 months or later after trabeculectomy and after the date of low IOP for patients in the ocular hypotony group; and (3) surgical failure, defined as the need for reoperation, vision loss, or occurrence of a bleb-related infection after the date of low IOP for patients in the ocular hypotony group. The occurrence of bleb-related infections was not examined as an independent outcome because an insufficient number of patients experienced these complications. Patients who met the definition for ocular hypotony but had reoperation, vision loss, or a bleb-related infection before the date of hypotony were included as controls rather than cases in this study, and follow-up time was stopped at the date of the poor outcome.

Descriptive statistics were performed for all study variables at baseline. To assess potential risk factors for ocular hypotony after trabeculectomy, separate univariate logistic regression models were created with each baseline covariate as independent predictors and ocular hypotony as the outcome. Preoperative IOP was included as a covariate in each of these models to account for baseline differences in IOP between cases and controls. Covariates with $P < 0.3$ in the univariate models were included in 1 multivariable model to assess for multivariable predictors of ocular hypotony after trabeculectomy. Univariate comparisons were made between patients with early-onset versus late-onset ocular hypotony. Early-onset ocular hypotony was defined as the first occurrence of hypotony within 3 months to 1 year after trabeculectomy, and late-onset ocular hypotony was defined as the first occurrence of hypotony 1 year or later after trabeculectomy. To assess long-term surgical outcomes, Cox proportional hazards regression was performed to compare the time between trabeculectomy and each long-term outcome in cases versus controls, controlling for all baseline covariates. Patients who did not experience surgical failure were censored on their last visit date or administratively censored on July 1, 2013. Because of a high number of patients with missing values for refractive error (19.6%) and CCT (37.1%), a second analysis was performed excluding refractive error and CCT as covariates. In patients who required reoperation or developed vision loss after trabeculectomy, the reasons for reoperation or vision loss were documented, and causes for reoperation and vision loss were analyzed as simple proportions. All statistical analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Of 3659 total trabeculectomies performed in our department between 1990 and 2013, there were 64 cases of ocular hypotony (1.7%). Of these 64 cases of ocular hypotony, 15 patients had hypotony maculopathy (23.4%). The study population included these 64 cases and 130 controls without ocular hypotony after trabeculectomy. Of the 194 eyes with trabeculectomy included in the study, 83 had the surgery performed by surgeon 1, 62 by surgeon 2, 35 by surgeon 3, 13 by surgeon 4, and 1 by surgeon 5. Patients in the study population were followed for a mean of 6.9±4.4 years after the date of trabeculectomy.

Descriptive statistics are outlined in Table 1. In the overall study population, the majority of patients were aged 60 to 79 years (n = 111; 57.2%), female (n = 114; 58.8%), white (n = 122; 62.9%), and diagnosed with primary open-angle glaucoma (n = 154; 79.4%). In addition, the majority of patients were phakic (n = 134; 69.8%) and myopic (n = 102; 52.6%). Mean preoperative IOP was 16.8±6.0 mmHg in cases and 20.3±8.8 mmHg in controls. Mean preoperative logarithm of the minimum angle of resolution (logMAR) VA was 0.24±0.28 logMAR units in cases and 0.36±0.44 logMAR units in controls. Patients in the ocular hypotony group (i.e., those with IOP ≤5 mmHg on 3 consecutive visits 3 months or later after trabeculectomy) had lower mean IOP within the first 30 days after trabeculectomy compared with control patients without ocular hypotony (7.1±5.6 vs. 10.1±5.7 mmHg, respectively; $P = 0.0005$), and a lower proportion of cases underwent laser suture lysis (n = 18; 28.1%) compared with controls without ocular hypotony (n = 66; 50.8%, $P = 0.004$). Table 2 compares baseline characteristics between patients with early-onset and late-onset ocular hypotony. There were no statistically significant differences in any baseline characteristics between the 2 groups.

Table 3 summarizes findings from the multivariable analysis of risk factors for ocular hypotony after trabeculectomy. All covariates except for sex, history of diabetes, preoperative number of glaucoma medications, number of sutures in the scleral flap, and eye of surgery had $P < 0.3$ in the univariate models. After accounting for differences in baseline IOP, covariates that had a statistically significant association with ocular hypotony in the multivariable model included laser suture lysis (odds ratio [OR], 0.33; 95% confidence interval [CI], 0.13−0.87 for lysis vs. no lysis; $P = 0.03$) and surgeon (OR, 5.32; 95% CI, 1.53−18.52 for surgeon 2 vs. surgeon 1; $P = 0.009$; overall P for surgeon = 0.0065). Compared with surgeon 2, surgeon 1 had a higher proportion of laser suture lysis (51.8% in surgeon 1 vs. 34.7% in surgeon 2; $P = 0.02$) and higher mean preoperative IOP (19.1±7.9 mmHg in surgeon 1 vs. 17.9±6.6 mmHg in surgeon 2; $P = 0.24$).

Table 1. Baseline Characteristics of Patients Undergoing Trabeculectomy with and without Postoperative Ocular Hypotony* (n = 251)

	No. (%) of Patients with Characteristic			
	Entire Study Population (n = 194)	*Patients with Postoperative Ocular Hypotony (n = 64)*	*Patients without Postoperative Ocular Hypotony (n = 130)*	**P Value**
Age (yrs)				
18–39	5 (2.6)	1 (1.6)	4 (3.1)	
40–59	48 (24.7)	21 (32.8)	27 (20.8)	
60–79	111 (57.2)	34 (53.1)	77 (59.2)	
≥80	30 (15.5)	8 (12.5)	22 (16.9)	0.29
Sex				
Male	80 (41.2)	28 (43.8)	52 (40.0)	
Female	114 (58.8)	35 (56.3)	78 (60.0)	0.62
Ethnicity				
White	122 (62.9)	45 (70.3)	77 (59.2)	
Nonwhite	65 (33.5)	16 (25.0)	49 (37.7)	
Missing	7 (3.6)	3 (4.7)	4 (3.1)	0.09
Glaucoma subtype				
Open angle	154 (79.4)	56 (87.5)	98 (75.4)	
Angle closure	17 (8.8)	1 (1.6)	16 (12.3)	
Other	23 (11.9)	7 (10.9)	16 (12.3)	0.04
Systemic comorbidities				
Diabetes	16 (8.3)	4 (6.3)	12 (9.2)	0.48
Hypertension	56 (28.9)	15 (23.4)	41 (31.5)	0.24
Lens status				
Phakic	134 (69.8)	40 (62.5)	94 (73.4)	
Pseudophakic	58 (30.2)	24 (37.5)	34 (26.6)	0.12
Refractive error[†]				
None	14 (7.2)	6 (9.4)	8 (6.2)	
Hyperopia	40 (20.6)	5 (7.8)	35 (26.9)	
Mild/moderate myopia	89 (45.9)	35 (54.7)	54 (41.5)	
High myopia	13 (6.7)	3 (4.7)	10 (7.7)	
Missing	38 (19.6)	15 (23.4)	23 (17.7)	0.01
No. of glaucoma medications preoperatively				
0–2	75 (38.7)	27 (42.2)	48 (36.9)	
≥3	119 (61.3)	37 (57.8)	82 (63.1)	0.48
Preoperative examination				
IOP, mean (SD)	19.2 (8.1)	16.8 (6.0)	20.3 (18.8)	0.005
Visual acuity (logMAR), mean (SD)	0.33 (0.40)	0.24 (0.28)	0.36 (0.44)	0.05
CCT, mean (SD)	545.2 (44.4) (missing = 72)	538.8 (39.5) (missing = 26)	548.1 (46.4) (missing = 46)	0.29
No. of sutures in scleral flap				
2	79 (40.7)	26 (40.6)	53 (40.8)	
3	45 (23.2)	16 (25.0)	29 (22.3)	
≥4	58 (29.9)	19 (29.7)	39 (30.0)	
Missing	12 (6.2)	3 (4.7)	9 (6.9)	0.95
Eye of surgery				
Right	92 (47.4)	28 (43.8)	64 (49.2)	
Left	102 (52.6)	36 (56.3)	66 (50.8)	0.47
Early postoperative factors				
Laser suture lysis	84 (43.3)	18 (28.1)	66 (50.8)	0.004
IOP within 30 days postoperatively, mean (SD)	9.1 (5.9)	7.1 (5.6)	10.1 (5.7)	0.0005

CCT = central corneal thickness; IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution; SD = standard deviation.
*Defined as IOP ≤5 mmHg on ≥3 consecutive visits ≥3 months after surgery.
[†]Hyperopia = refractive error >0.00 diopters (D); mild/moderate myopia = refractive error <0.00 D and >−6.00 D; high myopia = refractive error <−6.00 D.

Tables 4 and 5 summarize analyses of long-term outcomes after trabeculectomy. This study had 80% power to detect an OR of 2.5, 60% power to detect an OR of 2.0, and 20% power to detect an OR of 1.5. There were no statistically significant differences in the unadjusted incidence of reoperation, vision loss, or surgical failure in cases versus controls (Figs 1–3). Among patients with ocular hypotony, there was a higher unadjusted incidence of reoperation in patients who had hypotony maculopathy, but no significant differences in the incidence of vision loss or overall surgical failure (Table 4). In Cox proportional hazards modeling, there were no statistically significant associations between ocular hypotony and time to reoperation, vision loss, or surgical failure in the unadjusted or adjusted models. In addition, in patients with ocular hypotony, there were no statistically significant

Table 2. Baseline Characteristics of Patients Undergoing Trabeculectomy with Early-Onset versus Late-Onset Hypotony (n = 64)*

	No. (%) of Patients with Characteristic		
	Patients with Early-Onset Hypotony (n = 37)	*Patients with Late-Onset Hypotony (n = 27)*	*P Value*
Age (yrs)			
18–39	0 (0.0)	1 (3.7)	
40–59	15 (40.5)	6 (22.2)	
60–79	17 (46.0)	17 (63.0)	
≥80	5 (13.5)	3 (11.1)	0.27
Sex			
Male	15 (40.5)	13 (49.1)	
Female	22 (59.5)	14 (51.9)	0.54
Ethnicity			
White	27 (73.0)	18 (66.7)	
Nonwhite	8 (21.6)	8 (29.6)	
Missing	2 (5.4)	1 (3.7)	0.49
Glaucoma subtype			
Open angle	33 (89.2)	23 (85.2)	
Angle closure	0 (0.0)	1 (3.7)	
Other	4 (10.8)	3 (11.1)	0.50
Systemic comorbidities			
Diabetes	2 (5.4)	2 (7.4)	0.74
Hypertension	7 (18.9)	8 (29.6)	0.32
Lens status			
Phakic	24 (64.9)	16 (59.3)	
Pseudophakic	13 (35.1)	11 (40.7)	0.65
Refractive error[†]			
None	2 (5.4)	4 (14.8)	
Hyperopia	2 (5.4)	3 (11.1)	
Mild/moderate myopia	23 (62.2)	12 (44.4)	
High myopia	2 (5.4)	1 (3.7)	
Missing	8 (21.6)	7 (25.9)	0.38
No. of glaucoma medications preoperatively			
0–2	16 (43.3)	11 (40.7)	
≥3	21 (56.8)	16 (59.3)	0.84
Preoperative examination			
IOP, mean (SD)	16.3 (6.5)	17.5 (5.3)	0.45
VA (logMAR), mean (SD)	0.2 (0.2)	0.3 (0.4)	0.13
CCT, mean (SD)	545.4 (30.6) (missing = 12)	526.2 (51.8) (missing = 14)	0.16
No. of sutures in scleral flap			
2	16 (43.2)	10 (37.0)	
3	8 (21.6)	8 (29.6)	
≥4	12 (32.4)	7 (25.9)	
Missing	1 (2.7)	2 (7.4)	0.69
Eye of surgery			
Right	15 (40.5)	13 (48.2)	
Left	22 (59.5)	14 (51.9)	0.55
Early postoperative factors			
Laser suture lysis	10 (27.8)	8 (29.6)	0.87
IOP within 90 days postoperatively, mean (SD)	5.2 (2.9)	7.6 (6.0)	0.16

CCT = central corneal thickness; IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution; SD = standard deviation; VA = visual acuity.
*Early-onset hypotony = IOP ≤5 mmHg on 3 consecutive visits occurring for the first time between 3 months and 1 year after trabeculectomy, without a bleb leak; late-onset hypotony = IOP ≤5 mmHg on 3 consecutive visits occurring for the first time 1 year or later after trabeculectomy, without a bleb leak.
[†]Hyperopia = refractive error >0.00 diopters (D); mild/moderate myopia = refractive error <0.00 D and >−6.00 D; high myopia = refractive error <−6.00 D.

associations between hypotony maculopathy and time to surgical failure in the unadjusted and adjusted models (Table 5). Cox proportional hazards analyses of time to reoperation and vision loss in patients with versus without hypotony maculopathy could not be performed because of insufficient sample size.

Table 6 describes the reasons for bleb revision and vision loss in cases versus controls. Of 14 cases with reoperation after the initial trabeculectomy, the majority of patients underwent reoperation for hypotony maculopathy (n = 8; 57.1%) followed by bleb dysesthesia (n = 2; 14.3%) and clinical signs of hypotony other than maculopathy, such as choroidal effusions or a shallow anterior chamber (n = 2; 14.3%). Of 28 controls with reoperation after the initial trabeculectomy, the majority of patients underwent reoperation for glaucoma that was worsening (n = 15; 53.6%), followed by hypotony maculopathy (n = 5; 17.9%) and clinical signs of hypotony other than maculopathy

Table 3. Associations between Baseline Covariates and Ocular Hypotony after Trabeculectomy (n = 194)

Covariate	OR Adjusted for Preoperative IOP Only (95% CI)	OR Adjusted for Preoperative IOP and All Covariates with $P < 0.3$ in Univariate Models (95% CI)
Age (change in odds per 1-yr increase)	0.97 (0.95–1.00)	0.98 (0.94–1.02)
Sex (female vs. male)	0.82 (0.44–1.53)	–
Ethnicity (nonwhite vs. white)	0.59 (0.30–1.17)	0.81 (0.30–2.23)
Glaucoma subtype (angle closure vs. open angle)	0.13 (0.02–1.03)	0.14 (0.01–1.93)
Glaucoma subtype (other glaucoma vs. open angle)	0.83 (0.32–2.19)	0.81 (0.13–5.27)
History of diabetes (yes vs. no)	0.60 (0.18–1.97)	–
Hypertension (yes vs. no)	0.61 (0.30–1.23)	0.50 (0.17–1.42)
Lens status (pseudophakic vs. phakic)	1.76 (0.91–3.40)	1.41 (0.43–4.66)
Refractive error (myopia vs. no myopia)	2.39 (1.08–5.30)	2.19 (0.79–6.12)
Preoperative no. of glaucoma medications (≥3 vs. 0–2)	0.84 (0.45–1.57)	–
Preoperative logMAR VA (change in odds per 1 logMAR unit increase)	0.28 (0.08–0.96)	0.17 (0.02–1.58)
No. of sutures (3 vs. 2)	1.11 (0.50–2.48)	–
No. of sutures (≥4 vs. 2)	0.94 (0.45–1.96)	–
Laser suture lysis (yes vs. no)	0.38 (0.20–0.74)	0.33 (0.13–0.87)
Surgeon (2 vs. 1)	6.64 (2.99–14.77)	5.32 (1.53–18.52)
Surgeon (3 vs. 1)	4.26 (1.70–10.67)	2.35 (0.63–8.74)
Surgeon (4 or 5 vs. 1)	0.94 (0.18–4.85)	1.11 (0.14–8.46)
Eye (left vs. right)	1.17 (0.63–2.17)	–

CI = confidence interval; IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution; OR = odds ratio; VA = visual acuity.

(n = 3; 10.7%). Of 21 cases with vision loss after trabeculectomy, the majority of patients lost vision from glaucoma that was worsening (n = 7; 33.3%), followed by hypotony maculopathy (n = 5; 23.8%). Of 28 controls with vision loss after trabeculectomy, the majority of patients lost vision from cataract (n = 12; 41.3%), followed by advanced glaucoma (n = 7; 24.1%). Of 94 patients who were phakic before trabeculectomy in the group without ocular hypotony, 19 patients (20.2%) received a combined cataract extraction and trabeculectomy, 32 patients (34.0%) received cataract surgery after trabeculectomy, and 43 patients (45.7%) remained phakic until the end of the study or loss to follow-up. Of 40 patients who were phakic before trabeculectomy in the group with ocular hypotony, 3 patients (7.5%) received a combined cataract extraction and trabeculectomy, 16 patients (40.0%) received cataract surgery after trabeculectomy, and 21 patients (52.5%) remained phakic until the end of the study or loss to follow-up. Of note, 11 of 130 controls (8.5%) had signs of maculopathy on examination or optical coherence tomography without meeting the study criteria for ocular hypotony, although only 5 of these patients experienced

Table 4. Incidence of Surgical Failure in Patients Undergoing Trabeculectomy with and without Postoperative Ocular Hypotony* (n = 194)

	Patients with Postoperative Ocular Hypotony (n = 64)	Patients without Postoperative Ocular Hypotony (n = 130)	P Value, Log-Rank Test
Failure definition 1: need for bleb revision or additional glaucoma surgery	14 revisions/457.5 person-yrs (3.1 revisions/100 person-yrs)	28 revisions/830.1 person-yrs (3.3 revisions/100 person-yrs)	0.66
Failure definition 2: loss of ≥2 lines of Snellen VA from baseline	21 vision losses/335.2 person-yrs (6.3 vision losses/100 person-yrs)	29 vision losses/692.6 person-yrs (4.2 vision losses/100 person-yrs)	0.20
Failure definition 3: need for reoperation, vision loss, or bleb-related infection†	28 failures/320.7 person-yrs (8.7 failures/100 person-yrs)	52 failures/681.7 person-yrs (7.6 failures/100 person-yrs)	0.75
	Patients with Hypotony Maculopathy‡ (n = 15)	**Patients without Hypotony Maculopathy (n = 49)**	**P Value, Log-Rank Test**
Failure definition 1: need for bleb revision or additional glaucoma surgery	7 revisions/91.54 person-yrs (7.6 revisions/100 person-yrs)	7 revisions/365.92 person-yrs (1.9 revisions/100 person-yrs)	0.008
Failure definition 2: loss of ≥2 lines of Snellen VA from baseline	6 vision losses/78.60 person-yrs (7.6 vision losses/100 person-yrs)	15 vision losses/256.60 person-yrs (5.8 vision losses/100 person-yrs)	0.45
Failure definition 3: need for reoperation, vision loss, or bleb-related infection†	8 failures/78.32 person-yrs (10.2 failures/100 person-yrs)	20 failures/242.40 person-yrs (8.3 failures/100 person-yrs)	0.55

VA = visual acuity.
*Defined as IOP ≤5 mmHg on ≥3 consecutive visits 3 months or later after surgery.
†Includes 1 bleb-related infection in cases and 1 bleb-related infection in controls ($P = 0.82$, log-rank test).
‡Defined as ocular hypotony and the presence of macular folds or macular edema on examination or optical coherence tomography.

Table 5. Outcomes after Trabeculectomy in Patients with versus without Postoperative Ocular Hypotony (n = 105)*

	Hazards Ratio (95% Confidence Interval) of Outcome†		
Outcome	*Unadjusted*	*Adjusted for All Covariates*‡	*Adjusted for All Covariates Except Refractive Error and Central Corneal Thickness*§
Bleb revision	0.87 (0.45, 1.65)	0.10 (0.01, 1.16)	0.73 (0.32, 1.68)
Vision loss‖	1.44 (0.82, 2.54)	0.06 (0.00, 1.75)	1.77 (0.81, 3.88)
Surgical failure in patients with versus without hypotony¶	1.11 (0.70, 1.76)	0.38 (0.10, 1.53)	1.14 (0.62, 2.11)
Surgical failure in patients with hypotony with versus without hypotony maculopathy**	1.29 (0.56, 2.95)	6.80 (0.52, 88.35)	0.84 (0.21, 3.33)

*Defined as intraocular pressure ≤5 mmHg on ≥3 consecutive visits ≥3 months after surgery.
†Patients without postoperative ocular hypotony were used as a reference.
‡Adjusted for age, sex, ethnicity, glaucoma subtype, diabetes, hypertension, lens status, family history of glaucoma, refractive error, preoperative number of glaucoma medications, preoperative intraocular pressure, preoperative visual acuity, number of sutures in the scleral flap, laser suture lysis.
§Alternate model excluding refractive error and central corneal thickness was created because of the high number of missing values for these variables.
‖Defined as loss of ≥2 lines of Snellen visual acuity ≥3 months after trabeculectomy.
¶Defined as bleb revision, vision loss, or bleb-related infection ≥3 months after trabeculectomy.
**Hypotony maculopathy defined as the presence ocular hypotony and macular folds and/or macular edema on exam and/or optical coherence tomography imaging.

maculopathy that was severe enough to warrant reoperation as noted earlier. Of these 11 patients, the mean age at time of trabeculectomy was 61.2±17.3 years, 5 (45.5%) were female, 4 (36.4%) were pseudophakic, 1 (9.1%) had laser suture lysis, and 1 (9.1%) had high myopia. The mean preoperative IOP in this group was 18.8±80 mmHg, mean postoperative IOP within the first 30 days after surgery was 7.2±4.5 mmHg, and mean IOP at the time of maculopathy was 4.8±2.7 mmHg.

Discussion

In this study, we found that significant risk factors for ocular hypotony after trabeculectomy at Stein Eye Institute included the absence of laser suture lysis and surgeon. Patients with versus without ocular hypotony after trabeculectomy had similar rates of reoperation, vision loss, and overall surgical failure over long-term follow-up, although the majority of vision loss in patients with ocular hypotony was attributed to hypotony maculopathy, whereas the majority of vision loss in patients without ocular hypotony was attributed to advanced glaucoma.

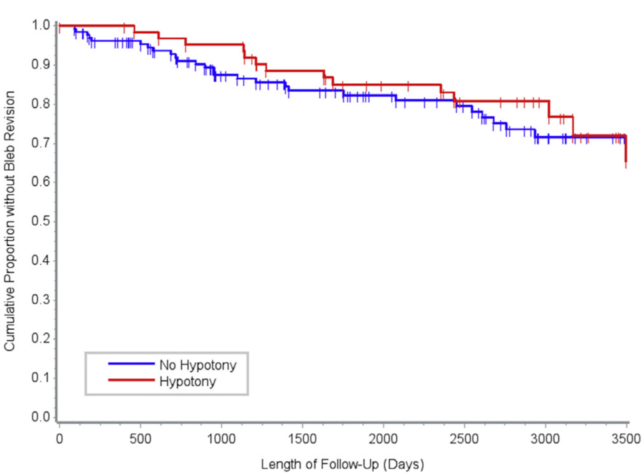

Figure 1. Kaplan–Meier plot of bleb revision in patients with versus without hypotony after trabeculectomy.

Laser suture lysis was associated with lower risk of ocular hypotony after trabeculectomy in this study. Conversely, in a previous study by Schultz et al,[13] of 30 patients with normal-tension glaucoma (NTG), patients who received laser suture lysis had a higher risk of IOP ≤5 mmHg on 2 consecutive postoperative visits compared with patients who did not receive laser suture lysis. One potential explanation for these differences is that the study by Schultz et al examined patients with NTG, whereas the present study included all glaucoma subtypes. Given that patients with NTG start with lower preoperative IOPs and have lower postoperative target pressures compared with patients with other types of glaucoma, it is expected that low IOP would result more often after laser suture lysis in patients with NTG compared with patients with other types of glaucoma. Conversely, this study included patients with all types of glaucoma, and it is likely that some patients who required laser suture lysis were those who were more prone to early failure with an increasing IOP, which could explain the observed association between laser suture lysis and a lower risk of ocular hypotony.

In this study, we also found an association between surgeon and ocular hypotony after trabeculectomy. Surgeon was found to be significantly associated with low IOP after trabeculectomy in a previous study by Saeedi et al,[14] which compared patients with IOP ≤5 mmHg 3 months or later after trabeculectomy with controls without low IOP after trabeculectomy. Saeedi et al[14] hypothesized that the association between surgeon and postoperative IOP in their study was due to differing target IOPs set by their 2 surgeons. Although specific target IOPs were not formally recorded for all of the patients in our study, all of our surgeons use similar doses and duration of mitomycin-C, and 4 of 5 surgeons use fornix-based flaps. Comparison of preoperative IOP and laser suture lysis rates between surgeon 2 and surgeon 1 in our study demonstrated lower preoperative IOP and less laser suture lysis in patients of

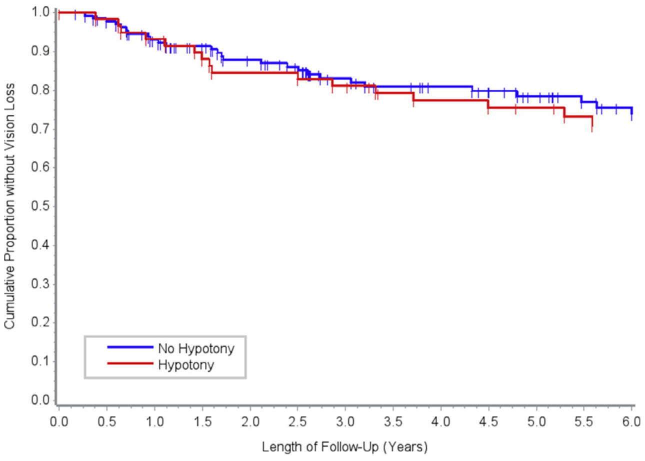

Figure 2. Kaplan–Meier plot of vision loss in patients with versus without hypotony after trabeculectomy.

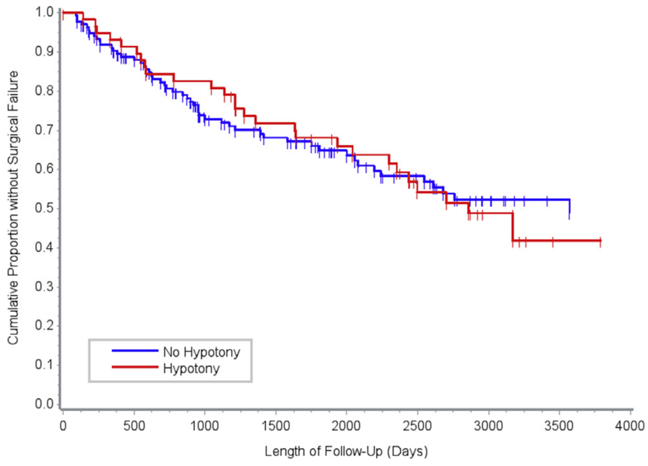

Figure 3. Kaplan–Meier plot of surgical failure in patients with versus without hypotony after trabeculectomy.

surgeon 2, suggesting that the differences in ocular hypotony rates between surgeon 2 and surgeon 1 are explained by lower target IOP for patients of surgeon 2.

Two previous studies have compared outcomes in patients with versus without chronic hypotony after trabeculectomy. The first study, which was reported by Schultz et al,[13] identified 9 cases of postoperative ocular hypotony over 50.8 months of follow-up in a population of 30 patients with NTG. The study reported that there was no difference in postoperative best-corrected VA in patients with versus without ocular hypotony, and that there was no change in vision from baseline in patients who had ocular hypotony. The second study, by Yun et al,[16] compared 34 eyes with chronic hypotony after trabeculectomy with 34 eyes without chronic hypotony and defined ocular hypotony as IOP <5 mmHg on at least 2 consecutive visits 3 months or later after surgery. Yun et al[16] reported that there were no statistically significant differences in logMAR VA or change in visual field mean deviation in patients with versus without ocular hypotony after trabeculectomy. Similar to these studies, we found in this study that there were no statistically significant differences in vision loss in patients with versus without ocular hypotony after trabeculectomy, although both the unadjusted and adjusted incidences of vision loss in patients with ocular hypotony after trabeculectomy were slightly higher than the incidences in patients without ocular hypotony. When we examined the reasons for vision loss, the most common reason for vision loss in patients with ocular hypotony was advanced glaucoma, possibly because this represented a group of patients with high risk of central vision loss from advanced glaucoma and thus with lower preoperative target pressures. Of note, the most common reason for vision loss in controls was cataract, and of the phakic patients in the 2 groups, the group with hypotony did not have a higher proportion of patients who required subsequent cataract extraction. Although these findings suggest that low postoperative IOP after trabeculectomy may not increase the risk of cataract, it is also possible that the study was not adequately powered to detect a significant difference in the incidence of cataract progression between the 2 groups.

In addition to examining VA outcomes, the present study expands on previous findings by examining the long-term risk of reoperation and overall surgical failure in patients with ocular hypotony after trabeculectomy and found no differences in the rates of reoperation and surgical failure in patients with versus without hypotony. Furthermore, the majority of cases with reoperation received additional surgery for hypotony maculopathy, whereas the majority of controls with reoperation received additional surgery because their glaucoma was worsening. Although these findings are insufficient to compare glaucoma progression outcomes in cases versus controls, they do suggest that additional surgery in patients with ocular hypotony may be reserved mainly for situations in which patients have developed hypotony maculopathy. An additional analysis in this study compared outcomes in patients with versus without hypotony maculopathy and found that there were no differences in overall long-term risk of surgical failure, although patients with maculopathy had a higher unadjusted incidence of bleb revisions. This suggests that even when clinical signs of low IOP are initially apparent, patients may still have favorable long-term outcomes after trabeculectomy, although they may require additional surgery. An interesting finding was that a small proportion of controls who did not have persistently low IOP still had clinical signs of maculopathy on examination and ancillary testing, suggesting that there may be further risk factors for maculopathy after trabeculectomy that are not related to low IOP alone. Potential explanations include IOP fluctuation or decreased scleral rigidity, although these factors were not examined in the present study and merit further examination in future studies. A functional definition of hypotony based on clinical signs of hypotony that threaten vision, and not an arbitrary IOP measurement alone, may benefit a further examination of risk factors and outcomes in patients with low IOP after glaucoma surgery.

Table 6. Reasons for Reoperation and Vision Loss in Patients Undergoing Trabeculectomy with and without Postoperative Ocular Hypotony* (n = 194)

Reason for Reoperation	No. (%) of Patients with Postoperative Ocular Hypotony with Subsequent Reoperation (n = 14)	No. (%) of Patients without Postoperative Ocular Hypotony with Subsequent Reoperation (n = 28)
Bleb dysesthesia	2 (14)	1 (4)
Bleb thinning	0 (0)	2 (7)
Clinical signs of hypotony without maculopathy	2 (14)	3 (11)
Corneal extension of bleb	0 (0)	1 (4)
Hypotony maculopathy	8 (57)	5 (18)
Worsening glaucoma	1 (7)	15 (54)
Other/unknown	1 (7)	1 (4)
Reason for Vision Loss	**No. (%) of Patients with Postoperative Ocular Hypotony with Subsequent Vision Loss (n = 21)**	**No. (%) of Patients without Postoperative Ocular Hypotony with Subsequent Vision Loss (n = 29)**
Advanced glaucoma	7 (33)	7 (24)
Age-related macular degeneration	0 (0)	1 (3)
Cataract	4 (19)	12 (41)
Central retinal vein occlusion	0 (0)	1 (3)
Corneal edema/decompensation	1 (5)	2 (7)
Fuchs' endothelial dystrophy	0 (0)	1 (3)
Hypotony maculopathy	5 (24)	0 (0)
Hypotony without signs of maculopathy or other explanations for vision loss	4 (19)	1 (3)
Posterior capsular opacification	0 (0)	1 (3)
Other/unknown	0 (0)	3 (10)

*Intraocular pressure ≤5 mmHg on ≥3 consecutive visits 3 months or later after surgery.

Study Limitations

The limitations of this study are mainly related to its retrospective nature. All data used in this study were abstracted from medical records, and it is possible that there were errors in documentation during the clinical visit, errors in abstraction, or relevant information missing from the medical record. Also, this study was underpowered to prove no association between ocular hypotony after trabeculectomy and poor long-term surgical outcomes. By assuming that point estimates in the present study are accurate, sample sizes of 4000 cases and 8000 controls for the reoperation outcome, 1000 cases and 2000 controls for the vision loss outcome, and 9000 cases and 18 000 controls for the reoperation outcome would be required to support their respective ORs with 80% power. At our academic institution with 5 busy glaucoma specialists, only 64 patients underwent trabeculectomy and met our case definition of ocular hypotony over a 23-year period. Therefore, to maintain the level of detailed data collection available from a chart review, it would not be feasible to achieve the adequately powered sample sizes. However, despite these sample size limitations, the data from the present study do show that some patients do, not uncommonly, tolerate low IOPs well after trabeculectomy, and we believe that this point alone is worth making regardless of the outcomes in the comparison group. Furthermore, to our knowledge, although underpowered, this is the largest study to date comparing surgical outcomes in patients with versus without hypotony after trabeculectomy. A future study using a large database such as the American Academy of Ophthalmology Intelligent Research in Sight Registry would provide additional useful information in a large cohort of patients with low IOP after trabeculectomy. A limitation in the risk factor analysis is the increased alpha error associated with stepwise regression with the potential for false-positives. However, in the analysis of risk factors for this study, we focused on the magnitude and direction of risk factor effects (point estimates and 95% CIs) and their biologic plausibility, rather than relying solely on statistical significance based on a fixed alpha error level. Therefore, even though some statistically significant effects might be subject to false-positive findings due to multiple comparisons, such associations might still be important and worth further investigation. A limitation of all case-control studies is the selection of controls, because controls are meant to represent the source population from which the cases arose, but it is impossible to verify the true source population, and control selection may thus bias study results. We attempted to minimize bias in the control selection process by selecting controls from all glaucoma surgeons at our institute using random selection. Finally, there may have been differences in surgical technique that could not be captured through the medical record, but we attempted to address this by controlling for surgeon in our multivariable analyses.

In summary, we found that laser suture lysis and surgeon were factors associated with ocular hypotony after trabeculectomy, and that patients with ocular hypotony had similar rates of reoperation, vision loss, and surgical failure as those patients without ocular hypotony. Although low IOP has been used as an independent criterion for failure in trials[9−11] and in guidelines for trials,[17] the combination of findings in this study suggest that low IOP alone is not a predictor of poor long-term clinical outcomes after trabeculectomy.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
CCT = central corneal thickness; **CI** = confidence interval; **HR** = hazard ratio; **IOP** = intraocular pressure; **logMAR** = logarithm of the minimum angle of resolution; **NTG** = normal-tension glaucoma; **OR** = odds ratio; **UCLA** = University of California, Los Angeles; **VA** = visual acuity.

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