0.05 % isoproterenol had no effect on the increase in the PGE2-induced aqueous flare ($P = 0.7823$).

Dunnett's post hoc test for multiple comparisons showed a significant difference between isoproterenol and apraclonidine ($P = 0.0056$) and between the isoproterenol group and the combination of brimonidine and phenylephrine ($P = 0.0011$).

Intraocular pressures

After the topical PGE2 application, the IOP in the control group increased, reaching a maximum of 39.0 ± 10.6 mmHg at 30 min. Thereafter, there was a decrease and return to the baseline value after 1.5 h (Fig. 4). The increase in the IOP after the application of 0.05 % isoproterenol or 5.0 % phenylephrine hydrochloride was similar to the increase in the control group (Table 3). Both groups showed a maximum IOP at 30 min after the instillation of PGE2, and the mean IOP was 42.8 ± 6.6 mmHg after 0.05 % isoproterenol and 34.6 ± 8.4 mmHg after 5.0 % phenylephrine hydrochloride.

None of adrenergic agents other than 0.1 % brimonidine tartrate was able to suppress the IOP changes caused by PGE2 application (Table 3). The comparison of all agents using one-way ANOVA with repeated measurements at each time point revealed a significant difference in the IOP at 0 h ($P = 0.0047$), 0.5 h ($P < 0.0001$), 1 h ($P < 0.0001$) and 4.5 h ($P = 0.0063$). The IOP values were significantly different between the NaCl group and the groups that received apraclonidine, brimonidine, dipivefrin, and the combination of brimonidine and phenylephrine at ½ h and 1 h after application (Table 4).

Discussion

The topical application of 2.5 μg PGE2 significantly increased the degree of ocular inflammation and IOP. In this study, we evaluated the effects of topical adrenergic

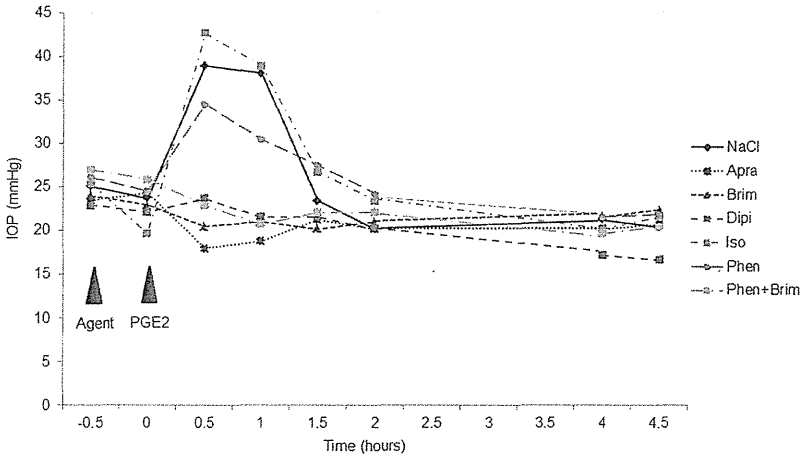

Fig. 4 Time courses of the change in the intraocular pressure. Fifty microliters of the adrenergic agents or 0.9 % NaCl (placebo) was topically instilled in the *left* eyes at time −0.5 h. Thirty minutes later, 50 μl of PGE2 (2.5 μg) was instilled into the eye

Table 3 IOP changes due to instillation of agents followed by PGE-2

Agents	Time course							*P*
	0 h	0.5 h	1 h	1.5 h	2 h	4 h	4.5 h	
NaCl	23.8 ± 2.0	39.0 ± 10.6	38.2 ± 13.2	23.5 ± 7.0	20.2 ± 4.0	21.3 ± 2.5	20.4 ± 1.9	<0.0001*
Apra	24.3 ± 3.0	18.0 ± 1.3	18.9 ± 3.9	21.3 ± 3.5	20.2 ± 3.2	20.2 ± 3.2	20.8 ± 2.5	0.0212*
Brim	22.9 ± 3.7	20.5 ± 1.9	21.0 ± 2.4	20.2 ± 5.5	21.0 ± 2.8	21.6 ± 2.3	22.4 ± 2.3	0.7487
Dipi	22.1 ± 1.2	23.8 ± 4.3	21.6 ± 4.0	21.6 ± 1.7	20.2 ± 2.5	17.2 ± 1.2	16.7 ± 1.7	0.0003*
Iso	19.7 ± 1.7	42.8 ± 6.6	39.0 ± 10.8	26.7 ± 9.3	23.5 ± 3.5	20.2 ± 2.2	21.6 ± 3.4	<0.0001*
Phen	24.6 ± 2.0	34.6 ± 8.4	30.5 ± 6.7	27.6 ± 7.6	24.3 ± 3.6	21.6 ± 3.1	21.8 ± 2.2	0.0013*
Phen + Brim	25.9 ± 3.2	22.9 ± 2.2	20.8 ± 2.9	22.2 ± 1.9	22.1 ± 3.6	19.7 ± 3.5	20.5 ± 2.4	0.0164*
P	0.0047*	<0.0001*	<0.0001*	0.2528	0.1998	0.0523	0.0063*	

The data are expressed as the mean ± SD. The number of rabbits was 6

NaCl NaCl 0.9 %; *Apra* apraclonidine 1.15 %; *Brim* brimonidine 0.1 %; *Dipi* dipivefrine 0.1 %; *Iso* isoproterenol 0.005 %; *Phen* phenirephrine 5 %; *Brim + Phen* combination of brimonidine 0.1 % and phenirephrine 5 %

* Significant difference using one-way ANOVA with repeated measurement ($P < 0.05$)

Table 4 Comparison of IOP among the agents at each time point

Time points (h)	Control agent	Agents IOP	*P* compared with each control
0	Control (NaCl)	23.8 ± 1.9	–
	Apra	24.3 ± 3.0	0.9981
	Brim	22.9 ± 3.7	0.9841
	Dipi	22.1 ± 1.2	0.7411
	Iso	19.7 ± 1.7	0.0388
	Phen	24.6 ± 2.0	0.9841
	Brim + Phen	25.9 ± 3.2	0.4809
0.5	Control (NaCl)	39.0 ± 10.6	–
	Apra	18.0 ± 1.3	<0.0001*
	Brim	20.5 ± 1.9	<0.0001*
	Dipi	23.8 ± 4.3	0.0006*
	Iso	42.8 ± 6.6	0.7621
	Phen	34.6 ± 8.4	0.6545
	Brim + Phen	22.9 ± 2.2	0.0003*
1	Control (NaCl)	38.2 ± 13.2	–
	Apra	18.9 ± 3.9	0.0004*
	Brim	21.0 ± 2.4	0.0016*
	Dipi	21.6 ± 4.0	0.0023*
	Iso	39.0 ± 10.8	1.0000
	Phen	30.5 ± 6.7	0.3088
	Brim + Phen	20.8 ± 2.9	0.0013*
4.5	Control (NaCl)	20.4 ± 1.9	–
	Apra	20.8 ± 2.5	0.9999
	Brim	22.4 ± 2.3	0.5391
	Dipi	16.7 ± 1.7	0.0492
	Iso	21.6 ± 3.4	0.9117
	Phen	21.9 ± 2.2	0.8084
	Brim + Phen	20.5 ± 2.4	1.0000

The data are expressed as the mean ± SD. The number of rabbits was 6

NaCl NaCl 0.9 %; *Apra* apraclonidine 1.15 %; *Brim* brimonidine 0.1 %; *Dipi* dipivefrine 0.1 %; *Iso* isoproterenol 0.005 %; *Phen* phenirephrine 5 %; *Brim + Phen* combination of brimonidine 0.1 % and phenirephrine 5 %

* Significant difference using Dunnett's mean comparison test ($P < 0.0071$)

agents on the increase in inflammation and IOP induced by PGE2 application. The flare in the control eyes increased and reached a peak 2 h after PGE2 application and then gradually decreased. The increase in the flare values was present for more than 4½ h. The IOP elevation after PGE2 application reached a peak at ½ h, after which it decreased to the baseline level by 1½ after the PGE2 application.

In our present study, the topical application of 2.5 μg of PGE2 caused a milder flare elevation (149.5 ± 74.1 photon counts/ms) in saline-treated eyes compared to the report by Hayasaka (470 ± 37 photon counts/ms) [14]. The coefficient of variation for the maximum flare values in our study was 22.5, while Hayasaka et al., using the glass cylinder method, report that the maximum flare value had a coefficient of variation of 7.9. A relatively high flare value variation is one problem associated with the topical application method.

We found that the inflammation caused by the application of 2.5 μg of PGE2 did not affect the results of experiments performed 1 week later (data are not shown) as reported previously [20]. Our method allowed us to reduce the number of rabbits used to a minimum. Although it took 3 months to complete the entire study, the body weights of the rabbits remained between 2.5 and 3.0 kg during the study. Thus, the effects of the body weight and aging on the results were small and seemed to be insignificant.

We found that the changes in the flare elevation caused by PGE2 were not identical for the different adrenergic agents. Hayasaka et al. report that two instillations of 0.1 %

dipivefrin eye drops strongly inhibited the PGE2-induced aqueous flare increase [14]. We found that even one drop of 0.1 % dipivefrin hydrochloride eye drops significantly inhibited the aqueous flare increase.

In contrast, in our study isoproterenol, a β receptor stimulant, had little effect on the aqueous flare levels. We assume that dipivefrin hydrochloride, an α and β stimulant, probably suppressed the aqueous flare rise through the α receptors.

Brimonidine tartrate and apraclonidine hydrochloride, both categorized as α2 receptor agonists, significantly suppressed the flare elevation caused by PGE2. Although the difference was not significant, the degree of suppression by apraclonidine hydrochloride seemed to be greater than that by brimonidine tartrate. Radio-ligand binding and bioassays previously showed that brimonidine has 23–32-fold more α2 selectivity than apraclonidine [5, 6]. The affinity of brimonidine to the α1 receptor is almost ten times lower than that of apraclonidine. Phenylephrine, an α1 agonist, showed a small suppression of the flare elevation. The combination of phenylephrine and brimonidine could suppress the degree of flare elevation in the same way as apraclonidine alone. These results suggest that the signals from α1 cooperate with the signals from α2 receptors to suppress the flare elevation induced by PGE2.

There is evidence that the autonomic nervous system can affect the immune system. Stress triggers the secretion of noradrenaline and adrenaline, and this stress-associated neurotransmitter release suppresses the secretion of inflammatory cytokines [22]. Dendritic cells play a major role in the regulation of immune responses to a variety of antigens. Dendritic cells capture the antigens, and this is necessary to stimulate the adaptive immune system. Noradrenaline alters the balance of cytokine production by dendritic cells by stimulating α2 receptors [22]. The stimulation of α2 receptors might decrease the level of inflammatory cytokines and protect the blood-aqueous barrier from breaking down. The mechanism(s) that protect the blood-ocular barriers from breakdown by the α2 agonists' signal remain to be investigated.

The results of the laser speckle method have shown that phenylephrine reduces the blood flow on the optic disc of normal volunteers [23]. Hayasaka et al. [14] suggest that vasoconstriction may be partly involved in the inhibition of the PGE2-induced aqueous flare elevation by some drugs in pigmented rabbits.

Our results show that stimulation of the β adrenergic receptor by isoproterenol did not alter the changes in the flare and IOP induced by PGE2. It has been demonstrated that β adrenergic agonists prevent not only airflow obstruction, but also airway inflammation by an attenuation of microvascular leakage [8]. Ebbinghaus et al. assessed the effects of sympathectomy on the course and severity of murine antigen-induced arthritis. They report that sympathectomized mice with antigen-induced arthritis had less hyperalgesia, and isoproterenol increased the severity of the antigen-induced arthritis [24]. Thus, the relationship between inflammation and the adrenergic nervous system is complex.

The blood aqueous barrier in the eye exists at the level of the non-pigmented ciliary epithelial cells and iris endothelial cells. The tight junctions between the non-pigmented ciliary epithelial cells and iris vessel endothelial cells prevent protein leakage from the ciliary body to the aqueous humor [25–27]. The ciliary processes and retina in rabbits showed a breakdown of the ocular-blood barrier after the application of PGF2α-isopropyl ester and PGE2 [28]. Green et al. [29] report that the initial phase of PGE2 induced ocular hypertension was caused by an increase in vascular permeability and vascular dilation.

The transient increase in IOP after the topical application of PGE2 preceded the flare elevation in our study. The IOP returned to the initial values an hour and half after PGE2 application, at the time when the aqueous flare value was still increasing. The flare values reached a maximum 2 h after PGE2 application. Camras et al. also report a discrepancy in the IOP elevation and aqueous protein concentration after topical application of PGE2 [19]. Our data do not support the idea that the increase of leakage from the disrupted blood-ocular barrier caused the IOP elevation. The mechanism(s) responsible for the increase of the IOP by PGE2 have not been definitively determined.

We could not completely blind the examiners to the type of agents applied. This was a limitation of our study. The aqueous flare and IOP values were digitally displayed; therefore, there was no way to control the values of the displays.

Our results show that signals from the α2 receptors suppress the flare and IOP elevation caused by PGE2 topical application. The time course of flare elevation caused by PGE2 application did not coincide with the IOP elevation. Thus, the mechanisms causing the elevation of the aqueous flare and IOP might be different. Brimonidine did not enhance the inflammation caused by PGE2 application to the eyes of pigmented rabbits. However, its effects on the aqueous flare after laser iridotomy or cataract surgery should be examined in humans because the possible species-dependent differences of inflammation might result in different reactions to the adrenergic agents.

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Conflicts of interest M. N. Shibasaki, None; M. A. Latief, None; J.-A. Ko, None; K. Funaishi, None; Y. Kiuchi, None.

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Intraocular Pressure Outcomes and Risk Factors for Failure in the Collaborative Bleb-Related Infection Incidence and Treatment Study

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Purpose: To evaluate the efficacy and safety of trabeculectomy for patients with glaucoma who were enrolled in the Collaborative Bleb-related Infection Incidence and Treatment Study (CBIITS).

Design: Multicenter, prospective, cohort study.

Participants: A total of 829 eyes in 829 patients with glaucoma who had undergone trabeculectomy alone or trabeculectomy combined with phacoemulsification at 34 clinical centers were examined in this study.

Main Outcome Measures: Intraocular pressures (IOPs, in millimeters of mercury), risk factors for surgical failure, and surgical complications.

Methods: The enrollment period was 2 years, and follow-up was conducted every 6 months for up to 5 years. Outcomes were measured at 6-month intervals. Four levels of success were defined by achievement of the following IOP: (A) $4 < IOP < 22$, (B) $4 < IOP < 19$, (C) $4 < IOP < 16$, and (D) $4 < IOP < 13$. The primary outcome was the qualified success rate according to the defined criteria. The secondary outcomes included IOP, risk factors for surgical failure, and surgical complications.

Results: Mean IOP and preoperative antiglaucoma medications were significantly decreased from 24.9±9.0 to 12.6±5.2 mmHg ($P < 0.0001$) and from 2.8±1.0 to 1.2±1.3 mmHg ($P < 0.0001$), respectively, 5 years after surgery. For criteria A, B, C, and D, the qualified success rates were 90.1%, 88.9%, 77.6%, and 57.7% at 1 year, respectively, and 71.9%, 66.7%, 50.1%, and 29.9% at 5 years, respectively. The third or subsequent trabeculectomy was less effective than the first and second trabeculectomies. Preoperative lens status and preoperative higher IOP were risk factors for trabeculectomy failure. The needling procedure and cataract surgery were associated with the risk of failure. The rates of postoperative hyphema, shallow anterior chamber, bleb leak, and choroidal detachment were 2.7%, 3.1%, 1.9%, and 7.2%, respectively, in our series.

Conclusions: Trabeculectomy with mitomycin C is an effective and safe procedure for reducing IOP in the CBIITS. The number of previous glaucoma surgeries, preoperative lens status and IOP, the needling procedure, and cataract surgery after trabeculectomy influenced the success rate, as determined by the target IOP. *Ophthalmology 2015;122:2223-2233 © 2015 by the American Academy of Ophthalmology.*

To improve the success rate of intraocular pressure (IOP) management and decrease the rate of surgical complications, surgical procedures for glaucoma, such as the use of glaucoma drainage devices (e.g., Baerveldt tube [Abbott Medical Optics, Abbott Park, IL], Express [Boston Scientific, Marlborough, MA], iStent [Glaukos, Laguna Hills, CA]), have been proposed as viable alternatives to trabeculectomy.[1–3] So far, trabeculectomy is the most common surgical procedure for controlling IOP in patients with glaucoma. The antimetabolite mitomycin C (MMC) was introduced as an adjunctive therapy for trabeculectomy and augmented the control of IOP.[4] However, the application of MMC at the time of trabeculectomy increased the incidence of bleb-related infection and hypotony maculopathy.[5,6]

The Japan Glaucoma Society initiated a prospective study to investigate the incidence and severity of bleb-related infection (Collaborative Bleb-Related Infection Incidence and Treatment Study [CBIITS]).[7,8] The 5-year cumulative incidence of bleb-related infection was 2.2%± 0.5% in eyes treated with MMC-augmented trabeculectomy or trabeculectomy combined with phacoemulsification and intraocular lens implantation. Bleb leakage and younger age were the main risk factors for infections.[7,8]

The amount of filtered aqueous flow under the conjunctiva might affect the prevalence of bleb-related infection. The limited aqueous flow in eyes with high IOP and those with high aqueous flow in the bleb with low IOP might result in the difference in the prevalence of bleb-related infections. Interpreting the report by the CBIITS group

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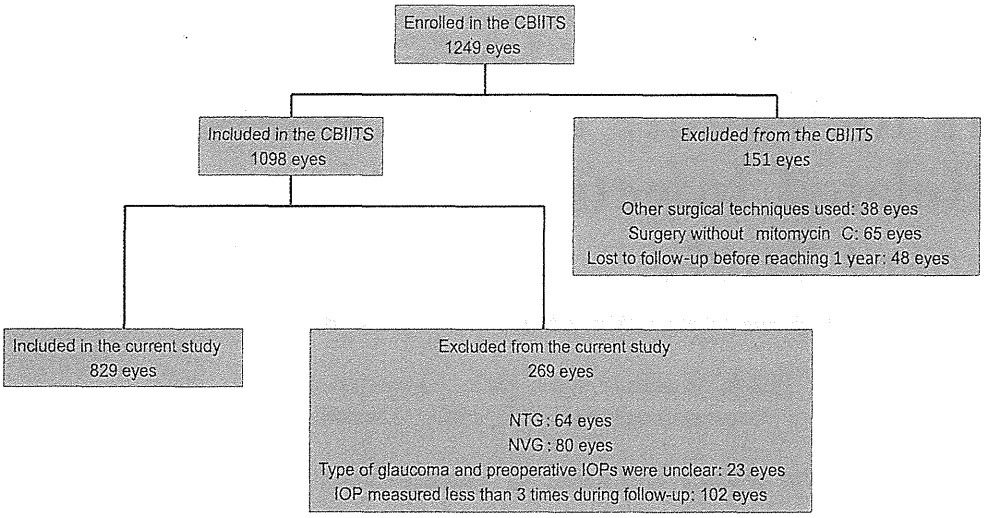

Figure 1. Flowchart showing the number of patients who were enrolled and analyzed in this study. CBIITS = Collaborative Bleb-Related Infection Incidence and Treatment Study; IOP = intraocular pressure; NTG = normal-tension glaucoma; NVG = neovascular glaucoma.

probably depends on the surgical IOP results of the CBIITS. Evaluation of the IOP results of the CBIITS revealed the outcome of trabeculectomy augmented by MMC, which represents the benchmark in Asia, especially in Japan, because all the board members of the Japan Glaucoma Society belong to the 34 institutes that participated in this study when the CBIITS started.

We reviewed the effect of trabeculectomy on IOP and surgical success rate, and explored the factors that affect the surgical success rate and incidence of surgical complications using the CBIITS data.

Methods

The CBIITS was planned in 2004, and principal investigators were recruited voluntarily from the board members of the Japan Glaucoma Society. All the 34 clinical centers directed by board members of the Japan Glaucoma Society participated and enrolled subjects. Institutional review board approval was obtained at each institution, and all patients gave written informed consent after a thorough explanation of the study. The enrollment criteria were as follows: any type of filtering surgery, including those concomitantly performed with cataract or other intraocular surgeries, and the first operated eye after study inclusion (in patients in whom both eyes were treated). There were no other concomitant surgeries, excluding cataract surgery, in the CBIITS.

The indications for surgery, selection of the operative procedure, operative technique, and postoperative medication or additional glaucoma treatment were at the discretion of local investigators. Consecutive eligible subjects were recruited at each clinical center. The follow-up period was set to a minimum of 1 year and a maximum of 5 years. The patients were recommended to visit the clinical center at 6-month intervals for up to 5 years. Additional visits to the clinical center or other ophthalmology clinics were at the discretion of the local investigators.

A total of 829 eyes in 829 patients with glaucoma were included in the present study. As previously reported, the CBIITS examined 1249 eyes in 1249 enrolled patients. The CBIITS finally included and analyzed 1098 eyes from among the 1098 patients who were treated by trabeculectomy with MMC or trabeculectomy plus cataract surgery.[7] In this study, a total of 269 eyes from among the 1098 subjects were excluded for the following reasons: The type of glaucoma and preoperative IOPs were unclear in 23 eyes, and IOP was measured <3 times during follow-up in 102 eyes. Moreover, we excluded subjects with neovascular glaucoma in 80 eyes and normal-tension glaucoma in 64 eyes. Neovascular glaucoma is a subtype of refractory glaucoma in which IOP control is more difficult to achieve than other subtypes of glaucoma.[9,10] The IOP of normal-tension glaucoma is always <21 mmHg, and the postoperative target IOP is lower than other glaucoma subtypes. Achieving clinical success with trabeculectomy for neovascular glaucoma and normal-tension glaucoma is more elusive than for other glaucoma subtypes. Therefore, we excluded subjects with neovascular glaucoma and normal-tension glaucoma from the study (Fig 1).

The IOP was measured by Goldmann applanation tonometry. From the medical records, we documented the average of 3 preoperative IOP measurements that were closest to the time of surgery and the IOP measurements closest to 6, 12, 18, 24, 32, 36, 42, 48, 54, and 60 months after surgery. Ten outcomes were measured at 6-month intervals.

We attempted to follow the outcome criteria proposed in the guidelines by the World Glaucoma Association. Four levels of success, defined by achievement of IOP (values in millimeters of mercury) were (A) $4 < IOP < 22$, (B) $4 < IOP < 19$, (C) $4 < IOP < 16$, and (D) $4 < IOP < 13$. Surgical success was stratified according to IOP control. When the IOP was above the upper limit or below the lower limit for 2 consecutive measurements, the surgery was considered to have failed at the first time point when IOP had exceeded the defined limit. In addition to the defined IOP criteria, we also examined the failure to achieve a 20% reduction in IOP to calculate the surgical success rate.

The primary outcome was the qualified success rate according to the defined criteria. Needling, resuturing the conjunctiva, subconjunctival injection of antimetabolite, and cataract surgery did not represent surgical failure. Reoperation for increased IOP and loss of perception of light were classified as failures. The secondary outcomes included the IOP, risk factors for bleb failure, and surgical complications after surgery.

Table 1. Demographics and Preoperative Ocular Characteristics

Total cases, no.	829	
Mean age, yrs (SD)	63.4	(±13.5)
Mean follow-up, mos (SD)	55.5	(±10.6)
Mean preoperative IOP, mmHg (SD)	24.9	(±9.0)
Mean preoperative medications, no. (SD)	3.1	(±1.2)
Laterality		
Right	421	50.80%
Left	408	49.20%
Sex		
Male	487	60.40%
Female	342	42.40%
Diagnosis		
POAG	433	53.70%
PACG	59	7.30%
DG	23	2.90%
PXG	95	11.80%
Other SG	219	27.20%
Conjunctival incision site		
Limbal incision	372	44.90%
Fornix incision	457	55.10%
Previous cataract surgery	253	30.50%
No. of previous glaucoma surgeries		
0	649	78.30%
1	122	14.70%
≥2	58	7.00%
Lens status		
Phakia	576	69.50%
Aphakia	29	3.50%
Pseudophakia	222	26.80%
Unknown	2	0.20%

DG = developmental glaucoma; IOP = intraocular pressure; PACG = primary angle-closure glaucoma; POAG = primary open-angle glaucoma; PXG = pseudoexfoliation glaucoma; SG = secondary glaucoma; SD = standard deviation.

Statistical analysis was performed using Kaplan–Meier survival analysis and the Cox proportional hazards model. The IOPs before and after surgeries were compared using the Student *t* test with Bonferroni correction. Analyses were conducted using JMP software version 9 (SAS Inc, Cary, NC). The level of significance was set at $P < 0.05$.

Results

A total of 829 eyes in 829 patients were available for analysis. The demographics and preoperative ocular characteristics are shown in Table 1.

Intraocular Pressure Control

The mean IOP significantly decreased from 24.9±9.0 to 12.6±5.2 ($P < 0.001$) and 12.7±5.3 mmHg ($P < 0.001$) at 1 year (Fig 2) and 5 years after surgery, respectively. The IOP course is shown in Figure 3. The graph reveals a significant reduction in IOP after surgery relative to baseline at all time points.

The use of preoperative antiglaucoma medications was significantly decreased from 3.1±1.2 to 1.2±1.3 at 5 years after surgery ($P < 0.001$) (Fig 4). For criteria A, B, C, and D, the qualified success rates were 90.1%, 88.9%, 77.6%, and 57.7% at 1 year and 71.9%, 66.7%, 50.1%, and 29.9% at 5 years, respectively (Fig 5). For these same criteria, the complete success rates were

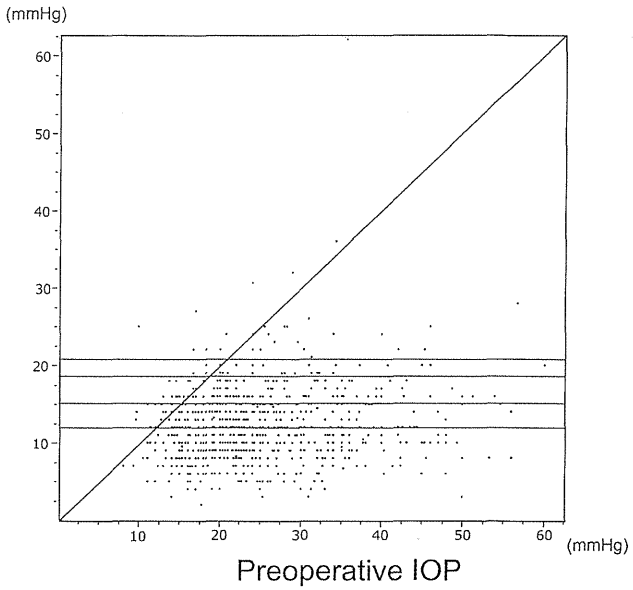

Figure 2. Scattergram of preoperative versus postoperative intraocular pressure (IOP) after 1 year. Each point represents 1 eye, with the preoperative IOP value as the abscissa and the postoperative IOP value as the ordinate.

66.3%, 65.8%, 60.9%, and 48.9% at 1 year and 30.6%, 30.4%, 28.2%, and 21.4%, at 5 years, respectively (Fig 6). For criteria A, B, C, and D or failure to achieve 20% reduction of preoperative IOP, the qualified success rates were 88.8%, 86.7%, 75.7%, and 56.4% at 1 year and 70.2%, 65.0%, 49.5%, and 29.3% at 5 years, respectively (Fig 7). For criteria A, B, C, and D or failure to achieve 20% reduction of preoperative IOP, the complete success rates were 64.7%, 64.2%, 59.3%, and 47.6% at 1 year and 30.1%, 29.9%, 27.7%, and 21.1% at 5 years, respectively (Fig 8).

Risk Factors for Surgical Failure

Under the qualified success criteria, factors not significantly associated with target IOP success rates included conjunctival incision site, laterality, sex, diagnosis, and age. Previous glaucoma surgery, preoperative lens status, and preoperative IOP were associated with the target IOP success rate (Table 2).

We found that there were significant differences between the first trabeculectomy group and third or more trabeculectomy group, and between the second trabeculectomy group and the third or more trabeculectomy group, taking into account a variety of risk factors in the multivariate analysis ($P = 0.0073$, Wilcoxon test). The third or more trabeculectomy group satisfied criteria A and B less than the first and second trabeculectomy groups. The percentages of eyes in the first trabeculectomy group, the second trabeculectomy group, and the third or more trabeculectomy group that satisfied criterion A were 91.6%, 94.8%, and 83.7% at 1 year and 72.7%, 72.6%, and 51.4% at 5 years, respectively (Fig 9).

Under the criteria for complete success, aphakia was a risk factor for failure at all IOP levels. The fornix-based conjunctiva flap was a risk factor for failure to satisfy criterion A, and the high preoperative IOP was a risk factor for failure to satisfy criterion D (Table 3).

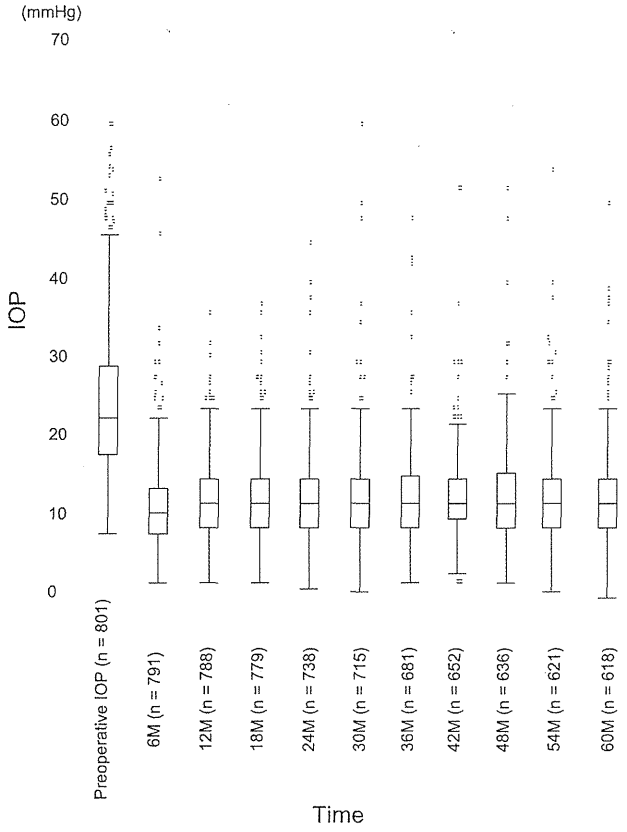

Figure 3. The intraocular pressure (IOP) versus observation time (11 time periods). The *box plots* show the median and the 25th and 75th percentiles of the data. *Dashes* denote outliers. The graph reveals a significant reduction in IOP after surgery.

We examined the postoperative risk factors for bleb failure. The needling procedure was always associated with the risk of failure regardless of IOP. Cataract surgery after trabeculectomy was a risk factor when the upper limit of IOP in the criterion was low, and

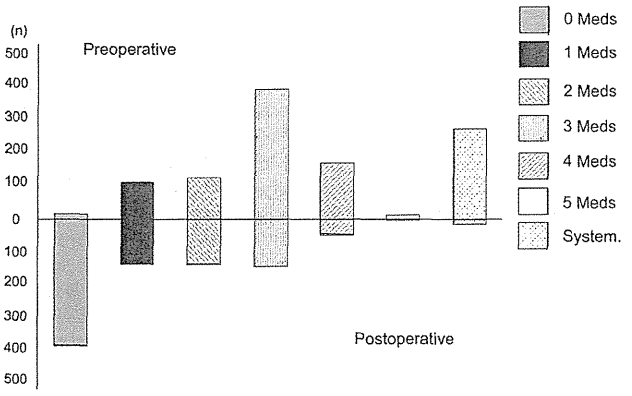

Figure 4. Bar graph showing the number of preoperative (top) versus postoperative medications (Meds; bottom). The use of antiglaucoma medications was significantly decreased 5 years after surgery ($P < 0.001$). System: systemic ocular hypotensive agents.

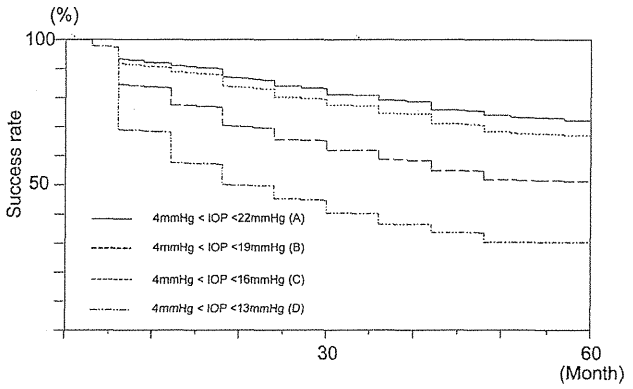

Figure 5. Kaplan–Meier survival curve showing the qualified success rates of the 4 intraocular pressure (IOP) criteria (values in mmHg): **(A)** 4 < IOP < 22, **(B)** 4 < IOP < 19, **(C)** 4 < IOP < 16, and **(D)** 4 < IOP < 13.

adding conjunctival suture was a risk factor when the upper limit of IOP in the criterion was high under qualified success criteria (Table 4).

Complications

The rates of intraoperative complications, complications in the early postoperative period (<1 month after surgery), and complications in the late postoperative period are shown in Table 5. The total number of early postoperative complications and late postoperative complications did not always equal the number of total postoperative complications because, in some cases, the early postoperative complication continued for more than 1 month.

Although there were 21 infected eyes in the CBIITS, 8 of 829 eyes (0.97%) were infected in this study. Of the 21 infected eyes in the CBIITS, we excluded 3 with normal-tension glaucoma, 2 with neovascular glaucoma, and 8 that were followed up for <1 year.

Discussion

The CIIBIT study is a multicenter clinical trial that was conducted to elucidate the incidence of bleb-related infections after trabeculectomy augmented by MMC. We

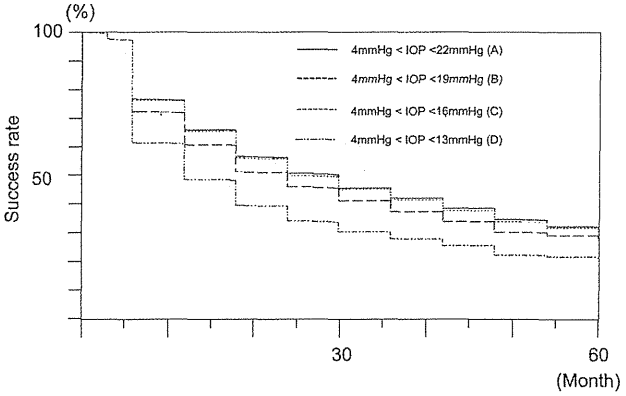

Figure 6. Kaplan–Meier survival curve showing the complete success rates of the 4 intraocular pressure (IOP) criteria (values in mmHg): **(A)** 4 < IOP < 22, **(B)** 4 < IOP < 19, **(C)** 4 < IOP < 16, and **(D)** 4 < IOP < 13.

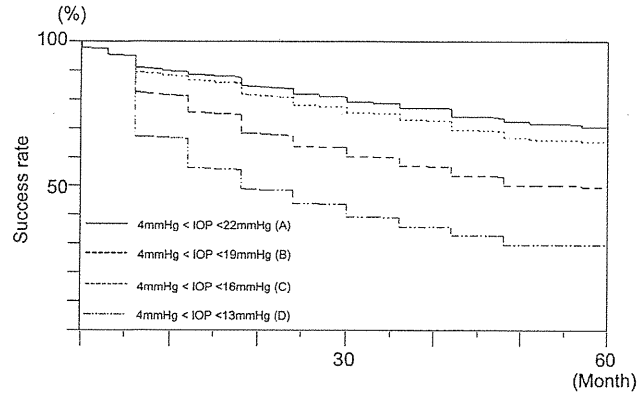

Figure 7. Kaplan–Meier survival curve showing the qualified success rates of the 4 intraocular pressure (IOP) criteria (values in mmHg): (A) 4 < IOP < 22, (B) 4 < IOP < 19, (C) 4 < IOP < 16, and (D) 4 < IOP < 13 or failure to reduce preoperative IOP by 20%.

examined the effect of trabeculectomy with MMC on IOP in CIIBT study subjects to determine the IOP outcomes, risk factors for failure, and complications of trabeculectomy in Japan. We included subjects who had previous cataract surgery (30.5%) and glaucoma surgery (21.7%). In this study, we excluded subjects with neovascular glaucoma and normal-tension glaucoma. Neovascular glaucoma is a subtype of refractory glaucoma in which IOP control is difficult to achieve. The IOP of normal-tension glaucoma is always <21 mmHg. The main outcome of this study was IOP control. This is the reason why we excluded subjects with neovascular glaucoma and normal-tension glaucoma from the study. As a result, our study included primary open-angle glaucoma (POAG), primary angle-closure glaucoma, developmental glaucoma, and secondary glaucoma, including pseudoexfoliation glaucoma. Those are the glaucoma subtypes with high IOP. Because the baseline IOP of some patients may be within the normal range under maximum medical therapy, some reports used percentage reduction of baseline IOP as an outcome in addition to absolute IOP levels. However, this criterion does not always satisfy all situations. We showed both simple success criteria using absolute IOP and the combination of absolute IOP and percentage reduction from baseline IOP as indicated in the guidelines.[11]

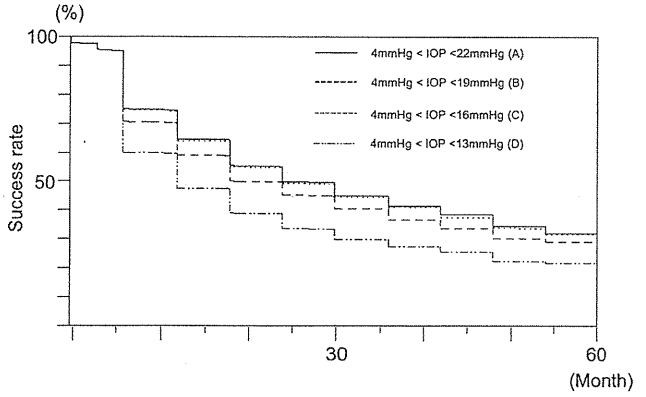

Figure 8. Kaplan–Meier survival curve showing the complete success rates of the 4 intraocular pressure (IOP) criteria (values in mmHg): (A) 4 < IOP < 22, (B) 4 < IOP < 19, (C) 4 < IOP < 16, and (D) 4 < IOP < 13 or failure to reduce preoperative IOP by 20%. IOP = intraocular pressure.

Our analysis showed that the qualified success rates for criteria A, B, C, and D were 90.1%, 88.9%, 77.6%, and 57.7% at 1 year and 71.9%, 66.7%, 50.1%, and 29.9% at 5 years, respectively (Fig 5), and for criteria A, B, C, and D or failure to reduce the preoperative IOP by 20%, the qualified success rates were 88.8%, 86.7%, 75.7%, and 56.4% at 1 year and 70.2%, 65.0%, 49.5%, and 29.3% at 5 years, respectively (Fig 7). The mean IOP at baseline was 24.9±9.0 mmHg with maximum tolerable drug management, and the mean IOP ranged between 12.0 and 13.0 mmHg in the 5-year period.

The mean and median of preoperative topical medications were 2.76±1.04 and 3 (range, 0–5), respectively. The mean and median of postoperative topical medications were 1.22±1.34 and 1 (range, 0–5), respectively.

There are several multicenter collaborative studies evaluating the effect of trabeculectomy with antifibrotic agents.[12–18] Kirwan et al[18] evaluated the efficacy and safety of current trabeculectomy surgery in the United Kingdom ("Trabeculectomy in the 21st Century"). Consecutive trabeculectomy cases with open-angle glaucoma and no history of incisional glaucoma surgery from 9 glaucoma units were evaluated retrospectively. Surgical success was stratified according to IOP control. Failure was defined as an IOP above the upper limit (22, 19, and 16 mmHg) and <20% reduction in IOP relative to the preoperative IOP or below the lower limit (5 mmHg) at 2 consecutive study visits after 3 months. The preoperative IOP was 23.0±5.5 mmHg, 80% of the subjects postoperatively had an IOP <21 mmHg without using medication, and 87% of the subjects achieved a low IOP level with the use of medication at the 3-year follow-up.[18] The mean number of preoperative and postoperative medications was 2.5±0.9 and 0.11±0.4, respectively.

The Tube Versus Trabeculectomy (TVT) study prospectively compared the surgical results after trabeculectomy and MMC with the Baerveldt glaucoma implant.[1,17] We can compare our results with their trabeculectomy results. They enrolled subjects with a history of cataract extraction surgery or filtration surgery in the study. They included subjects who underwent cataract surgery (48%) and glaucoma surgery (without the use of an antifibrotic agent, 22%; trabeculectomy with MMC, 14%; glaucoma surgery combined with cataract surgery, 17%) in the trabeculectomy group. The preoperative IOP in the trabeculectomy group was 25.6±5.3 mmHg, and the mean IOP after surgery was 12.6±5.9 mmHg in the 5-year period. The success rates were 86.1% at 1 year, 71.8% at 2 years, 69.3% at 3 years, and 53.1% at 5 years, based on the success criteria of IOP <21 mmHg, reduction of >20%, or IOP >5 mmHg. Trabeculectomy combined with 5-fluorouracil in the Fluorouracil Filtering Surgery Study was a prospective multicenter clinical trial evaluating the effect of subconjunctival 5-fluorouracil injection.[12] It enrolled patients with a history of cataract surgery or previous failed filtering surgery. Treatment failure was defined as IOP >21 mmHg. The failure rate was similar to the TVT study results.

Table 2. Multivariate Cox Proportional Hazard Ratios for Risk Factors for Failure to Achieve Qualified Success

	Criterion A (4 < IOP < 22 mmHg)			Criterion B (4 < IOP < 19 mmHg)			Criterion C (4 < IOP < 16 mmHg)			Criterion D (4 < IOP < 13 mmHg)		
	Risk Ratio	*P Value*	*95% CI*	*Risk Ratio*	*P Value*	*95% CI*	*Risk Ratio*	*P Value*	*95% CI*	*Risk Ratio*	*P Value*	*95% CI*
Conjunctival incision		0.55			0.63			0.2			0.89	
Limbal base	1			1			1			1		
Fornix base	0.93	0.59	0.7–1.21	0.94	0.63	0.73–1.21	0.89	0.2	0.75–1.06	1.01	0.89	0.85–1.20
Laterality		0.77			0.69			0.95			0.48	
Right	1			1			1			1		
Left	1.04	0.77	0.79–1.36	1.05	0.69	0.82–1.35	1.01	0.95	0.85–1.19	0.94	0.48	0.8–1.11
Sex		0.56			0.59			0.54			0.56	
Male	1			1			1			1		
Female	1.09	0.56	0.82–1.43	1.07	0.59	0.83–1.38	0.95	0.54	0.8–1.12	1.05	0.56	0.89–1.25
No. of previous glaucoma surgeries		0.03*			0.04*			0.05			0.07	
0	1			1			1			1		
1	0.83	0.38	0.54–1.24	0.84	0.34	0.57–1.2	0.81	0.09	0.63–1.03	0.89	0.34	0.69–1.13
≥2	1.73	0.02*	1.08–2.67	1.63	0.03*	1.06–2.46	1.26	0.16	0.91–1.72	1.37	0.06	0.99–1.86
≥2/1	2.07	0.01*	1.19–3.60	1.96	0.01*	1.17–3.25	1.56	0.02*	1.08–2.23	1.54	0.02*	1.06–2.21
Lens status		0.02*			0.01*			<0.01*			0.01*	
Phakia	1			1			1			1		
Aphakia	2.35	0.01*	1.27–4.08	2.18	0.01*	1.21–3.69	1.62	0.04*	1.02–2.49	1.83	0.01*	1.17–2.74
Pseudophakia	1.32	0.11	0.94–1.85	1.51	0.01*	1.1–2.05	1.49	<0.01*	1.19–1.84	1.26	0.04*	1.02–1.56
Pseudophakia/aphakia	0.56	0.06	0.32–1.03	0.69	0.2	0.41–1.24	0.91	0.69	0.60–1.46	0.69	0.1	0.46–1.08
Diagnosis		0.39			0.33			0.97			0.75	
POAG	1			1			1			1		
PXG	1.09	0.73	0.67–1.69	1.07	0.74	0.70–1.60	1.03	0.86	0.77–1.35	1.15	0.33	0.86–1.51
SG	1.31	0.12	0.93–1.84	1.2	0.24	0.88–1.64	1.05	0.68	0.84–1.30	0.98	0.29	0.90–1.40
DG	0.94	0.89	0.32–2.20	0.71	0.46	0.24–1.66	0.99	0.96	0.55–2.00	1.16	0.6	0.65–1.93
PACG	0.77	0.4	0.40–1.37	0.71	0.21	0.38–1.20	0.92	0.63	0.64–1.29	1	0.99	0.70–1.40
With/without cataract surgery		0.53			0.95			0.09			0.16	
TLE only	1			1			1			1		
TLE with cataract surgery	0.88	0.53	0.57–1.32	0.99	0.95	0.67–1.43	1.24	0.09	0.96–1.58	1.19	0.16	0.93–1.52
Age	1	0.55	0.99–1.02	1	0.86	0.99–1.01	1	0.62	0.99–1.01	1	0.21	0.99–1
Preoperative IOP	1.01	0.1	1–1.03	1.02	0.02*	1–1.03	1.01	0.12	1–1.02	1.01	0.03*	1–1.02

CI = confidence interval; DG = developmental glaucoma; IOP = intraocular pressure; PACG = primary angle-closure glaucoma; POAG = primary open-angle glaucoma; PXG = pseudoexfoliation glaucoma; SG = secondary glaucoma; TLE = trabeculectomy.
*$P < 0.05$.

In a single-center study, Fontana et al[19] reported the surgical outcome of trabeculectomy with MMC and the risk factors for failure in phakic open-angle glaucoma. They recruited 225 subjects (292 eyes) without a history of cataract or glaucoma surgery. The mean IOP at baseline was 18.8±6.1 mmHg and the mean IOP was 11.1±4.2 mmHg at 3 years. By using the criteria of IOP ≤18 mmHg and IOP reduction of 20%, their success rate was 85% at 1 year and 62% at 3 years.[19]

Use of the guidelines that reported glaucoma surgical results is recommended, and many studies used success criteria similar to those indicated in the guidelines.[11] It is difficult to simply compare the surgical results among different studies. There are small differences in the success criteria and background of the subjects, including race, surgical history, and glaucoma subtypes. With respect to IOP levels and success rate after trabeculectomy, the studies that included only surgery-naïve subjects seemed to show results that were better than those with subjects who

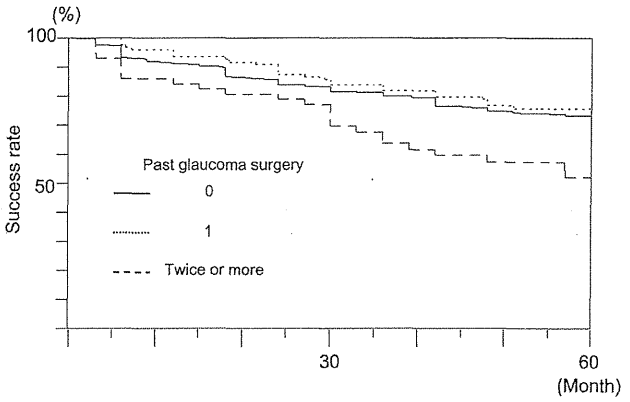

Figure 9. Kaplan–Meier survival curve showing the qualified success rates of criterion A (4 < intraocular pressure < 22 mmHg) of the first trabeculectomy group, the second trabeculectomy group, and the third or more trabeculectomy group. There were significant differences among the groups ($P = 0.0073$, Wilcoxon test).

Table 3. Multivariate Cox Proportional Hazard Ratios for Risk Factors for Failure to Achieve Complete Success

	Criterion A			Criterion B			Criterion C			Criterion D		
	4 < IOP < 22 mmHg			*4 < IOP < 19 mmHg*			*4 < IOP < 16 mmHg*			*4 < IOP < 13 mmHg*		
	Risk Ratio	*P Value*	95% CI	*Risk Ratio*	*P Value*	95% CI	*Risk Ratio*	*P Value*	95% CI	*Risk Ratio*	*P Value*	95% CI
Conjunctival incision		0.04*			0.05			0.2			0.74	
Limbal base	1			1			1			1		
Fornix base	1.21	0.04*	1.01–1.44	1.19	0.05	0.99–1.42	1.12	0.2	0.94–1.33	1.03	0.74	0.87–1.21
Laterality		0.8			0.78			0.95			0.78	
Right	1			1			1			1		
Left	1.02	0.8	0.86–1.21	1.02	0.78	0.86–1.22	1.01	0.95	0.85–1.19	1.02	0.78	0.87–1.20
Sex		0.36			0.53			0.54			0.71	
Male	1			1			1			1		
Female	1.09	0.36	0.91–1.30	1.05	0.53	0.89–1.26	1.06	0.54	0.89–1.25	1.03	0.71	0.88–1.21
No. of previous glaucoma surgeries		0.05*			0.04*			0.05			0.04*	
0	1			1			1			1		
1	0.84	0.17	0.65–1.07	0.83	0.15	0.64–1.07	0.81	0.09	0.63–1.03	0.88	0.26	0.69–1.10
≥2	1.34	0.08	0.96–1.83	1.35	0.07	0.97–1.85	1.26	0.16	0.91–1.72	1.38	0.04*	1.00–1.84
≥2/1	1.6	0.01*	1.10–2.30	1.62	0.01*	1.11–2.33	1.56	0.02*	1.08–2.23	1.57	0.01*	1.10–2.21
Lens status		<0.01*			<0.01*			<0.01*			0.02*	
Phakia	1			1			1			1		
Aphakia	1.47	<0.01*	1.18–1.82	1.47	<0.01*	1.18–1.82	1.49	<0.01*	1.19–1.84	1.28	0.02*	1.04–1.57
Pseudophakia	1.6	0.06	0.99–2.46	1.57	0.06	0.97–2.42	1.63	0.04*	1.02–2.49	1.58	0.04	1.01–2.37
Pseudophakia/aphakia	1.09	0.71	0.67–1.68	1.07	0.78	0.61–1.51	0.64	0.02*	0.45–0.93	1.24	0.34	0.79–1.87
Diagnosis		0.97			0.56			0.97			0.94	
POAG	1			1			1			1		
PXG	0.99	0.97	0.74–1.32	0.98	0.87	0.73–1.29	1.03	0.86	0.77–1.35	1.06	0.65	0.81–1.38
SG	1.06	0.64	0.84–1.32	1.04	0.74	0.83–1.29	1.05	0.68	0.84–1.30	1.09	0.42	0.88–1.34
DG	1.05	0.86	0.57–1.80	1.02	0.94	0.55–1.76	0.99	0.96	0.54–1.67	1.08	0.78	0.62–1.77
PACG	0.93	0.7	0.65–1.31	0.91	0.59	0.63–1.28	0.92	0.63	0.64–1.29	1	1	0.71–1.22
With/without cataract surgery		0.2			0.17			0.09			0.27	
TLE only	1						1			1		
TLE with cataract surgery	1.18	0.2	0.91–1.51	1.2	0.17	0.93–1.53	1.24	0.09	0.96–1.58	1.14	0.27	0.89–1.43
Age	1	0.68	0.99–1.01	1	0.71	0.99–1.01	1	0.62	0.99–1.01	1	0.59	0.90–1.01
Preoperative IOP	1.01	0.34	0.99–1.02	1	0.28	0.99–1.02	1	0.12	0.99–1.02	1.01	0.03*	1.00–1.02

CI = confidence interval; DG = developmental glaucoma; IOP = intraocular pressure; PACG = primary angle-closure glaucoma; POAG = primary open-angle glaucoma; PXG = pseudoexfoliation glaucoma; SG = secondary glaucoma; TLE = trabeculectomy.
*$P < 0.05$.

had a surgical history. Our results seemed to be compatible with the results of the TVT study.

Risk Factors

In this study, the number of previous glaucoma surgeries, preoperative lens status, and preoperative IOP were associated with the success rate that was determined by target IOP. Law et al[20] reported that repeat trabeculectomy with MMC was less successful than the initial trabeculectomy in combination with MMC at achieving IOP reduction in open-angle glaucoma.[20] In our study, the third or subsequent trabeculectomy was less effective than the first and second trabeculectomies. Awai-Kasaoka et al[21] reported that a short interval between the current trabeculectomy and the previous trabeculectomy was associated with surgical failure of the subsequent trabeculectomy with MMC.

Trabeculectomy at an inferior site was associated with more bleb-related infections than trabeculectomy at the superior area.[22] Surgeons will try to select the superior area as the surgical site. We can select the upper temporal area or upper nasal area as the trabeculectomy site for the first and second surgeries. Those areas provide fresh conjunctival area for surgeries. However, the third filtration surgical area overlaps with the first and second surgical sites. This might be the reason why the third trabeculectomy result was worse than the first and second surgeries.

The TVT study reported that patients with prior trabeculectomy or cataract surgery had a higher success rate with the Baerveldt glaucoma implant compared with trabeculectomy.[8] The percentages of eyes in the first trabeculectomy group, the second trabeculectomy group, and the third or more trabeculectomy group that satisfied criterion A were 72.7%, 72.6%, and 51.4%, respectively, at 5 years in this study. The success rate of the Baerveldt glaucoma implant

Table 4. Multivariate Cox Proportional Hazard Ratios for Risk Factors for Failure to Achieve Qualified and Complete Success after Surgery

	4 < IOP < 22 mmHg			4 < IOP < 19 mmHg			4 < IOP < 16 mmHg			4 < IOP < 13 mmHg		
	Risk Ratio	*P Value*	95% CI	*Risk Ratio*	*P Value*	95% CI	*Risk Ratio*	*P Value*	95% CI	*Risk Ratio*	*P Value*	95% CI
Qualified success												
Needling	1.44	<0.01*	1.14–1.73	1.48	<0.01*	1.21–1.76	1.48	<0.01*	1.24–1.71	1.51	<0.01*	1.31–1.72
Conjunctival suture	2.17	<0.01*	1.31–3.16	1.9	0.02*	1.14–2.79	1.52	0.08	0.94–2.20	1.22	0.36	0.78–1.72
Cataract surgery	0.8	0.38	0.46–1.29	0.74	0.2	0.44–1.16	0.7	0.06	0.46–1.02	0.71	0.02*	0.51–0.96
Other surgery	1.36	0.56	0.42–3.21	1.1	0.86	0.34–2.58	1.41	0.39	0.60–2.76	1.49	0.22	0.77–2.57
Complete success												
Needling	1.55	<0.01*	1.34–1.76	1.54	<0.01*	1.33–1.75	1.5	<0.01*	1.30–1.71	1.49	<0.01*	1.29–1.69
Conjunctival suture	1.34	0.17	0.86–1.90	1.33	0.19	0.86–1.88	1.33	0.17	0.87–1.85	1.16	0.46	0.76–1.63
Cataract surgery	0.92	0.59	0.67–1.23	0.92	0.57	0.67–1.23	0.88	0.4	0.64–1.17	0.83	0.2	0.62–1.09
Other surgery	1.41	0.34	0.67–2.56	1.39	0.36	0.66–2.52	1.33	0.42	0.63–2.41	1.36	0.34	0.70–2.35

CI = confidence interval; IOP = intraocular pressure.
*$P < 0.05$.

group in the TVT study was 70.2% at 5 years, based on the success criteria of IOP <21 mmHg, reduction >20%, or IOP >5 mmHg. In the Ahmed Baerveldt Comparison study, the success rate based on the success criteria of IOP <21 mmHg, reduction >20%, or IOP >5 mmHg during 5 years of follow-up was 56.3% in the Ahmed glaucoma valve group and 60.6% in the Baerveldt glaucoma implant group.[23] These success rates of glaucoma drainage device surgery fall in between that of the first or second trabeculectomy group and that of the third or more trabeculectomy group in this study. This information is useful for determining the surgical procedure for patients who have undergone multiple glaucoma surgeries. Cataract surgery and needling procedure after trabeculectomy were also found to be risk factors for filtration failure. Fontana et al[24] also reported that cataract extraction after trabeculectomy was associated with a risk of failure for several criteria. The general concern is the induction of inflammation by cataract surgery after trabeculectomy, which is strong enough to promote a fibrotic reaction in the bleb.[25]

Combined glaucoma and cataract surgery in the era of intracapsular or extracapsular cataract extraction associated with a long corneal-scleral incision was a risk factor for surgical failure.[26] Small-incision cataract surgery and augmentation by antifibrotic agents in trabeculectomy improved the IOP results after combined surgery.[27] Our results also showed that combined cataract surgery did not affect the IOP reduction achieved by trabeculectomy.

Some studies showed that the results of trabeculectomy and phaco-combination surgery was not as effective as trabeculectomy in reducing IOP.[28,29] Ogata-Iwao et al[29] speculated that the higher degree of inflammation caused by phacotrabeculectomy compared with trabeculectomy alone could be blamed for the poor surgical result in phacotrabeculectomy.

Preoperative high IOP was found to be a risk factor for trabeculectomy failure under the qualified success criteria B and D. In the Collaborative Initial Glaucoma Treatment Study (CITGS), higher baseline IOP was associated with higher IOP during the 9 years of follow-up.[16] Patients with high baseline IOP have low outflow facility at the trabecular meshwork. The small decrease in the filtering outflow through the trabeculectomy site might cause a large fluctuation of IOP during follow-up, because the poor outflow facility through the meshwork cannot counter the IOP fluctuation.

In our study, 116 eyes (14.0%) had glaucoma secondary to uveitis. There is a recent report showing that trabeculectomy with MMC was less effective in maintaining IOP reduction in glaucoma associated with uveitis than in POAG eyes.[9] Iwao et al[9] reported that the 3-year probabilities of success after trabeculectomy were 71.3% and 89.7% for uveitic glaucoma and POAG, respectively. However, secondary glaucoma was not a risk factor for surgical failure in our study. Granulomatous uveitis was one of the risk factors for failure in the study by Iwao et al.[9] The cause of uveitis in our study might be different from that in the previous study.

Trabeculectomy has a moderate rate of success, ranging from 36% to 96%, with lower success rates seen in younger children.[29–34] In our study, 23 eyes had developmental glaucoma. The age of patients with a diagnosis of developmental glaucoma was 41.2±16.2 (range, 16–69) years. All patients with developmental glaucoma in our study might have late-onset disease; thus it might be more appropriately called juvenile glaucoma. Pathania et al[34] reported that the probabilities of complete and qualified success in juvenile glaucoma were 89% and 96% at 5 years, respectively. We could not show the effect of glaucoma subtype on surgical results. Fontana et al[19] also reported that the glaucoma subtype was not associated with a risk of failure in their study. The TVT study reported that none of the baseline factors, including age, sex, race, diabetes mellitus, hypertension, lens status, number of previous intraocular surgeries, time since last intraocular surgery, glaucoma type, and preoperative number of medications, predicted the failure of trabeculectomy with MMC.[17] Needling procedures are

Table 5. Summary of the Complications

	Intraoperative Complications		Total Postoperative Complications		Early Postoperative Complications (<6 Months after Surgery)		Late Postoperative Complications (<6 Months after Surgery)	
Hyphema	3	0.36%	22	2.65%	22	2.65%	1	0.12%
Shallow anterior chamber	1	0.12%	26	3.14%	26	3.14%	1	0.12%
Wound leak	5	0.60%	28	3.38%	28	3.38%	N/A	
Bleb leak	N/A		16	1.93%	N/A		16	1.93%
Choroidal detachment	N/A		60	7.24%	47	5.67%	16	1.93%
Infection	N/A		8	0.97%	0	0%	8	0.97%
Hypotony maculopathy	N/A		26	3.14%	17	2.05%	11	1.33%
Iris capture	0	0%	3	0.36%	2	0.24%	1	0.12%
Suprachoroidal hemorrhage	0	0%	1	0.12%	1	0.12%	0	0%
Vitreous hemorrhage	0	0%	3	0.36%	0	0%	3	0.36%
Malignant glaucoma	N/A		1	0.12%	1	0.12%	0	0%
Cystoid macular edema	N/A		4	0.48%	1	0.12%	3	0.36%
Bullous keratopathy	N/A		6	0.72%	0	0%	6	0.72%
Corneal ulcer	N/A		2	0.24%	0	0%	2	0.24%
Encapsulated bleb	N/A		3	0.36%	0	0%	3	0.36%
Total	9	1%	209	23.43%	145	16.26%	71	7.96%

N/A = not available.
Early postoperative complications: onset during hospitalization after surgery or <6 months after surgery. Late postoperative complications: onset ≥6 months after surgery.

performed when the adhesion between the sclera and the conjunctiva or between the scleral flap and the scleral bed becomes firm. A need for the needling procedure indicates low filtration and can be a predictor of filtration failure.

Fontana et al[19] previously reported a 62% success rate after 3 years in phakic eyes.[19] They also found a 67% success rate after 2 years using the same success criterion in pseudophakic eyes and concluded that previous phacoemulsification cataract surgery is not a risk factor for trabeculectomy failure.[24] However, the history of cataract surgery was found to be a risk factor for trabeculectomy failure in our study. Takihara et al[35] showed that among patients with open-angle glaucoma, trabeculectomy with MMC after phacoemulsification was less successful in pseudophakic eyes than in phakic eyes. The inflammatory cytokines that appeared in the aqueous humor after phacoemulsification surgery may induce bleb failure.[36] It has been hypothesized that high monocyte chemotactic protein-1 levels in the aqueous humor enter filtration blebs through a filtration route created by the trabeculectomy, resulting in the recruitment of inflammatory cells into the bleb walls and enhanced formation of cicatricial tissue.[37]

Complications

The most frequent surgical complications in the early postoperative stage were common to many studies. We can compare our complication rate with that of the TVT study,[38] the CIGTS,[39] and Trabeculectomy in the 21st Century.[18] The prevalence of complications in our study was as follows: choroidal detachment, 7.2% (TVT study 14%, CIGTS 11%, Trabeculectomy in the 21st Century 5%); shallow anterior chamber, 3.1% (TVT study 10%, CIGTS 13%, Trabeculectomy in the 21st Century 0.9%); and anterior chamber bleeding, 2.7% (TVT study 8%, CIGTS 11%, Trabeculectomy in UK 6%). Vision-threatening late complications (>1 month after surgery) were hypotony maculopathy and bleb-related infections. The prevalence of hypotony maculopathy was 1.3% (TVT study 5%, CIGTS 0.9%, Trabeculectomy in UK 3%), and the prevalence of bleb-related infections was 0.97% (TVT study 5%, CIGTS 3.9%, Trabeculectomy in UK 1%).

Despite the difference in the study design and background of subjects, the surgical complication rates were similar. We experienced 8 bleb-related infections in 829 cases (0.97%). However, the CBIITS showed 21 bleb-related infections in 1098 eyes, with an incidence of 2.2% at the 5-year follow-up. In this study, we excluded 8 infected eyes with an observation period less than 1 year. This may be one reason for the small incidence rate of bleb-related infection in our study.

Study Limitations

The main outcome of the original study (CBIITS) was to examine the prevalence of bleb-related infections. The surgical technique was not identical among the centers or surgeons because the indication for surgery and selection of the operative procedure were at the discretion of each investigator. Each institute performed trabeculectomy using their preferred methods. We did not examine corneal thickness, which is associated with the IOP value.

We did not check the use of IOP control maneuvers in the early postoperative period, such as laser suture lysis and ocular massage, and we could not determine the cause of secondary glaucoma and developmental glaucoma. Despite this limitation, we could examine the effect of the difference in the conjunctival incision site (fornix or limbus) on the

surgical results. We found that the conjunctival incision site had a marginally significant effect ($P = 0.05$) on surgical outcome when the target pressure was <21 mmHg under complete success criteria. However, under other conditions, the difference in conjunctival incision site did not affect the surgical results, as was reported in a meta-analysis.[25]

The success of trabeculectomy largely depends on the structure and shape of the filtering blebs.[40] We collected data on the bleb shape, height, thickness, and area of the avascular zone in this study. We will investigate the relationship between bleb shape and surgical results in the future.

In conclusion, the IOP-lowering effect and surgical complication rates in the follow-up period in CBIITS were comparable with the results of recent randomized multicenter studies.[12–18] The number of previous glaucoma surgeries, preoperative lens status, and preoperative IOP were associated with the rate of achievement of the target IOP. The needling procedure was always associated with the risk of failure regardless of IOP. These results can be used as a benchmark for IOP-reduction surgery in Asia, including Japan.

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Abbreviations and Acronyms:
CBIITS = Collaborative Bleb-Related Infection Incidence and Treatment Study; **CIGTS** = Collaborative Initial Glaucoma Treatment Study; **IOP** = intraocular pressure; **MMC** = mitomycin C; **POAG** = primary open-angle glaucoma; **TVT** = Tube Versus Trabeculectomy.

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