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Effectiveness of trabeculectomy with mitomycin C for glaucomatous eyes with low intraocular pressure on treatment eye drops

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ABSTRACT.
Purpose: **To examine the efficacy and safety of current trabeculectomy with mitomycin C in Japan for glaucomatous eyes with low intraocular pressure (IOP).**
Methods: **Two hundred ninety-four eyes of 294 patients with IOP ≤21 mmHg before surgery were studied; all patients were participants in the Collaborative Bleb-related Infection Incidence and Treatment Study (CBIITS), a multicentre, prospective, cohort study conducted at 34 ophthalmological institutions throughout Japan. All eyes had an intraocular pressure ≤ 21 mmHg and had undergone trabeculectomy alone or phacotrabeculectomy. Two success criteria were used: Criterion A comprised 20% reduction of baseline IOP and Criterion B comprised 30% reduction of baseline IOP. The primary outcome was the success rate for each of these criteria.**
Results: **The qualified success rates were 87.3% for Criterion A and 42.0% for Criterion B at 5 years. Mean IOP was significantly reduced, from 16.7 ± 2.7 to 11.6 ± 4.0 mmHg at 5 years after trabeculectomy ($p < 0.0001$); the number of anti-glaucoma medications significantly decreased from 2.7 ± 1.1 to 1.0 ± 1.2 ($p < 0.0001$) at 5 years after the surgery. Three or more trabeculectomies, and needling were related to increased risk of failure. Incidences of postoperative hyphema, infection, shallow anterior chamber and bleb leakage were 2.4%, 2.4%, 2.0% and 3.4%, respectively.**
Conclusions: **This study showed that trabeculectomy with mitomycin C is an effective procedure with few surgical complications for reducing IOP in patients, even if preoperative IOP was within the normal range.**

Key words: complication – efficacy – intraocular pressure – trabeculectomy

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Introduction

Reducing intraocular pressure (IOP) is an important method for treating glaucoma. However, even if IOP is controlled at ≤ 21 mmHg, visual field loss may progress in some patients. Surgery is performed when IOP cannot be sufficiently reduced to maintain the visual field of glaucoma subjects by IOP-lowering medications (Jongsareejit et al. 2005; Aoyama et al. 2010). Trabeculectomy with mitomycin C (MMC) is the most common surgical procedure used to lower IOP. Thus, it is important to know the performance of trabeculectomy among subjects who exhibit IOP within normal range and its complications. Trabeculectomy on eyes with normal IOP reportedly exhibits risks of hypotony, hypotony maculopathy and choroidal effusion, especially in eyes with very low IOP (Hagiwara et al. 2000; Membrey et al. 2000; Jongsareejit et al. 2005).

The Collaborative Bleb-related Infection Incidence and Treatment Study (CBIITS) was a 5-year multicentre prospective study involving institutions at which board members of the Councilors of the Japan Glaucoma Society were staff physicians (Yamamoto et al. 2014; Sugimoto et al. 2015). The purpose of this collaborative study was to determine the incidences of bleb-related infections and postoperative complications after trabeculectomy in normal-tension and high-tension glaucomatous eyes. Among 1098 eyes that were studied, 2.2% developed infections during the 5-year follow-up period. Among the 1249 eyes that were enrolled, 294 eyes exhibited primary open-angle glaucoma with IOP ≤ 21 mmHg, including eyes with normal-tension glaucoma (NTG).

The purpose of this study was to determine the effectiveness of trabeculectomy in lowering the IOP of eyes in which IOP was within the normal range (10–21 mmHg) before surgery. To accomplish this, we reviewed the data of eyes that were part of the CBIITS, in which baseline IOP was ≤ 21 mmHg with or without medications. We determined the success rates, factors that affected the success rate and incidence of complications after trabeculectomy.

Methods

The enrolment period for the 5-year CBIITS was begun in 2004, and post-operative evaluations were performed at 6-month intervals for 5 years. We obtained informed consent from all patients, as well as institutional review board approval at all 34 institutions. The study was performed in accordance with the Declaration of Helsinki. The participating ophthalmologists were members of the Japan Glaucoma Society, and IRB approval was prospectively obtained to assess post-operative complications and interventions performed during the 5-year postoperative period. The criteria and methods used to classify complications were decided by each surgeon.

If both eyes in a patient were suitable for analyses, the data of the eye that first underwent operation were used for analyses. The indications for glaucoma surgeries, as well as surgical techniques and postoperative management, were determined by the individual surgeons at each clinical centre. mitomycin C (MMC) was used in all eyes.

Among the 1249 eyes, there were 294 eyes with primary open-angle glaucoma with IOP ≤ 21 mmHg with medical treatment, regardless of previous surgical history. The data from these 294 eyes were analysed for our study. The primary outcome measure of trabeculectomy was the success rate according to defined criteria. The secondary outcomes were IOP, factors associated with surgical failure and incidence of surgical complications. The Goldman applanation tonometer was used to measure IOP, which was measured every 6 months for 5 years after trabeculectomy. Measurement of IOP was performed by each physician. Preoperative IOP was regarded as the mean IOP measure at three visits prior to the surgery.

Classifications of surgical results

The Collaborative Normal-Tension Glaucoma Study reported that lowering IOP by ≥ 30% (relative to preoperative IOP) resulted in 20% of the eyes showing progression of visual field disorders, compared with 60% of the eyes that showed progression of visual field disorder if left untreated (The Collaborative Normal-Tension Glaucoma Study Group 1998). Based on these results, we divided our patients into those who showed reduction of IOP by Criterion A (20% reduction of IOP) and those who showed reduction of IOP by Criterion B (30% reduction). Because we could not determine IOP without anti-glaucoma medications, our subjects included both NTG and high-tension primary open-angle glaucoma patients with controlled IOP of ≤ 21 mmHg with medication. Success was further defined as 'qualified success' when the reduction in IOP required anti-glaucoma medications; 'complete success' was defined as IOP reduction without topical medications. The performance of needling, conjunctival re-suturing or cataract surgery was not included in the definition of complete success. Surgical failure was defined as encountered hypotony of < 5 mmHg at two consecutive measurements, a need for reoperation due to elevated IOP, or a loss of light perception. The numbers of postoperative complications and changes in the number of postoperative IOP medications were analysed.

Statistical analyses

Kaplan–Meier survival curves were used to determine the success of the trabeculectomy, and Cox proportional hazard, univariate analysis, multivariate analysis and *t*-tests were used to determine the significance of postoperative changes relative to baseline values. JMP software, version 9 (SAS Inc, Cary, NC, USA), was used for statistical analyses, and $p < 0.05$ was considered to be significant.

Results

The demographics of the patients at the baseline are shown in Table 1. Two hundred ninety-four eyes of 294 patients were analysed (Fig. 1). There were 156 men and 138 women whose

Table 1. Demographics and preoperative ocular characteristics.

Total case number	294	
Mean age, years (±SD)	63.3	(±12.4)
Mean follow-up, months (±SD)	55.3	(±11.1)
Mean preoperative IOP mmHg (±SD)	16.7	(±2.7)
Mean preoperative visual acuity (±SD)	0.8	(±0.4)
Mean preoperative medications (±SD)	2.7	(±1.2)
Laterality		
Right	154	52.40%
Left	140	47.60%
Sex		
Male	156	53.10%
Female	138	46.90%
Previous cataract surgeries	54	18.37%
Previous glaucoma surgeries		
0	258	87.80%
1	28	9.50%
2 or more	7	2.40%
Unknown	1	0.30%
Lens status		
Phakia	240	81.60%
Aphakia	5	1.70%
Pseudophakia	48	16.30%
Unknown	1	0.30%
Conjunctival incision		
Limbal base	180	61.22%
Fornix base	114	38.78%
Surgical technique		
Trabeculectomy	244	83.0%
Phacotrabeculectomy	50	17.0%

IOP = intraocular pressure.

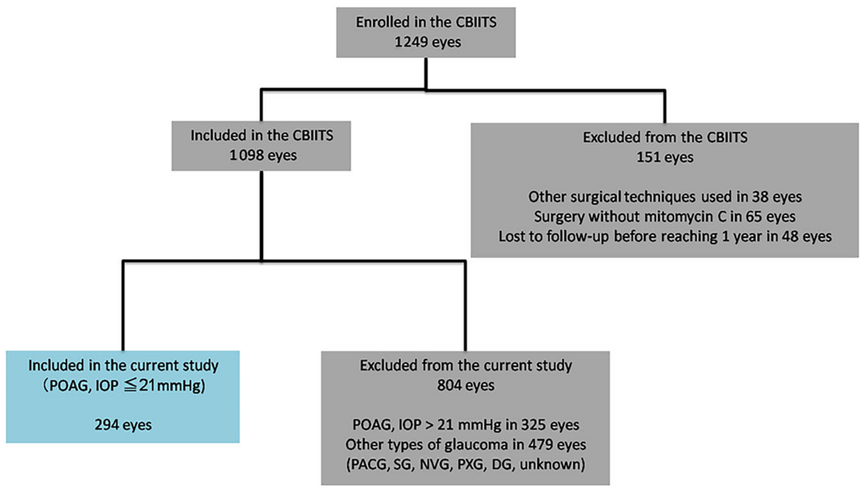

Fig. 1. Flow chart showing the numbers of patients who were enrolled and analysed. CBIITS = Collaborative Bleb-related Infection Incidence and Treatment Study; DG = developmental glaucoma; IOP = intraocular pressure; NVG = neovascular glaucoma; PACG = primary angle-closure glaucoma; POAG = primary open-angle glaucoma; PXG = pseudoexfoliation glaucoma.

average age was 63.3 ± 12.4 years (± standard deviation). The average observation period was 55.3 ± 11.1 months; the right eye of 154 patients and the left eye of 140 patients were studied. There were 258 eyes without prior glaucoma surgery and 36 eyes with prior glaucoma surgery. The conjunctival incision was performed in 180 eyes with limbal base incision and 114 with fornix base incision. Two hundred forty-four eyes underwent trabeculectomy alone, whereas 50 eyes underwent phacotrabeculectomy. The mean IOP before surgery was 16.7 ± 2.7 mmHg; IOP was 10.6 ± 3.8 mmHg at 12 months, 11.3 ± 3.8 mmHg at 24 months, 11.6 ± 4.0 mmHg at 36 months, 11.5 ± 3.8 mmHg at 48 months and 11.6 ± 4.0 mmHg at 60 months. The IOP decreased significantly relative to baseline IOP at all postoperative times (Fig. 2).

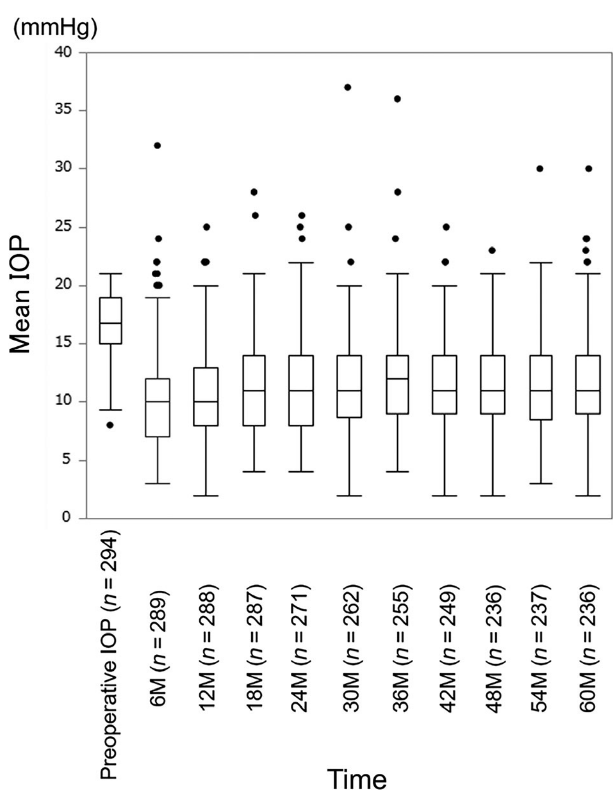

Fig. 2. Box plot of intraocular pressure (IOP) versus 11 observation time-points. The medians and the 25th and 75th percentiles of the IOP are plotted. Dashes denote outliers. The graph shows a significant reduction in the IOP after trabeculectomy.

The average number of medications used before surgery was 2.72 ± 1.18 (median, 3; range, 0–6); this value included 24 patients taking oral acetazolamide. The average number of medications used after surgery was 1.01 ± 1.21 (median, 0; range, 0–4) (Fig. 3).

The qualified success rates at 1 year were 94.9% for eyes in the Criterion A group and 74.1% for eyes in the Criterion B group; at 5 years, these rates were 87.3% for eyes in the Criterion A group and 42.0% for eyes in the Criterion B group. The complete success rates at 1 year were 72.2% for eyes in the Criteria A group and 63.3% for eyes in the Criteria B group. After 5 years, the respective percentages of patients who obtained an IOP reduction of ≥ 20% or ≥ 30% were 44.4% and 28.9% (Figs 4 and 5).

Intraoperative complications comprised one patient with rupture of the posterior capsule; none had hyphema or shallow anterior chamber. Both early and late postoperative complications comprised seven eyes with hyphema (2.4%), seven eyes with infection (2.4%), six eyes with shallow anterior chamber (2.0%), 10 eyes with bleb leakage (3.4%), six eyes with choroidal detachment (2.0%) and eight eyes with hypotony (2.7%; Table 2).

Better results were obtained in eyes with higher baseline IOP. The patient age, patient sex, and laterality of the surgery, and location of the conjunctival incision were not significantly correlated with the success of the surgery. (Table 3) There was no significant effect of prior cataract surgery or trabeculectomy combined with cataract surgery on surgical success. (Table 3) Twenty-nine patients required postoperative needling. Needling was high risk in Criteria A and B. Results were improved with reduction of needling procedures (Needling: p < 0.001 for association with the complete success rate of Criterion A; Table 4). Results were improved with a reduced number of preoperative glaucoma surgeries (p = 0.03; Fig. 6).

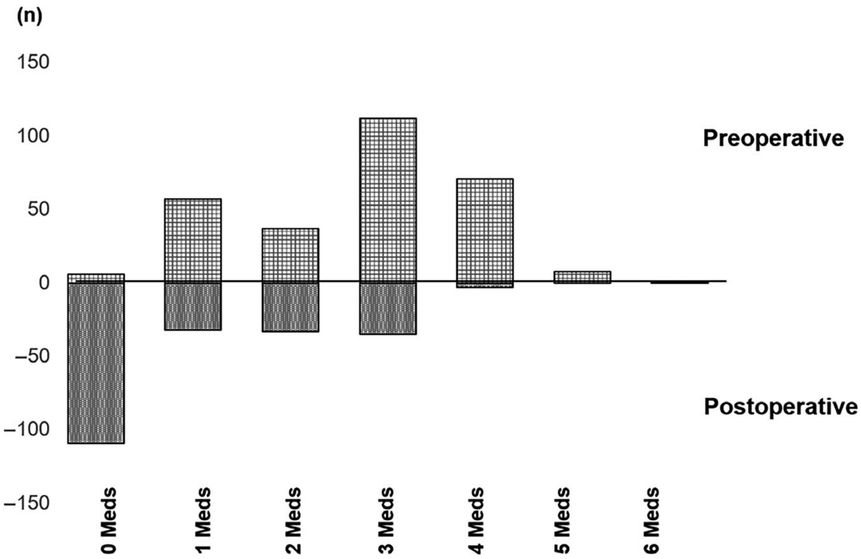

Fig. 3. Bar graph showing the numbers of preoperative (top) and postoperative medications (Meds; bottom). The number of anti-glaucoma medications decreased significantly after surgery ($p < 0.001$).

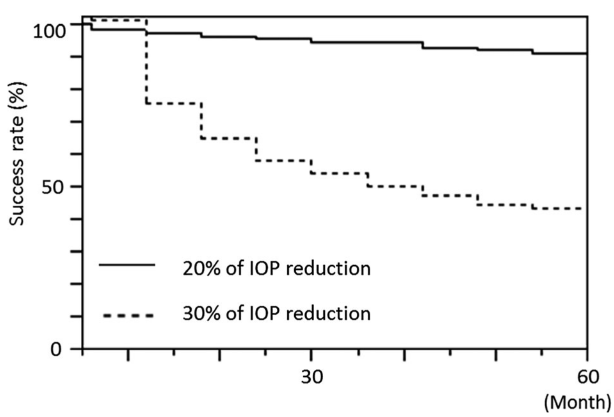

Fig. 4. Kaplan–Meier survival curve showing the qualified success rates of the two intraocular pressure (IOP) criteria: 20% reduction of baseline IOP and 30% reduction of baseline IOP.

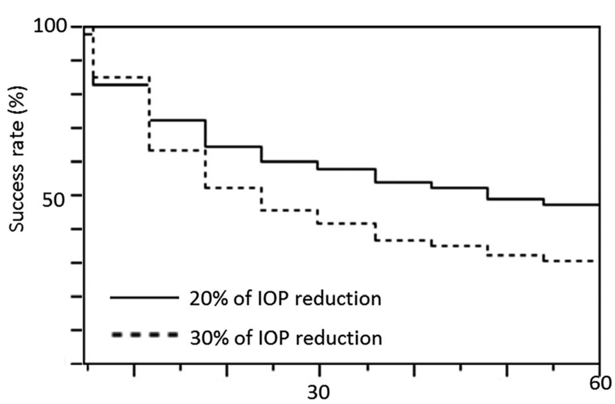

Fig. 5. Kaplan–Meier survival curve showing the complete success rates of the two intraocular pressure (IOP) criteria: 20% reduction in baseline IOP and 30% reduction in baseline IOP.

Discussion

Several studies have reported on the long-term changes in IOP after trabeculectomy on eyes with NTG. Jongsareejit et al. (2005) analysed 39 eyes of Japanese patients and reported that the final mean IOP was 11.1 ± 1.3 mmHg; this was a reduction of 30.1% from the baseline IOP of 15.9 ± 1.9 mmHg after trabeculectomy with MMC, which persisted for up to 4 years after trabeculectomy. For an IOP reduction of ≥ 20% with surgery, the rate was 41.3% after 4 postoperative years; for an IOP reduction of ≥ 30%, the rate was 39.4% during the same period. Schultz et al. (2016) performed trabeculectomy on 30 eyes of 28 glaucomatous patients with a mean baseline IOP of ≤ 15 mmHg. They reported that 68% of the patients showed postoperative IOP reduction by ≥ 20% of the baseline IOP at 8 years with medication. For IOP reduction by ≥ 30%, the qualified success rate was 45% at 8 years. None showed progression of visual field defects. Jayaram et al. (2016) performed trabeculectomy on 131 eyes of 98 patients with NTG. The preoperative mean IOP was 14.7 ± 1.9 mmHg; those investigators were able to control IOP for 4 years at 10.2 ± 2.1 mmHg with medication. Intraocular pressure (IOP) reduction of > 30% was achieved in 62% of 131 NTG patients, which was higher than the success rate in the present study. One possible source of this difference may be a discrepancy in fibrotic reactions after trabeculectomy between Japanese patients and European patients. Another possible source of difference may be that the study by Jayaram et al. (2016) excluded patients who underwent phacotrabeculectomy. Notably, Ogata-Iwao et al. (2013) previously reported that phacotrabeculectomy resulted inadequate IOP reduction, compared with trabeculectomy alone.

Complications

Wound leakage developed in 2.4% of the patients within 1 month after surgery. This was followed by choroid detachment and shallow anterior chamber in 1.7% and 1.02% of the patients, respectively. Wound leakage is important because it can lead to very low IOP and bleb failure in the late phase. In eyes with high IOP, wound leakage was reported in 11% in the Tube Versus Trabeculectomy (TVT) study, 14% in the Trabeculectomy in the 21st Century Study and 6% in the Collaborative Initial Glaucoma Treatment Study (CIGTS) (Jampel et al. 2001; Gedde et al. 2012; Kirwan et al.

Table 2. Summary of complications after surgery.

	Total case (%)	Early (≤1 month) (%)	Late (>1 month) (%)
Hyphema	7 (2.4)	7 (2.4)	0
Infection	7 (2.4)	0	7 (2.4)
Shallow anterior chamber	6 (2.0)	3 (1.0)	3 (1.0)
Bleb leak	10 (3.4)	7 (2.4)	3 (1.0)
Choroidal detachment	6 (2.0)	5 (1.7)	1 (0.3)
Hypotony	8 (2.7)	N/A	8 (2.7)
Encapsulated bleb	4 (1.4)	0	4 (1.4)
Cystoid macular oedema	1 (0.3)	1 (0.3)	0
Iris capture	1 (0.3)	0	1 (0.3)
Ptosis	1 (0.3)	0	1 (0.3)
Dacryocystitis	1 (0.3)	0	1 (0.3)
Total	44 (14.8)	23 (7.8)	21 (7.0)

N/A = not available.

2013). Choroidal detachment was present in 13% of the eyes in the TVT study, 5% in the Trabeculectomy in the 21st Century Study and 11% in the CIGTS (Jampel et al. 2001; Gedde et al. 2012; Kirwan et al. 2013). A shallow anterior chamber was found in 10% of the eyes in the TVT study, 0.9% in the Trabeculectomy in the 21st Century Study and 13% in the CIGTS (Jampel et al. 2001; Gedde et al. 2012; Kirwan et al. 2013). In our study, the frequency of early complications was relatively low, at 7.8% (Table 2).

In our study, the frequency of late complications was 7.0%. The most often late complication was infection at 2.4%. Infections were present in 2.4% of the eyes in the TVT study, 1% in the Trabeculectomy in the 21st Century study, 6% in the CIGTS and 2.2% in the CBIITS during the late phase after glaucoma surgery. Regardless of preoperative IOP, infections occurred at a certain frequency after trabeculectomy.

If IOP is low after trabeculectomy, patients experience a risk of hypotony and its associated complications, including hypotony maculopathy, choroidal detachment and cataract development (Hagiwara et al. 2000; Musch et al. 2008). Among our 294 eyes, none had hypotony maculopathy, three (1.02%) exhibited a shallow anterior chamber for > 1 month postoperatively and one showed choroidal detachment. In previous reports on NTG, late hypotony occurred in 0.8–30% of the eyes (Membrey et al. 2000; Higashide et al. 2016; Jayaram et al. 2016; Schultz et al. 2016). Our rate of complications was not higher than that in other reports, and we speculate that the target IOP after trabeculectomy might have been too low in the study (Schultz et al. 2016).

Risk factors for surgical failure

The number of prior glaucoma surgeries, preoperative lens status and preoperative low IOP was significantly associated with achieving success based on Criterion A. Bleb needling was associated with a risk of not attaining either Criterion A or B (Table 3). We suspected that needling treatment

Table 3. Univariate Cox proportional hazard ratios for risk factors of failure to achieve qualified and complete success after surgery.

	The complete success rate of criteria A			The qualified success rate of criteria A			The complete success rate of criteria B			The qualified success rate of criteria B		
	RR	p value	95% CI	RR	p value	95% CI	RR	p value	95% CI	RR	p value	95% CI
Age per year	1.04	0.04	0.98–1.11	1.01	0.67	0.97–1.03	1.01	0.08	0.99–1.02	1.01	0.27	0.99–1.02
Preoperative IOP per mmHg	1.02	0.12	0.96–1.09	1.06	0.33	0.94–1.21	0.96	0.10	0.91–1.01	0.87	<0.001	0.83–0.92
Laterality												
Right	1			1			1			1		
Left	0.79	0.16	0.57–1.09	0.72	0.36	0.36–1.43	1.01	0.97	0.76–1.33	0.92	0.61	0.68–1.25
Sex												
Male	1			1			1			1		
Female	0.97	0.85	0.70–1.33	0.91	0.79	0.46–1.79	0.98	0.91	0.74–1.30	1.14	0.39	0.84–1.55
Number of previous glaucoma surgeries												
0	1			1			1			1		
1	0.87	0.63	0.47–1.48	1.05	0.92	0.25–2.99	0.86	0.56	0.50–1.38	0.90	0.72	0.50–1.51
2 or more	4.30	0.002	1.80–8.68	4.23	0.04	1.01–11.94	3.67	0.005	1.55–7.32	1.42	0.47	0.50–3.11
2 or more/1[†]	4.93	0.002	1.83–12.17	3.99	0.10	0.74–21.57	4.24	0.004	1.63–9.90	1.56	0.41	0.50–4.08
Lens status												
Phakia	1			1			1			1		
Pseudophakia	1.77	0.005	1.18–2.58	0.87	0.78	0.29–2.07	1.35	0.11	0.92–1.93	0.99	0.99	0.64–1.49
Conjunctival incision												
Limbal base	1			1			1			1		
Fornix base	1.16	0.38	0.83–1.5	1.51	0.23	0.76–2.97	1.13	0.39	0.85–1.50	1.35	0.06	0.98–1.84
With/without cataract surgery												
TLE only	1			1			1			1		
TLE with cataract surgery	1.16	0.46	0.76–1.73	0.62	0.34	0.18–1.58	1.37	0.09	0.94–1.93	1.25	0.26	0.83–1.84
Bleb needling												
Without	1			1			1			1		
With	3.29	<0.001	2.06–5.03	2.98	0.02	1.19–6.50	2.39	<0.001	1.53–3.60	2.15	0.002	1.33–3.31

CI = confidence interval; RR = risk ratio; TLE = trabeculectomy.
[†]Comparison of 1 and 2 or more.

Table 4. Multivariate Cox proportional hazard ratios for risk factors of failure to achieve qualified and complete success after surgery.

	The complete success rate of criteria A			The qualified success rate of criteria A			The complete success rate of criteria B			The qualified success rate of criteria B		
	RR	p value	95% CI	RR	p value	95% CI	RR	p value	95% CI	RR	p value	95% CI
Age per year	1.00	0.75	0.98–1.01	1.00	0.76	0.97–1.03	1.00	0.53	0.99–1.01	1.00	0.35	0.99–1.01
Preoperative IOP per mmHg	1.03	0.27	0.97–1.10	1.05	0.41	0.92–1.21	0.94	0.05	0.89–0.99	0.86	<0.001	0.81–0.91
Number of previous glaucoma surgeries												
0	1			1			1			1		
1	0.75	0.35	0.38–1.34	1.23	0.74	0.28–3.79	0.94	0.83	0.53–1.57	1.13	0.68	0.60–1.95
2 or more	3.51	0.007	1.46–7.16	3.66	0.07	0.86–10.64	3.86	0.004	1.61–7.82	1.48	0.42	0.51–3.32
2 or more/1†	4.66	0.004	1.71–11.83	2.95	0.20	0.53–16.38	4.08	0.006	1.55–9.74	1.30	0.62	0.41–3.52
Lens status												
Phakia	1			1			1			1		
Pseudophakia	1.97	0.004	1.25–3.02	0.86	0.78	0.27–2.27	1.37	0.13	0.90–2.02	1.05	0.83	0.65–1.61
Bleb needling												
Without	1			1			1			1		
With	3.40	<0.001	2.10–5.29	2.63	0.04	1.04–5.83	2.44	<0.001	1.55–3.72	2.27	0.001	1.38–3.54

CI = confidence interval; RR = risk ratio; TLE = trabeculectomy.
†Comparison of 1 and 2 or more.

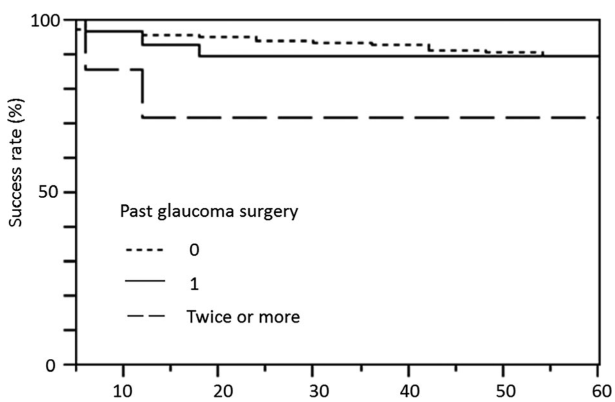

Fig. 6. Kaplan–Meier survival curve showing the qualified success rates of criteria A (20% of IOP reduction) of the first, second and the third or more trabeculectomy groups. There were significant differences among the groups (p = 0.03, Wilcoxon test).

would lower IOP. However, some patients developed low IOP in a short period of time. We speculate that IOP did not decrease sufficiently because wound healing may have already been strong in our study population. For successful filtration surgery, an appropriate amount of filtration might be necessary, beginning in the early stage. High preoperative IOP has been reported as a risk factor for poor IOP control (Sugimoto et al. 2015). In the CITGS, higher baseline IOP was associated with higher IOP during the 9-year follow-up period (Musch et al. 2008). In contrast, low preoperative IOP made it difficult to achieve IOP reduction of ≥ 30% in our patients. It is difficult for subjects with low baseline IOP to achieve much lower IOP without experiencing complications related to low IOP (Schultz et al. 2016).

Awai-Kasaoka et al. (2013) reported that a short interval between glaucoma surgeries and the number of prior trabeculectomies constituted factors that were significantly associated with failures of subsequent trabeculectomies with MMC. Law et al. (2009) also reported that a repeat trabeculectomy with MMC was less successful in achieving reduction of IOP, relative to the initial trabeculectomy with MMC, in eyes with open-angle glaucoma. Indeed, we found that the number of previous glaucoma surgeries influenced the success rate, as determined by the target IOP.

There were some limitations in this study. First, the surgical technique for trabeculectomy was not consistent among all patients because the indications for surgery and operative procedures used were chosen at the discretion of each investigator. Thus, surgeons performed trabeculectomy using their preferred methods. Second, because the data used in our study were originally collected to examine the incidence of filtration bleb infections, information regarding visual field or postoperative procedures was not properly collected. Therefore, we do not know whether it was possible to slow or halt the progression of visual field loss by trabeculectomy in our subjects. Many patients may continue to experience disease progression, although they have IOP within the normal range (Shiose et al. 1991; Anderson et al. 2003). Many studies (Aoyama et al. 2010; Jayaram et al. 2016; Schultz et al. 2016; Naito et al. 2017; Oie et al. 2017) have shown that trabeculectomy can significantly reduce IOP and prevent progression of visual field disorders. We presume that maintenance of visual function can be expected when trabeculectomy is performed in glaucoma patients with IOP maintained in the normal range by topical medications. However, Kashiwagi et al. (2016) reported that visual function may deteriorate, despite effective control of IOP after trabeculectomy.

In conclusion, our results indicate that baseline IOP can be lowered by ≥ 20% in eyes with IOP within the normal range; this can be achieved with relatively minor complications. Thus, we conclude that trabeculectomy can be performed safely in eyes with IOP ≤ 21 mmHg.

References

Anderson DR, Drance SM & Schulzer M (2003): Factors that predict the benefit of lowering intraocular pressure in normal tension glaucoma. Am J Ophthalmol **136**: 820–829.

Aoyama A, Ishida K, Sawada A & Yamamoto T (2010): Target intraocular pressure for stability of visual field loss progression in normal-tension glaucoma. Jpn J Ophthalmol **54**: 117–123.

Awai-Kasaoka N, Inoue T, Inatani M, Takihara Y, Ogata-Iwao M & Tanihara H (2013): Prognostic factors in trabeculectomy with mitomycin C having history of previous glaucoma surgery. Jpn J Ophthalmol **57**: 514–519.

Gedde SJ, Herndon LW, Brandt JD, Budenz DL, Feuer WJ & Schiffman JC (2012): Postoperative complications in the Tube Versus Trabeculectomy (TVT) study during five years of follow-up. Am J Ophthalmol **153**: 804–814.

Hagiwara Y, Yamamoto T & Kitazawa Y (2000): The effect of mitomycin C trabeculectomy on the progression of visual field defect in normal-tension glaucoma. Graefes Arch Clin Exp Ophthalmol **238**: 232–236.

Higashide T, Ohkubo S, Sugimoto Y, Kiuchi Y & Sugiyama K (2016): Persistent hypotony after trabeculectomy: incidence and associated factors in the Collaborative Bleb-Related Infection Incidence and Treatment Study. Jpn J Ophthalmol **60**: 309–318.

Jampel HD, Quigley HA, Kerrigan-Baumrind LA, Melia BM, Friedman D & Barron Y (2001): Risk factors for late-onset infection following glaucoma filtration surgery. Arch Ophthalmol **119**: 1001–1018.

Jayaram H, Strouthidis NG & Kamal DS (2016): Trabeculectomy for normal tension glaucoma: outcomes using the Moorfields Safer Surgery technique. Br J Ophthalmol **100**: 332–338.

Jongsareejit B, Tomidokoro A, Mimura T, Tomita G, Shirato S & Araie M (2005): Efficacy and complications after trabeculectomy with mitomycin C in normal-tension glaucoma. Jpn J Ophthalmol **49**: 223–227.

Kashiwagi K, Kogure S, Mabuchi F, Chiba T, Yamamoto T, Kuwayama Y & Araie M (2016): Change in visual acuity and associated risk factors after trabeculectomy with adjunctive mitomycin C. Acta Ophthalmol **94**: e561–e570.

Kirwan JF, Lockwood AJ, Shah P, Macleod A, Broadway DC, King AJ, McNaught AI & Agrawal P (2013): Trabeculectomy in the 21st century: a multicenter analysis. Ophthalmology **120**: 2532–2539.

Law SK, Shih K, Tran DH, Coleman AL & Caprioli J (2009): Long-term outcomes of repeat vs initial trabeculectomy in open-angle glaucoma. Am J Ophthalmol **148**: 685–695.

Membrey WL, Poinoosawmy DP, Bunce C & Hitchings RA (2000): Glaucoma surgery with or without adjunctive antiproliferatives in normal tension glaucoma: intraocular pressure control and complications. Br J Ophthalmol **84**: 586–590.

Musch DC, Gillespie BW, Niziol LM, Cashwell LF & Lichter PR (2008): Factors associated with intraocular pressure before and during 9 years of treatment in the Collaborative Initial Glaucoma Treatment Study. Ophthalmology **115**: 927–933.

Naito T, Fujiwara M, Miki T et al. (2017): Effect of trabeculectomy on visual field progression in Japanese progressive normal-tension glaucoma with intraocular pressure < 15 mmHg. PLoS One **12**(8): e0184096.

Ogata-Iwao M, Inatani M, Takihara Y, Inoue T, Iwao K & Tanihara H. (2013): A prospective comparison between trabeculectomy with mitomycin C and phacotrabeculectomy with mitomycin C. Acta Ophthalmol **91**: e500–e501.

Oie S, Ishida K & Yamamoto T (2017): Impact of intraocular pressure reduction on visual field progression in normal-tension glaucoma followed up over 15 years. Jpn J Ophthalmol **61**: 314–323.

Schultz SK, Iverson SM, Shi W & Greenfield DS (2016): Safety and efficacy of achieving single-digit intraocular pressure targets with filtration surgery in eyes with progressive normal-tension glaucoma. J Glaucoma **25**: 217–222.

Shiose Y, Kitazawa Y, Tsukahara S, Akamatsu T, Mizokami K, Futa R, Katsushima H & Kosaki H (1991): Epidemiology of glaucoma in Japan: a nationwide glaucoma survey. Jpn J Ophthalmol **35**: 133–155.

Sugimoto Y, Mochizuki H, Ohkubo S, Higashide T, Sugiyama K & Kiuchi Y (2015): Intraocular pressure outcomes and risk factors for failure in the Collaborative Bleb-Related Infection Incidence and Treatment Study. Ophthalmology **122**: 2223–2233.

The Collaborative Normal-Tension Glaucoma Study Group (1998): The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am J Ophthalmol **126**: 498–505.

Yamamoto T, Sawada A, Mayama C, Araie M, Ohkubo S, Sugiyama K & Kuwayama Y (2014): The 5-year incidence of bleb-related infection and its risk factors after filtering surgeries with adjunctive mitomycin C: collaborative bleb-related infection incidence and treatment study 2. Ophthalmology **121**: 1001–1016.

Appendix

Group institutions are provided below:

Gifu University Graduate School of Medicine, Nippon Telegraph and Telephone Corporation West, Kyushu General Hospital, Tokyo Metropolitan Police Hospital, Osaka Medical College, Osaka Koseinenkin Hospital, Tokyo Teishin Hospital, Graduate School of Medical and Dental Sciences, Niigata University, Kobe University Graduate School of Medicine, University of Occupational and Environmental Health, Juntendo University School of Medicine, St. Marianna University School of Medicine, Kanazawa University Graduate School of Medical Science, Mie University Graduate School of Medicine, Kansai Medical University, Japan Red Cross Hospital, Jikei University School of Medicine, Yokohama Municipal Citizen's Hospital, Keio University School of Medicine, The University of Tokyo Graduate School of Medicine, JR Tokyo General Hospital, Saga University Faculty of Medicine, Kitasato University Hospital, Akita University School of Medicine, University of Yamanashi Faculty of Medicine, Teikyo University School of Medicine, Hiroshima University Graduate School of Biomedical Science, University of Ryukyus, Faculty of Medicine, Kumamoto University Graduate School of Medical Sciences, Ogaki Municipal Hospital, Nihon University School of Medicine, Kyoto Prefectural University of Medicine, Nakano General Hospital, Tokai University School of Medicine, and Osaka University Medical School.

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