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CLINICAL INVESTIGATION

Persistent hypotony after trabeculectomy: incidence and associated factors in the Collaborative Bleb-Related Infection Incidence and Treatment Study

Tomomi Higashide[1] · Shinji Ohkubo[1] · Yosuke Sugimoto[2] · Yoshiaki Kiuchi[2] · Kazuhisa Sugiyama[1]

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Abstract

Purpose To investigate the incidence of and factors associated with persistent hypotony after trabeculectomy with mitomycin C in the Collaborative Bleb-Related Infection Incidence and Treatment Study (CBIITS), a 5-year prospective multicenter study.

Methods A total of 955 eyes of 955 patients who underwent trabeculectomy with mitomycin C were studied. Surgical failure was defined as insufficient intraocular pressure (IOP) reduction (IOP $>$ 21 mmHg or $<$20 % IOP reduction, or further glaucoma surgeries), loss of light perception, or persistent hypotony (IOP $\leq$ 5 mmHg persisting for $>$6 months). Factors associated with persistent hypotony in eyes with sufficient IOP reduction were determined by survival analysis and logistic regression analysis.

Results The cumulative probabilities of surgical success and persistent hypotony at 5 years were 62.0 $\pm$ 1.7 % ($\pm$standard error) and 7.7 $\pm$ 0.9 %, respectively. In 685 eyes with sufficient IOP reduction, preoperative IOP (mmHg), limbus-based conjunctival flap, or choroidal detachment that occurred within 6 months of the surgery were significant risk factors for persistent hypotony [Cox proportional hazards regression model: hazard ratio, 0.95, 2.27, 3.24; 95 % confidence interval (CI), 0.91–0.98, 1.21–4.23, 1.51–6.95; $P = 0.005$, 0.01, 0.003, respectively]. Bleb infection and final visual acuity (logarithm of the minimal angle of resolution) were significantly associated with persistent hypotony (logistic regression: odds ratio, 8.74, 1.37; 95 % CI, 1.89–40.4, 1.03–1.82; $P = 0.006$, 0.029, respectively).

Conclusions In the CBIITS, eyes with successful IOP reduction, a limbus-based conjunctival flap, lower preoperative IOP, and choroidal detachment that occurred within 6 months of the surgery were identified as risk factors for persistent hypotony.

Keywords Trabeculectomy · Persistent hypotony · Risk factor · Prospective study · Mitomycin C

Introduction

Although adjunctive use of antifibrotic agents improves the success rate of trabeculectomy, secured filtration may increase the risk of postoperative adverse events, including hypotony. Several retrospective studies have reported a higher incidence of persistent hypotony in association with the adjunctive use of mitomycin C (MMC) [1, 2]. Persistent hypotony is regarded as an important cause of visual loss after trabeculectomy through hypotony maculopathy and other ocular pathologies [3–5]. In addition, persistent hypotony has become one of the principal failure criteria of filtration surgery in recent studies [4–7], as recommended by the guidelines of the World Glaucoma Association [8]. An increase in persistent hypotony may decrease the overall surgical success rate.

Identification of risk factors for persistent hypotony may facilitate the implementation of appropriate measures to prevent visual loss. However, the risk factors have not been

✉ Tomomi Higashide
eyetomo@med.kanazawa-u.ac.jp

1 Department of Ophthalmology and Visual Science, Kanazawa University Graduate School of Medical Science, 13-1 Takara-machi, Kanazawa 920-8641, Japan

2 Department of Ophthalmology and Visual Science, Hiroshima University Graduate School of Biomedical Sciences, Hiroshima, Japan

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evaluated in multicenter prospective studies, although single-site retrospective studies reported that a limbus-based conjunctival flap [9, 10] and a low early postoperative intraocular pressure (IOP) level [3] were associated with hypotony. The Collaborative Bleb-Related Infection Incidence and Treatment Study (CBIITS), a 5-year prospective multicenter study with over a thousand participants, was conducted in Japan to investigate the incidence and treatment outcomes of bleb-related infection after trabeculectomy with MMC [11, 12]. Although surgical success rates and risk factors for surgical failure in CBIITS have been reported, the influence of persistent hypotony on surgical outcome was unknown [13, 14]. Therefore, in the study reported in the present paper, we investigated the incidence of and factors associated with persistent hypotony after trabeculectomy with MMC in the CBIITS.

Materials and methods

The multicenter prospective study, CBIITS, was performed in accordance with the tenets of the Declaration of Helsinki, and was approved by the institutional review board of each clinical center. Written informed consent was obtained from all patients.

Study participants

As described in detail previously [11, 12], the enrollment period for the CBIITS, which ended on March 31, 2007, was 2 years, and the follow-up period ranged from 1 to 5 years, with assessments performed at 6-month intervals, at which time postoperative complications and interventions were reported. The criteria and procedures for diagnosing complications were at the discretion of each investigator. A total of 1249 eyes of 1249 patients who underwent any type of filtering surgery with or without cataract surgery or other intraocular surgeries were enrolled. Thirty-four institutions participated, and consecutive eligible participants were recruited at each site. The first operated eye was included when both eyes were eligible. The surgical technique and postoperative management were at the discretion of the local investigators. Among all the CBIITS participants, 1098 eyes of 1098 patients treated with MMC-augmented trabeculectomy with or without cataract surgery were included in this study.

Examinations and outcome definitions

The IOP was measured by Goldmann applanation tonometry. The average of the three preoperative IOP measurements closest to the time of surgery and the IOP measurements closest to the follow-up assessments was adopted. Best-corrected visual acuity (BCVA) was measured at baseline and each follow-up visit. Persistent hypotony was defined as a sustained low IOP of $\leq$5 mmHg lasting longer than 6 months. Surgical failure was defined as insufficient IOP reduction (IOP $>$ 21 mmHg or $<$20 % IOP reduction from baseline at two consecutive follow-up visits or further glaucoma surgeries), loss of light perception, or persistent hypotony. Regarding the IOP-related criteria, the time of failure was counted as the second consecutive follow-up visit at which the criteria were met. Laser suture lysis and bleb needling were not regarded as further glaucoma surgeries. Patients with incomplete IOP data, which rendered the judgment of the IOP-related failure inconclusive, were excluded. Patients with no light perception at baseline, a lack of baseline or follow-up visual acuity data, or an unknown glaucoma type were also excluded.

Statistical analyses

For the continuous variables, the Kolmogorov–Smirnov test was used to examine distribution normality. For variables with a nonnormal distribution (i.e., nonparametric variables), the median and range were reported instead of the standard deviation, which was reported for variables with a normal distribution. For comparisons between eyes with and without persistent hypotony, an independent sample *t*-test and a Mann–Whitney test was used for the parametric and nonparametric variables, respectively. For categorical variables, the Fisher exact test or chi-square test was employed. For the comparisons between two groups adjusting for confounding factors, logistic regression analysis was used. BCVA was converted into the logarithm of the minimal angle of resolution (logMAR) format (counting fingers, 2.3; hand movements, 2.6; light perception, 3.0; no light perception, 3.6). A marked decrease in BCVA was defined as a >0.3 unit increase in the logMAR value [15]. The cumulative probabilities of surgical success and the incidence of persistent hypotony were analyzed using the Kaplan–Meier method.

To identify the factors associated with persistent hypotony, subsequent analyses focused on cases with sufficient IOP reduction after trabeculectomy (IOP $\leq$ 21 mmHg and $\geq$20 % IOP reduction from baseline), given that hypotony usually occurs because of excess filtration. Various factors at baseline (baseline factors) or during surgery (intraoperative factors) and surgical complications and additional interventions that took place before the development of persistent hypotony (postoperative factors) were examined using Kaplan–Meier survival curves as well as the log-rank test (univariate analysis) and the Cox proportional hazards

Table 1 Baseline patient characteristics

Number of patients/eyes	955/955
Age (years), mean, median (range)	63.3, 65 (13–91)
Sex (F/M)	390/565
Types of glaucoma	
POAG/NTG	477 (49.9 %)
Primary angle-closure glaucoma	59 (6.2 %)
Exfoliative glaucoma	108 (11.3 %)
Neovascular glaucoma	72 (7.5 %)
Uveitic glaucoma	102 (10.7 %)
Others	137 (14.4 %)
Preoperative IOP (mmHg), mean, median (range)	24.9, 23 (8–70)
Number of preoperative IOP-lowering medications, mean, median (range)[a]	2.8, 3 (0–5)
Preoperative systemic carbonic anhydrase inhibitors[a]	351 (37.1 %)
Preoperative best-corrected visual acuity (logMAR), mean, median (range)	0.44, 0.15 (−0.18 to 3.0)
Previous cataract surgery	256 (26.8 %)
Previous glaucoma surgery	200 (20.9 %)
Previous pars plana vitrectomy	52 (5.4 %)
Follow-up periods after trabeculectomy (months), mean, median (range)	52.8, 60 (12–60)

POAG primary open-angle glaucoma, *NTG* normal-tension glaucoma, *logMAR* logarithm of the minimal angle of resolution

[a] 10 cases were excluded owing to a lack of medication information

regression model (univariate or multivariate analysis) to identify factors significantly associated with persistent hypotony. Factors with probability values below 0.2 in the log-rank test or univariate Cox regression analysis underwent stepwise multivariate Cox regression analysis. When two factors were strongly correlated ($\rho > 0.7$ or $\rho < -0.7$, $P < 0.05$; Spearman rank correlation), only the factor with the smaller probability value was entered into the multivariate regression analysis. Statistical analysis was performed with SPSS software (IBM SPSS Statistics 20; IBM, New York, USA). MedCalc (v15.11.4; MedCalc Software, Ostend, Belgium) was used to draw Kaplan–Meier survival curves with 95 % CIs. For all analyses, probability values below 0.05 were considered significant.

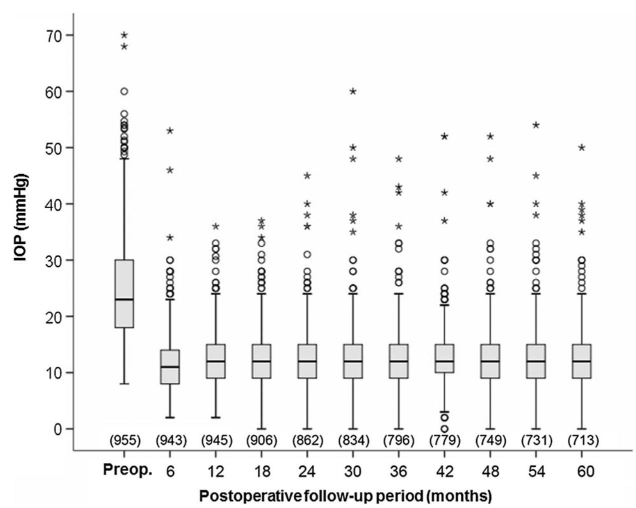

Fig. 1 Postoperative intraocular pressure course after trabeculectomy. *Box plot* of intraocular pressure at each time point is shown. *Box* interquartile range, *whiskers* nonoutlier minimum and maximum, *circles* outliers defined as >1.5 times the interquartile range above the 75th percentile or below the 25th percentile, *asterisk* extreme value defined as >3 times the interquartile range above the 75th percentile. The number of eyes measured at each time point is shown in *parentheses*. *IOP* intraocular pressure

Results

The baseline patient characteristics are shown in Table 1. A total of 955 of 1098 CBIITS cases were included; 138 cases were excluded because of incomplete IOP data. Two and three cases were excluded because of no light perception at baseline and incomplete visual acuity data, respectively. Regarding the trabeculectomy procedure, a limbus-based conjunctival incision was selected in 550 eyes (57.6 %), and simultaneous cataract surgery was performed in 163 eyes (17.1 %). The 5-year follow-up was completed in 75.0 % of the cases. As shown in Fig. 1, the mean postoperative IOP remained stable at about 12 mmHg.

A Venn diagram of the surgical failure by each criterion is shown in Fig. 2. Overall surgical success was achieved in 622 of 955 eyes (65.1 %). A total of 270 eyes (28.3 %)

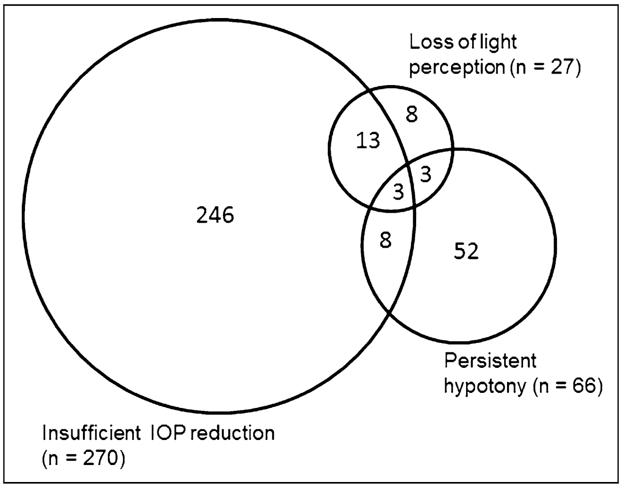

Fig. 2 Venn diagram of surgical failure by each criterion. All surfaces presented in this diagram are proportional to the number of eyes in each area. The *rectangle* indicates the total number of eyes. Definition of insufficient IOP reduction was IOP > 21 mmHg, <20 % IOP reduction, or further glaucoma surgeries. *IOP* intraocular pressure

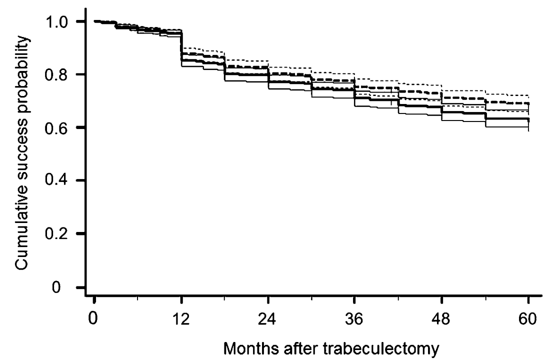

Fig. 3 Kaplan–Meier survival analysis of surgical success. Cumulative probabilities of overall surgical success (*solid line*) and surgical success regardless of persistent hypotony (*dotted line*) are shown. The *gap between two curves* implies the occurrence of surgical failure owing to persistent hypotony. The *thinner lines* indicate the 95 % CIs

failed owing to insufficient IOP reduction. Of these, 96 eyes (35.6 %) underwent further glaucoma surgeries, 28 eyes (10.4 %) failed owing to IOP > 21 mmHg, and 146 eyes (54.1 %) failed owing to <20 % reduction from baseline. Twenty-seven eyes (2.8 %) lost light perception postoperatively. Among them, 8 eyes failed solely on the basis of the visual acuity criteria. Sixty-six eyes (6.9 %) developed persistent hypotony. Of these, 52 eyes failed solely on the basis of the hypotony criteria.

The Kaplan–Meier survival curves of surgical success are shown in Fig. 3. Overall surgical success was 62.0 ± 1.7 % (±standard error) at 5 years, and surgical success regardless of persistent hypotony was 68.0 ± 1.6 % at 5 years. The Kaplan–Meier survival curves of persistent hypotony are shown in Fig. 4. The cumulative incidence of persistent hypotony at 5 years, expressed as the proportion to the total number of eyes, was 7.7 ± 0.9 % in all eyes, 6.4 ± 0.8 % in eyes with sufficient IOP reduction, 0.6 ± 0.3 % in eyes with IOP reduction <20 %, and 0.7 ± 0.3 % in eyes with further glaucoma surgeries. Among the 66 eyes with persistent hypotony, 55 eyes had sufficient IOP reduction. In contrast, 11 eyes exhibited persistent hypotony despite insufficient IOP reduction. Of these, none required treatment for hypotony. Six eyes developed persistent hypotony only after further glaucoma surgeries: surgical bleb revision in four eyes, trabeculectomy at a different site in one eye, and cyclophotocoagulation in two eyes. One eye underwent two procedures. The remaining five eyes had low preoperative IOP (8–16 mmHg) and met the IOP criteria of <20 % reduction from baseline during the follow-up period.

In 685 eyes with sufficient IOP reduction (i.e., IOP ≤ 21 mmHg and ≥20 % IOP reduction from baseline), the respective incidences of persistent hypotony were 2.9 ± 0.6, 6.1 ± 0.9, and 9.1 ± 1.2 % at 1, 3, and 5 years postoperatively. Persistent hypotony developed after a median period of 24 months (range 12–60) in 55 eyes. Of these, 3 eyes (5.5 %) developed sustained hypotony maculopathy. Treatments for hypotony were performed in 6 eyes (10.9 %): scleral flap sutures in 2 eyes, compression suture in 1 eye, conjunctival autograft for bleb leak in 1 eye, intrableb injection of autologous blood in 1 eye, and a choroidal tap for choroidal detachment in 1 eye. In contrast, 19 eyes (35 %) showed a subsequent IOP elevation (≥6 mmHg) without any treatments or cataract surgery. The follow-up period was significantly longer in eyes with an elevation of IOP after choroidal detachment without any intervention or cataract surgery than in eyes without an IOP elevation ($P = 0.02$, Mann–Whitney test). No other factors were significantly different between eyes with and without an IOP elevation. Marked visual acuity loss occurred in 17 eyes (30.9 %). A limbus-based conjunctival flap was more frequent in eyes with marked vision loss than in eyes without (94.1 vs. 68.4 %, $P = 0.035$, Fisher exact test). No other factors were significantly different between eyes with and without marked vision loss.

Comparisons of factors between eyes with ($n = 55$) and without ($n = 630$) persistent hypotony are shown in Table 2. Preoperative IOP was significantly higher in nonhypotonic eyes than in hypotonic eyes ($P = 0.006$). Limbus-based conjunctival incision was significantly more frequent in hypotonic eyes than in nonhypotonic eyes ($P = 0.003$). The percentage of eyes with choroidal

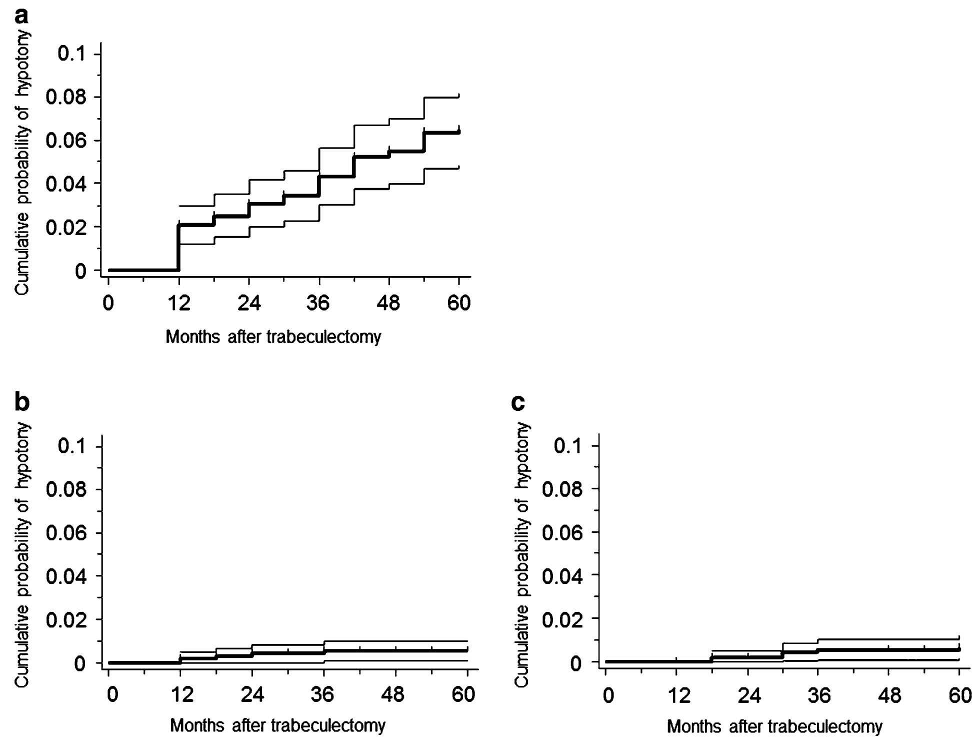

Fig. 4 Kaplan–Meier survival analysis of persistent hypotony. Cumulative probability of persistent hypotony in eyes with sufficient IOP reduction (**a**); eyes that failed on the basis of the criteria of <20 % IOP reduction (**b**) or of further glaucoma surgeries (**c**). The probability is expressed as the proportion to the total number of eyes ($n = 955$). The *thinner lines* indicate the 95 % CIs. No eyes that failed owing to IOP > 21 mmHg developed persistent hypotony

detachment that occurred within 6 months of surgery was larger in the hypotony group than in the nonhypotony group ($P = 0.02$). The follow-up period after trabeculectomy was significantly longer in the hypotonic eyes than in the nonhypotonic eyes ($P = 0.02$).

Results of Kaplan–Meier survival analysis and Cox regression analysis of factors associated with persistent hypotony are shown in Table 3. Multivariate Cox regression analysis showed that preoperative IOP (mmHg), a limbus-based conjunctival flap, and choroidal detachment that occurred within 6 months of the surgery were significant risk factors for persistent hypotony. Every 1-mmHg increase in preoperative IOP reduced the risk of developing persistent hypotony by 5 %.

Bleb infection was noted in 3 eyes with hypotony 46–49 months postoperatively. Of note, persistent hypotony preceded the late-onset bleb infection in all 3 eyes. Two of the 3 infected eyes had anterior chamber involvement, and one had vitreous involvement. The association of bleb infection and visual outcome with persistent hypotony was examined by comparing two groups: eyes with and without hypotony. Because the follow-up period was significantly longer in the eyes with hypotony than in the eyes without (Table 2), and because it was supposedly a confounding variable for both factors, logistic regression analysis was performed with the follow-up period as an additional explanatory variable to adjust for its effect. Bleb infection and final visual acuity (logMAR) were significantly associated with persistent hypotony [logistic regression analysis: odds ratio (OR), 8.74, 1.37; 95 % CI, 1.89–40.4, 1.03–1.82; $P = 0.006$, 0.029, respectively].

Discussion

Persistent hypotony is a representative late complication of trabeculectomy. Theoretically, excess filtration or reduced aqueous humor production, due to inflammation or a compromised ciliary body, underlies the condition. There are two major concerns about the effect of sustained hypotony on the outcome of trabeculectomy: adverse effects on postoperative vision and the influence on surgical success. Although many eyes may tolerate low IOP, persistent hypotony is regarded as an important cause of visual loss after trabeculectomy [3–5]. Hypotony may cause visual impairment through various pathologies, including hypotony maculopathy, accelerated cataract formation, corneal edema, and irregular astigmatism [16, 17]. The incidence of maculopathy in hypotonic eyes varied considerably among previous studies, i.e., 3–38 % [3–5, 18, 19], partly owing to the variability of the definition or the detection modalities used. Optical coherence tomography facilitated the detection of macular chorioretinal folds, even in eyes with subclinical hypotony maculopathy [16]. In our study, hypotony maculopathy was relatively infrequent (5.5 %) in eyes with persistent hypotony.

Table 2 Comparisons of factors between eyes with and without persistent hypotony in cases with sufficient IOP reduction

Factors	No hypotony (630 eyes, 92.0 %)	Hypotony (55 eyes, 8.0 %)	*P* value
Baseline factors			
Age (years), mean, median (range)	63.3, 65.5 (16–88)	61.4, 62 (31–87)	0.11[d]
Sex (male)	379 (60.2 %)	35 (63.6 %)	0.61[e]
Types of glaucoma			
POAG/NTG	301 (47.8 %)	29 (52.7 %)	0.48[e]
Primary angle-closure glaucoma	41 (6.5 %)	1 (1.8 %)	0.13[f]
Exfoliative glaucoma	72 (11.4 %)	7 (12.7 %)	0.77[e]
Neovascular glaucoma	58 (9.2 %)	2 (3.6 %)	0.12[f]
Uveitic glaucoma	73 (11.6 %)	8 (14.5 %)	0.52[e]
Preoperative IOP (mmHg), mean, median (range)	26.7, 24.7 (11.0–70.0)	23.0, 24.0 (11.0–50.0)	0.006[d]
Number of preoperative IOP-lowering medications, mean, median (range)[a]	2.8, 3 (1–5)	2.8, 3 (0–5)	0.73[d]
Preoperative systemic carbonic anhydrase inhibitors[a]	260 (41.6 %)	21 (38.2 %)	0.62[e]
Preoperative BCVA (logMAR), mean, median (range)	0.44, 0.15 (−0.18 to 3.0)	0.52, 0.15 (−0.08 to 3.0)	0.52[d]
Previous cataract surgery	176 (27.9 %)	15 (27.3 %)	0.92[e]
Previous glaucoma surgery	131 (20.8 %)	11 (20.0 %)	0.89[e]
Previous pars plana vitrectomy	32 (5.1 %)	4 (7.3 %)	0.33[e]
Intraoperative factors			
Conjunctival incision (limbus-based)	352 (55.9 %)	42 (76.4 %)	0.003[e]
Concentration of mitomycin C (>0.2 mg/mL)[b]	427 (95.3 %)	24 (88.9 %)	0.15[f]
Duration of mitomycin C application (>2 min)[c]	209 (82.6 %)	13 (76.5 %)	0.36[f]
Simultaneous cataract surgery	104 (16.5 %)	4 (7.3 %)	0.07[e]
Postoperative factors			
Postoperative choroidal detachment (onset, within 6 months of surgery)	37 (5.9 %)	8 (14.5 %)	0.02[f]
Postoperative bleb leak (occurred before persistent hypotony)	50 (7.9 %)	4 (7.3 %)	0.56[f]
Postoperative cataract surgery (performed before persistent hypotony)	49 (7.8 %)	2 (3.6 %)	0.20[e]
Postoperative bleb infection	11 (1.7 %)	3 (5.5 %)	0.10[f]
BCVA at the final follow-up visit (logMAR), mean, median (range)	0.58, 0.22 (−0.18 to 3.6)	0.81, 0.30 (−0.18 to 3.6)	0.15[d]
Change in BCVA (logMAR), final follow-up visit vs baseline, mean, median (range)	0.14, 0.05 (−2.50 to 3.60)	0.28, 0.08 (−0.70 to 2.38)	0.20[d]
Marked decrease in BCVA (>0.3 in logMAR value)	138 (21.9 %)	17 (30.9 %)	0.13[e]
Postoperative follow-up periods (months), mean, median (range)	51.2, 60 (12–60)	56.4, 60 (18–60)	0.02[d]

IOP intraocular pressure, *POAG* primary open-angle glaucoma, *NTG* normal-tension glaucoma, *BCVA* best-corrected visual acuity, *logMAR* logarithm of the minimal angle of resolution

[a] 5 cases were excluded owing to a lack of medication information

[b] 475 cases (69.3 %) were informative

[c] 270 cases (39.4 %) were informative

[d] Mann–Whitney test

[e] Chi-square test

[f] Fisher exact test

In terms of the determination of surgical success, persistent hypotony has been adopted as one of the principal failure criteria of filtration surgery in a number of studies. The guidelines of the World Glaucoma Association recommend setting a lower IOP limit (i.e., 6 mmHg) for IOP success [8]. Although it has been argued that patients with postoperative IOP in the hypotony range are often visually asymptomatic and represent a favorable surgical outcome [20], several studies have pointed out a significant link between hypotony and vision loss [4, 5], providing the

Table 3 Results of Kaplan–Meier survival analysis and Cox regression analysis to identify risk factors for significant hypotony

Factors	No. of eyes[a] (%)	Kaplan–Meier survival analysis	Univariate Cox			Multivariate Cox[b]		
		Log-rank test *P* value	Hazard ratio	95 % CI	*P* value	Hazard ratio	95 % CI	*P* value
Baseline factors								
Age (years)	–	NA	0.99	0.97–1.01	0.41			
Sex (male)	414 (60.4)	0.62	1.15	0.66–1.99	0.62			
Types of glaucoma								
POAG/NTG	330 (48.2)	0.53	1.19	0.70–2.01	0.53			
Primary angle-closure glaucoma	42 (6.1)	0.17	0.28	0.04–2.00	0.20			
Exfoliative glaucoma	79 (11.5)	0.68	1.18	0.54–2.61	0.68			
Neovascular glaucoma	60 (8.8)	0.18	0.40	0.10–1.63	0.20			
Uveitic glaucoma	81 (11.8)	0.58	1.23	0.58–2.61	0.58			
Preoperative IOP (mmHg), median (range)	–	NA	0.95	0.92–0.99	0.007	0.95	0.91–0.98	0.005
Number of preoperative IOP-lowering medications[c]	–	NA	0.99	0.76–1.29	0.96			
Preoperative systemic carbonic anhydrase inhibitors[c]	281 (41.0)	0.63	0.88	0.51–1.51	0.63			
Preoperative BCVA (logMAR)	–	NA	1.24	0.87–1.77	0.24			
Previous cataract surgery	191 (27.9)	0.98	0.99	0.55–1.80	0.98			
Previous glaucoma surgery	142 (20.7)	0.85	0.94	0.48–1.81	0.85			
Previous pars plana vitrectomy	36 (5.3)	0.45	1.47	0.53–4.07	0.46			
Intraoperative factors								
Conjunctival incision (limbus-based)	394 (57.5)	0.004	2.42	1.30–4.51	0.005	2.27	1.21–4.23	0.01
Concentration of mitomycin C (>0.2 mg/mL)[d]	451 (94.9)	0.17[e]	0.44	0.13–1.47	0.19[e]			
Duration of mitomycin C application (>2min)[f]	222 (82.2)	0.55	0.71	0.23–2.18	0.55			
Simultaneous cataract surgery	108 (15.8)	0.09	0.42	0.15–1.17	0.10			
Postoperative factors								
Choroidal detachment[g]	45 (6.6)	0.008	2.63	1.24–5.57	0.01	3.24	1.51–6.95	0.003
Postoperative bleb leak[h]	54 (7.9)	0.90	0.90	0.34–2.60	0.90			
Postoperative cataract surgery[i]	51 (7.4)	0.20	0.42	0.10–1.70	0.22			

CI confidence interval, *POAG* primary open-angle glaucoma, *NTG* normal-tension glaucoma, *IOP* intraocular pressure, *BCVA* best-corrected visual acuity, *logMAR* logarithm of the minimal angle of resolution, *NA* not applicable

[a] Cases with sufficient IOP reduction were analyzed ($n = 685$)

[b] Variables with *P* values <0.05 are shown

[c] 5 cases were excluded owing to a lack of medication information

[d] 475 cases (69.3 %) were informative

[e] Omitted from the multivariate analysis owing to a large number of cases with missing values

[f] 270 cases (39.4 %) were informative

[g] Onset within 6 months of surgery

[h] Occurred before persistent hypotony

[i] Performed before persistent hypotony

rationale for hypotony as a criterion of surgical failure. A significant association was also found between persistent hypotony and worse final visual acuity in our study.

Adding the hypotony criterion to surgical failure decreases the surgical success rate. Bindlish et al. reported that delayed hypotony occurred after a mean follow-up of 26 months in 42 % of 123 eyes with no previous intraocular surgeries and primary trabeculectomy with MMC [3]. The success rate decreased from 83.0 to 57.7 % at year 5 when hypotony and the loss of four or more lines of vison were included in the definition of surgical failure. The authors indicated that eyes with successful IOP reduction at one or more years postoperatively may eventually develop hypotony after a longer follow-up. In the present study, the surgical success at 5 years deteriorated by 6 % when persistent hypotony was considered a failure. The incidence of persistent hypotony may depend on several factors, including the surgical procedure, patient background, length of the study period, and definition of hypotony, which reflects the huge variability in the incidence of persistent hypotony at 5 years: from 1.5 % in the Collaborative Initial Glaucoma Treatment Study to 42 % in the study by Bindlish et al. [3, 4, 18, 21]. The impact of persistent hypotony on surgical success may be better appreciated by drawing separate Kaplan–Meier curves with or without inclusion of hypotony as a failure criterion, especially in a long-term study [6].

Given the related undesirable side effects, the risk factors for persistent hypotony provide vital information for the long-term follow-up of patients after trabeculectomy. Of note, our study was the first long-term, large-scale, prospective study to address the risk factors for persistent hypotony after trabeculectomy with MMC. Multivariate Cox regression analysis identified three independent risk factors: lower preoperative IOP (mmHg), a limbus-based conjunctival flap, and choroidal detachment that occurred within 6 months of the surgery. Regarding the preoperative IOP, every 10-mmHg decrease in preoperative IOP (e.g., 20 vs. 30 mmHg) may increase the risk of developing persistent hypotony by 60 %. The result verified the general concept that eyes with low preoperative IOP, such as normal tension glaucoma, are at greater risk of hypotony given the lower target pressure [2, 22].

As for the type of conjunctival flap, several reports indicated more hypotony in eyes with a limbus-based conjunctival flap [9, 10], and our study results were in line with that conclusion. A limbus-based conjunctival flap showed a greater risk of forming a cystic and avascular bleb [10] accompanied by a larger number of epithelial microcysts on the bleb surface [23], which are considered the channels for the passage of aqueous humor [24]. The morphological differences between blebs with limbus-based and those with fornix-based conjunctival flaps may underlie the likelihood of persistent hypotony. However, another retrospective study reported a controversial result that limbus-based flaps were associated with a lower incidence of symptomatic hypotony [25]. Of note, the subsequent report from the same study group revealed that late low IOP was more common with techniques used by one of two surgeons [19]. Therefore, the surgical procedure may also have a significant impact on the incidence of persistent hypotony.

Choroidal detachment that occurred within 6 months of the surgery was also identified as a risk factor for persistent hypotony. In this regard, Bindlish et al. found that postoperative IOP at month 1 was the single predictor for late-term hypotony [3]. Although postoperative IOP earlier than 6 months was not available in the CBIITS database, the choroidal detachment that emerged within 6 months of the surgery may indicate the presence of overfiltration or low IOP in the early postoperative period.

We also found a significant association between bleb infection and persistent hypotony. Previous studies including the CBIITS indicated that bleb infection may result in bleb scarring and subsequent IOP elevation, possibly owing to inflammation caused by the infection itself or by additional surgeries to treat the infection, or by both [26–28]. Regarding the preinfection status, bleb leakage appeared to be a representative risk factor for bleb infection in multiple studies including the CBIITS [10, 29, 30], so lower IOP was associated with subsequent bleb infection [29, 30]. Poulsen et al. reported that 11 of 20 infected eyes (55 %) had hypotony with Seidel-positive bleb leaks on presentation [31]. However, no previous study has clearly mentioned how many eyes had persistent hypotony before bleb infection. In our study, persistent hypotony was significantly associated with bleb infection. Given that hypotony preceded the late-onset bleb infection in all three eyes that exhibited both hypotony and bleb infection, persistent hypotony may be a predisposing condition for bleb infection. Before infection, an avascular area appeared in all three infected blebs, and bleb leakage was found in one of them.

Regarding the application of MMC, Kupin et al. reported that eyes with MMC exposure (0.5 mg/mL for 3 min) had a significantly higher incidence of prolonged hypotony ($IOP < 6$ mmHg) than did control eyes (15 vs. 0 % at 9 months, $P = 0.05$) in patients with phakic primary-open angle glaucoma [1]. Regarding normal-tension glaucoma, Membrey et al. reported that eyes with adjunctive MMC more often experienced late hypotony ($IOP \leq 5$ mmHg on two successive occasions at least 4 weeks apart) than did eyes with no treatment or adjunctive 5-FU (28 vs. 0 %, $P = 0.002$) [2]. In terms of the duration of MMC application, Zacharia et al. reported an overall 32.7 % incidence of hypotony ($IOP < 5$ mmHg on 2 visits ≥ 4 weeks apart and ≥6 weeks postoperatively) and a significantly longer MMC exposure time in eyes with hypotony [32]. However, the association between MMC duration and hypotony was not confirmed in later studies [3, 19]. In our study, the concentration and duration of MMC application were not associated with persistent hypotony.

This study has several limitations. First, since the primary end point was the incidence of bleb-related infection, more than 10 % of cases were excluded owing to incomplete IOP data, and a considerable proportion of the cases were not informative in terms of MMC application, which may have affected the results. Second, the surgical technique and the indication for surgery were not uniform among the centers or surgeons, which may have introduced bias regarding the surgical procedure, e.g., the type of conjunctival flap. This concern may be lessened by the large number of surgeons participating in the CBIITS. Third, there were no standard definitions or diagnosis and treatment procedures for complications. This lack may have resulted in an underestimation of complications such as hypotony maculopathy, and made it difficult to study the reasons for visual loss due to persistent hypotony, although we did find a significant association between persistent hypotony and worse final visual acuity. Despite these limitations, the prospective study design with a large number of cases and a long follow-up period enabled us to successfully identify several factors significantly associated with persistent hypotony after trabeculectomy with MMC.

In conclusion, in the CBIITS, the incidence of persistent hypotony increased over time after successful IOP reduction by trabeculectomy with MMC, and a limbus-based conjunctival flap, lower preoperative IOP, and choroidal detachment that occurred within 6 months of surgery were identified as risk factors for persistent hypotony.

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