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TABLES

Table 1. Selective inhibitory effect of Y-39983 on ROCK

Compounds	IC_{50} μM		
	ROCK	PKC	CaMKII
Y-39983	0.0036 (0.0025 - 0.0051)	0.42 (0.36 - 0.49) <117 times>	0.81 (0.67 - 0.97)] <225 times>
Y-27632	0.11 (0.074 - 0.17)	9.0 (7.1 - 11) <82 times>	26 (21-32) <236 times>
Staurosporine	0.0011 (0.00078 - 0.0015)	0.00026 (0.00024 - 0.00030) <0.24 times>	0.00036 (0.00033 - 0.00040) <0.33 times>

( ) ; 95% confidential limit < > ; Comparison with the value of IC_{50} of ROCK

Table 2. Effect of 0.05% of Y-39983 on outflow facility in rabbit eyes

	Outflow facility (μl/min/mmHg)	Uveoscleral outflow (μl/min)
Y-39983	0.168 ± 0.018	0.470 ± 0.034
Vehicle	0.111 ± 0.014	0.478 ± 0.031
Significance*	p<0.001	N.S.
% Change	+65.5%	-0.9%

Each value represents the means ± SE (n=10).

N.S. ; Not significant

The significance of the data was evaluated by paired t-test, one-side.

LEGENDS

Figure 1. Molecular structures of Y-27632 and Y-39983.

Figure 2. Effect of topical administration of Y-39983 on IOP in rabbit eyes.

Y-39983 or its vehicle was topically administered to one eye in rabbits. The contralateral eyes were treated with the same volume of saline (n = 5). (A) Time course of changes in IOP. (○) vehicle ; (×) 0.003% ; (●) 0.01% ; (▲) 0.03% ; (◆) 0.05% ; and (■) 0.1% Y-39983. IOPs were calculated as the difference between the value with Y-39983 or its vehicle-treated eye and the contralateral saline-treated eyes at each time point. Each value is the mean ± SE. The significance of findings was evaluated by Dunnett's test (one-sided); *p < 0.05 **p < 0.01 and ***p < 0.001, compared with the vehicle group at each time point. (B) Maximal IOP reduction. Each value is the mean + SE. The significance of findings was evaluated by Williams' test (one-sided); ***p < 0.001, compared with the vehicle group. Baseline IOP values were 20.7±0.9, 20.5±1.2, 22.9±0.6, 19.6±0.5, 22.0±0.6, and 21.5±0.7 mmHg (mean ± SE) with vehicle, 0.003%, 0.01%, 0.03%, 0.05%, and 0.1% Y-39983, respectively.

Figure 3. Effects of repeated topical administration of Y-39983 on IOP in rabbit eyes.

0.03% Y-39983 or its vehicle was topically administered to one eye in rabbits 4 times a day for 28 days (n = 6). The contralateral eyes were not treated. IOPs were measured 2 hours after administration in the morning. (○) vehicle ; (●) 0.03% Y-39983. IOPs were calculated as the difference between the value with Y-39983 or its vehicle-treated eye and the contralateral non-treated eyes at each time point. Each value is the mean ± SE. The significance of findings was evaluated by t-test (one-sided); **p < 0.01 and ***p < 0.001, compared with the vehicle group at each time point. Baseline IOP values were 20.9±0.5 and 21.0±0.5 mmHg (mean ± SE) with vehicle and 0.03% Y-39983, respectively.

Figure 4. Effects of topical administration of Y-39983 on IOP in monkey eyes.

Y-39983 or its vehicle was topically administered to one eye in monkeys. The contralateral eyes were treated with the same volume of saline (n = 5). (A) Time course of changes in IOP. (○) vehicle ; (×) 0.003% ; (●) 0.01% ; (▲) 0.03% ; and (◆) 0.05% of Y-39983 ; (□) 0.005% latanoprost. IOPs were calculated as the difference between the value with Y-39983 or its vehicle-treated eye and the contralateral saline-treated eyes at each time point. Each value is the mean +/- SE. The significance of findings was evaluated by Dunnett's test (one-sided); *$p < 0.05$ and **$p < 0.01$, compared with the vehicle group at each time point. (B) Maximal IOP reduction. Each value is the mean + SE. The significance of findings was evaluated by Williams' test (one-sided); *$p < 0.05$, and by t-test (one-sided); ###$p < 0.001$, compared with the vehicle group. Baseline IOP values were 17.8±0.2, 17.9±0.2, 17.8±0.4, 17.3±0.2, and 17.5±0.2 mmHg (mean ± SE) with vehicle, 0.003%, 0.01%, 0.03%, and 0.05% Y-39983, respectively.

Figure 5. Examples of subconjunctival hemorrhage in rabbit and monkey eyes. Y-39983 was topically administered into eyes 4 times a day (at 2-hour intervals) for 4 and 26 weeks in rabbits and monkeys, respectively. (A) A rabbit eye administered 0.03% Y-39983. (B) A monkey eye administered 0.03% Y-39983.

Figure 6. Effects of Y-39983 on morphology of HUVECs.

Phase-contrast microscopic observation of HUVECs in the same region. (A) Non-treatment, (B) Treatment with 1 μM Y-39983 for 15 minutes or (C) for 30 minutes. Arrows show contracted cells. (D) Replacement with medium without Y-39983 for 1 hour.

FIGURES

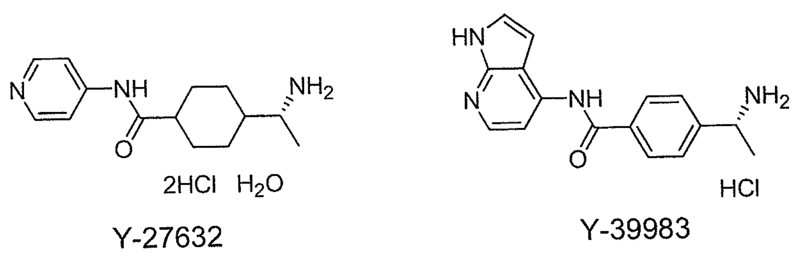

Figure 1

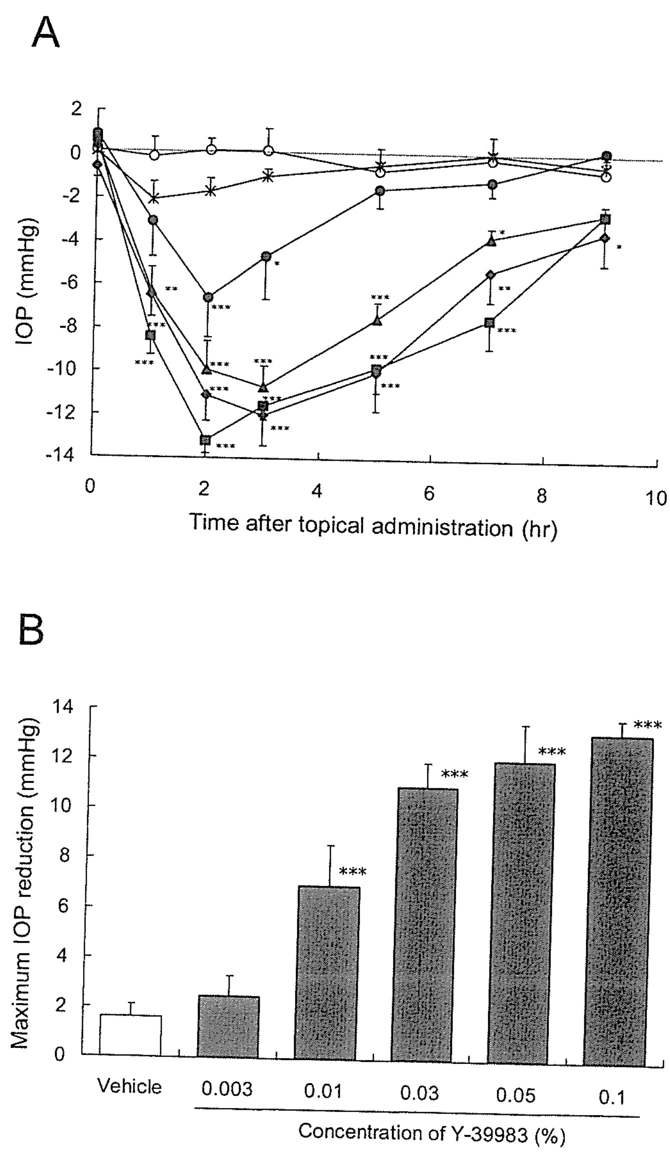
A
2
0
-2
-4
-6
-8
-10
-12
-14
IOP (mmHg)
0
2
4
6
8
10
Time after topical administration (hr)
B
14
12
10
8
6
4
2
0
Maximum IOP reduction (mmHg)
Vehicle
0.003
0.01
0.03
0.05
0.1
Concentration of Y-39983 (%)

Figure 2

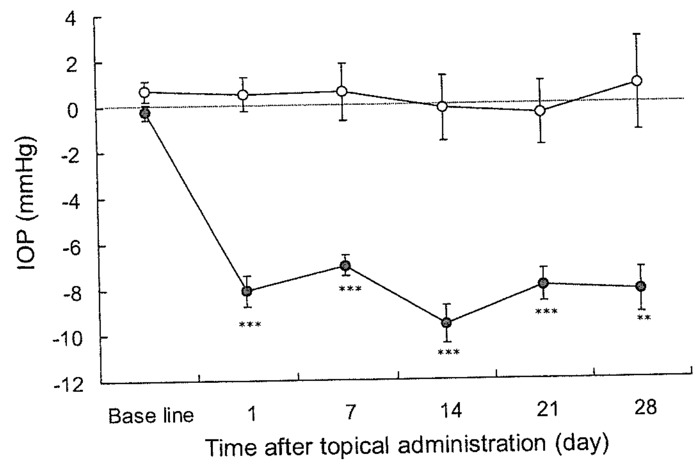
4
2
0
-2
-4
-6
-8
-10
-12
IOP (mmHg)
***
***
***
***
**
Base line
1
7
14
21
28
Time after topical administration (day)

Figure 3

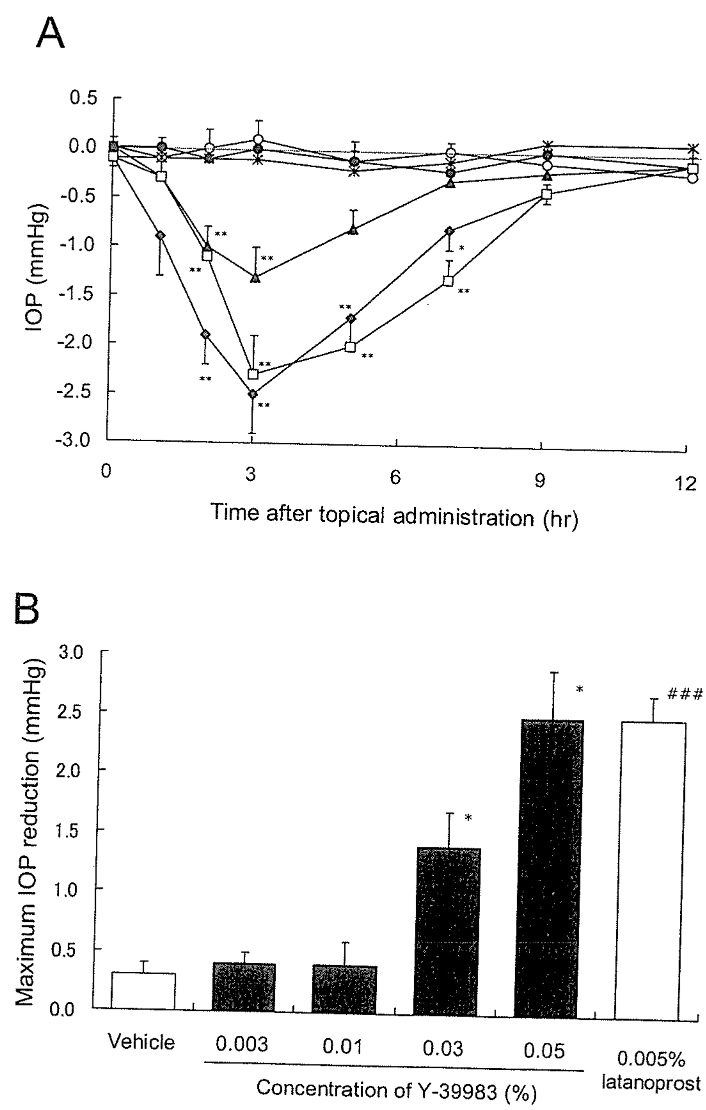
A
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
IOP (mmHg)
0
3
6
9
12
Time after topical administration (hr)
B
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Maximum IOP reduction (mmHg)
###
Vehicle
0.003
0.01
0.03
0.05
Concentration of Y-39983 (%)
0.005%
latanoprost

Figure 4

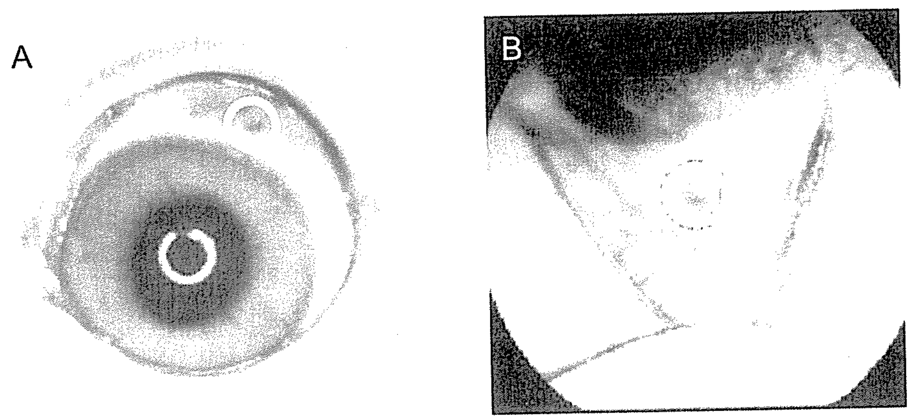

Figure 5

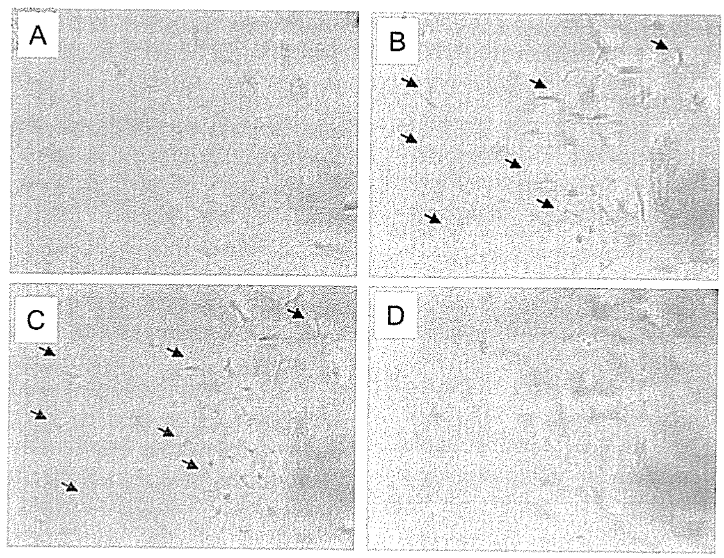

Figure 6

ORIGINAL ARTICLE

Incidence of Disc Hemorrhages in Open-angle Glaucoma Before and After Trabeculectomy

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Purpose: To investigate the effects of reduction of intraocular pressure (IOP) by surgical intervention on the frequency of disc hemorrhages in eyes with primary open-angle glaucoma (POAG) and normal-tension glaucoma (NTG).

Design: Retrospective study.

Methods: We studied 99 eyes of 99 patients with POAG and 50 eyes of 50 patients with NTG, who underwent trabeculectomy with adjunctive mitomycin C (MMC) and were followed regularly at 1 to 3-month intervals at the Glaucoma Service of Gifu University Hospital. We applied Kaplan-Meier life-table analysis for the detection of disc hemorrhages before and after trabeculectomy.

Results: Trabeculectomy significantly reduced IOP (in POAG: 19.6 ± 4.4 down to 11.1 ± 4.2 mm Hg; in NTG: 15.3 ± 1.5 down to 11.3 ± 4.5 mm Hg; mean ± SD). Life-table analysis revealed that the final cumulative probability of detecting a disc hemorrhage after surgery in POAG was 5.5 ± 2.2% (calculated probability ± SE) and was significantly lower than that (33.4 ± 7.8%) before surgery ($P < 0.0001$, log-rank test). Likewise, the final probability after surgery in NTG was 23.1 ± 6.3% and was significantly lower than that (42.1 ± 8.8%) before surgery ($P = 0.0063$, log-rank test).

Conclusions: IOP reduction via surgical intervention significantly decreases the frequency of disc hemorrhages in open-angle glaucoma patients.

Key Words: trabeculectomy, disc hemorrhage, POAG, NTG

(*J Glaucoma* 2006;15:164–171)

Disc hemorrhages were first reported by Bjerrum[1] in 1889. Since a rediscovering report by Drance[2] in 1970, a close association has been well recognized between disc hemorrhages and retinal nerve fiber layer defects in glaucomatous optic neruropathy,[3] and with the deterioration of the glaucomatous visual field changes associated with them.[4–13]

Although some investigators[14–16] had some suggestions on the mechanisms underlying disc hemorrhages in glaucomatous eyes, there are still no established theories on the subject. Begg et al[14] found similarities between disc hemorrhage and a small infarction within the optic nerve head. In an experimental study in primates, Sugiyama et al[15] showed that disc hemorrhage was a venous hemorrhage of the retina surface, and they also speculated that it originated in a retinal circulation disorder. Conversely, Quigley et al[16] suggested that it might occur secondary to stretching of the anterior capillaries with posterior bowing of the lamina cribrosa.

Many researchers believe that disc hemorrhage is a prognostic factor of glaucomatous optic neuropathy. Our research group[11,17] previously demonstrated that disc hemorrhage in normal-tension glaucoma (NTG) is the most significant factor that leads to the progression of visual field disorder. Moreover, Drance et al[18] pointed out disc hemorrhage as a factor likely to cause the progression of visual field changes alongside women and migraine in a study of 160 NTG patients.

Ocular hypotensive therapy is well known to reduce the risks of visual field progression toward glaucoma.[19,20] Therefore, if disc hemorrhage is highly implicated in the deterioration of glaucomatous visual fields, it is conceivable that the incidence of hemorrhage may change after intraocular pressure (IOP) reduction via surgical intervention. Hendrickx et al[21] studied alterations in the incidence of disc hemorrhages with antiglaucoma treatment. They found that no alterations in the incidence of disc hemorrhages were seen before and after treatment in NTG patients, as opposed to significant decreases observed in primary open-angle glaucoma (POAG) patients and glaucoma suspects.

In the present longitudinal study, we explored whether the incidences of disc hemorrhages in POAG and NTG eyes decrease as a result of IOP reduction via trabeculectomy with the intraoperative adjunctive use of MMC.

PATIENTS AND METHODS

Of a total of 404 eyes from 265 patients with POAG, and 164 eyes from 115 patients with NTG who underwent

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trabeculectomy at Gifu University Hospital between April 1990 and August 1997, patients had to meet the following criteria to be eligible for the present study: (1) preoperative follow-up period of at least 6 months, (2) postoperative period of at least 12 months, (3) reliable preoperative and postoperative perimetric test results, meaning less than 20% fixation loss and less than 33% false-positive or false-negative answers, using a Humphrey Field Analyzer (Program 30-2, Zeiss-Humphrey Instruments, Inc, San Leandro, CA), (4) abnormal Glaucoma Hemifield Test result with a mean deviation (MD) better than −20.00 dB at the time of surgery, and (5) best-corrected visual acuity better than or equal to 20/40. When both eyes of a patient fulfilled the above criteria, only the right eye was subjected to the study. This study was approved by the Institutional Review Board of Gifu University School of Medicine, and verbal informed consent was obtained from all patients.

The diagnosis of NTG was carried out based on the following criteria: (1) IOP measured with Goldmann applanation tonometry including the 24-hour diurnal curve had a peak equal to or less than 21 mm Hg in both eyes without any medication for glaucoma; (2) both eyes demonstrated a gonioscopically normal open angle; (3) at least 1 eye showed the presence of typical visual field defects corresponding to glaucomatous disc changes; and (4) neuroradiologic, rhinologic, and general medical examinations did not disclose any pathology responsible for optic nerve damage other than glaucoma. Diagnostic criteria for POAG were the same as those for NTG except for preoperative IOP, where an IOP equal to or greater than 22 mm Hg should have been recorded in at least 1 eye in our clinic or in other medical institutions.

Antiproliferative surgery was adopted when an eye was judged to have a progressive visual field defect with the maximum of tolerable medical treatments. All surgeries were performed according to a modification of Cairns technique.[22] In short, a limbal-based conjunctival incision and a 4 × 4 mm half-layer scleral flap were made; mitomycin C was then applied as described in detail elsewhere.[22] After 5 minutes, the wound was irrigated with copious amounts of balanced salt solution. Thereafter, an approximately 0.5 × 3 mm limbal block was dissected and a peripheral iridectomy was performed. The scleral flap was closed with interrupted 10-0 nylon sutures, and the anterior chamber was reformed by injecting balanced salt solution. The conjunctival wound was closed tightly with a continuous 10-0 nylon shoelace suture.

The patients were followed up regularly at the Department of Ophthalmology, Gifu University Hospital, Japan at 1 to 3-month intervals (mean 1.5 mo). At each visit, patients had ocular examinations including visual acuity, IOP measurements with a Goldmann applanation tonometer, and direct ophthalmoscopy. Visual field examinations were conducted at intervals of 3 to 12 months (mean 5.5 mo).

A disc hemorrhage was defined as an isolated hemorrhage seen on the optic disc tissue or in the peripapillary retina extending to the disc rim. Alternative causes of the hemorrhage were excluded by diagnostic testing for ischemic optic neuropathy, papillitis, central retinal vein occlusion, diabetic retinopathy, and posterior vitreous detachment. The incidence rate of disc hemorrhages was calculated from the number of all detected disc hemorrhages per patient per year, in time periods before or after trabeculectomy.

We classified the subjects into high and low postoperative IOP groups according to their postoperative IOP, to investigate the relationships between postoperative IOP and incidence of disc hemorrhages in open-angle glaucoma. Postoperative IOP was defined as an average value obtained from 5 consecutive recordings at the latest visits. High postoperative IOP in POAG patients was defined when their postoperative IOP was 15 mm Hg or above, whereas in NTG patients it was defined as a postoperative IOP exceeding 9 mm Hg. The low postoperative IOP group in POAG patients consisted of subjects whose postoperative IOP was 14 mm Hg or below, whereas that in NTG patients consisted of subjects whose postoperative IOP was below 10 mm Hg. A study by Quigley and Maumenee[23] and other reports[24,25] documented that POAG patients whose IOPs after ocular hypotensive therapy were 15 mm Hg or less had comparatively stable visual field defects. The American Academy of Ophthalmology guidelines suggest that in NTG patients the initial target IOP should be reduction from a baseline of at least 30%.[26] We set here a borderline IOP between the high and the low postoperative IOP groups in the NTG patients as 10 mm Hg, because in the present study a 30% decrease of IOP from baseline (preoperative averaged IOP in NTG patients was 15.3 mm Hg as described in the results) was calculated to be 10.71 mm Hg. In addition, we compared the detection of disc hemorrhages at postoperative stages between eyes with disc hemorrhages before surgery and those without hemorrhages.

Statistical analysis was performed using the χ^2 test, Fisher exact probability test, Mann-Whitney U test, or unpaired t test to compare the patients' demographic data in NTG and POAG cases, or in each case with and without disc hemorrhage. IOP alteration before and after surgery was analyzed by using a paired t test. The comparison in the incidence rate or prevalence of disc hemorrhages before and after surgery was analyzed by Wilcoxon signed-rank test or Fisher exact probability test. The data were also analyzed using the Kaplan-Meier life-table method using a PC-SAS (Statview for Windows version 5.0, SAS Institute Inc, Cary, NC) to calculate the cumulative probabilities of detection of disc hemorrhages per eye before and after trabeculectomy. When a disc hemorrhage was noticed, the eye was defined to have reached the end point. The survival curves were compared using a log-rank test. We calculated the probability of nondetection of the disc hemorrhages, and converted it to the probability of detecting disc hemorrhages. The cumulative incidence of patients with disc hemorrhages was based on the first disc hemorrhage observed within the follow-up period of the study. A P value less than 0.05 was considered to be significant.

RESULTS

A total of 99 eyes from 99 patients with POAG, and 50 eyes from 50 patients with NTG met the criteria for inclusion in the present study. Patients' characteristics are listed in Table 1. Patients with and without an observed disc hemorrhage are shown in Tables 2 and 3. There were 34 eyes with disc hemorrhages and 115 without. The age at the time of surgery averaged 56.9 years (mean ± SD, range: 27 to 83 y). The preoperative follow-up period averaged 3.6 years and ranged from 0.6 to 14.5 years. The postoperative follow-up period averaged 6.8 years and ranged from 1.3 to 11.8 years.

Trabeculectomy significantly reduced IOP from 19.6 ± 4.4 to 11.1 ± 4.2 mm Hg (mean ± SD) in POAG eyes, and from 15.3 ± 1.5 to 11.3 ± 4.5 mm Hg in NTG eyes ($P < 0.001$, $P < 0.001$, respectively; paired t test). In POAG, the disc hemorrhages before and after surgical intervention were found in 18 (18.2%) and 4 eyes (4.0%), respectively ($P = 0.0026$, Fisher exact probability test). On the other hand, in NTG, disc hemorrhages before and after surgical intervention were found in 16 (32.0%) and 9 eyes (18.0%), respectively ($P = 0.1659$, χ^2 test). In POAG, there were 2 eyes with disc hemorrhages and 79 eyes without disc hemorrhages, in both preoperative and postoperative periods ($P = 0.1501$, Fisher exact probability test, Tables 3 and 4). In NTG, there were 6 eyes with disc hemorrhages and 31 eyes without disc hemorrhages, in both preoperative and postoperative periods ($P = 0.0219$, Fisher exact probability test, Tables 2 and 5).

The life-table analysis revealed that the cumulative probability of detecting disc hemorrhages before surgery in NTG was significantly higher than that in POAG ($P = 0.0341$, log-rank test, Fig. 1). The final cumulative probability of detecting a disc hemorrhage after surgery in POAG was calculated to be 5.5 ± 2.2% (calculated probability ± SE) and was significantly lower than that (33.4 ± 7.8%) before surgery ($P < 0.0001$, log-rank test). Likewise, the final probability after surgery in NTG was 23.1 ± 6.3% and was significantly lower than that (42.1 ± 8.8%) before surgery ($P = 0.0063$, log-rank test). The cumulative probability of detecting disc hemorrhages after surgery in NTG was significantly higher than that in POAG ($P = 0.0059$, log-rank test, Fig. 2).

The incidence rate of disc hemorrhages before and after surgery in POAG was 0.08 ± 0.24 (range: 0.00 to 1.95) and 0.01 ± 0.06 (range: 0.00 to 0.47) times per year, respectively (mean ± SD). There was a significant difference between them ($P = 0.0014$, Wilcoxon signed-rank test). Similarly, the incidence rate in NTG was 0.26 ± 0.50 (range: 0.00 to 1.91) and 0.04 ± 0.10 (range: 0.00 to 0.53) times per year, respectively. There was a significant difference between them ($P = 0.0029$, Wilcoxon signed-rank test). The mean interval for the appearance of disc hemorrhages was 1.04 ± 1.33 (range: 0.00 to 3.30) years for patients with NTG (16 eyes) and 2.08 ± 2.19 (range: 0.00 to 7.12) years for POAG eyes (18 eyes).

The high postoperative IOP group included 27 NTG subjects and 26 POAG subjects, and the low postoperative IOP group included 23 NTG subjects and 73 POAG subjects. Comparing the incidence of disc hemorrhages after filtering surgery between the high and

TABLE 1. Patients' Demographic Data

	NTG (50 Patients)	POAG (99 Patients)	P
Age (y)	58.3 ± 9.8 (34-75)	56.3 ± 14.6 (27-83)	0.5707
Sex (male/female)	18/32	53/46	0.0642
Follow-up periods (y)			
Preoperative	3.4 ± 2.7 (0.6-11.9)	3.7 ± 3.1 (0.6-14.5)	0.5736
Postoperative	7.7 ± 2.6 (1.3-11.3)	6.3 ± 3.0 (1.3-11.8)	0.0059
Visual acuity			
Preoperative	0.9 ± 0.4 (0.2-1.5)	0.9 ± 0.4 (0.3-1.5)	0.7612
At the last visit	0.5 ± 0.5 (HM-1.5)	0.5 ± 0.5 (LS-1.5)	0.6731
IOP (mm Hg)			
Preoperative	15.3 ± 1.5 (12-18)	19.6 ± 4.4 (13-41)	< 0.0001
Postoperative	11.3 ± 4.5 (2-20)	11.1 ± 4.2 (1-23)	0.7613
HFA program central 30-2 MD (dB)			
Preoperative	− 11.7 ± 4.4 (− 19.9∼ − 1.5)	− 12.1 ± 5.0 (− 19.6∼ − 0.1)	0.4344
Postoperative	− 16.5 ± 7.8 (− 32.8∼ − 3.0)	− 18.1 ± 8.1 (− 32.0∼ − 0.1)	0.1950
DH (positive/negative)			
Preoperative	16/34	18/81	0.0905
Postoperative	9/41	4/95	0.0104
Past history (positive/negative)			
DM	3/47	11/88	0.3857
HT	12/38	25/74	> 0.9999

DH indicates disc hemorrhage; DM, diabetes mellitus; HFA, Humphrey Field Analyzer; HM, hand motion; HT, hypertension; LS, light sense.

Values indicate means ± SD (range).

TABLE 2. Patients' Background and Occurrence of Disc Hemorrhages Both Before and After Trabeculectomy (NTG)

	With DH (Preoperative) (16 Patients)	Without DH (Preoperative) (34 Patients)	*P*
Age (y)	55.8 ± 10.6 (34-75)	59.4 ± 9.3 (40-75)	0.2003
Sex (male/female)	6/10	12/22	> 0.9999
Follow-up periods (y)			
Preoperative	3.6 ± 2.4 (0.6-8.9)	3.2 ± 2.9 (0.6-11.9)	0.4991
Postoperative	8.4 ± 2.4 (1.4-11.1)	7.4 ± 2.7 (1.3-11.3)	0.2484
Visual acuity			
Preoperative	1.2 ± 0.3 (0.4-1.5)	0.8 ± 0.4 (0.2-1.5)	0.0012
At the last visit	0.5 ± 0.4 (HM-1.5)	0.5 ± 0.5 (CF-1.5)	0.7127
IOP (mm Hg)			
Preoperative	15.6 ± 1.5 (12-18)	15.2 ± 1.4 (12-18)	0.3169
Postoperative	12.6 ± 4.8 (4-20)	10.7 ± 4.3 (2-20)	0.0773
HFA program central 30-2 MD (dB)			
Preoperative	− 11.0 ± 4.3 (− 17.3∼ − 1.5)	− 12.1 ± 4.5 (− 19.9∼ − 1.8)	0.5191
Postoperative	− 16.0 ± 7.6 (− 29.9∼ − 4.5)	− 16.8 ± 8.0 (− 32.8∼ − 3.0)	0.1410
DH (positive/negative)			
Postoperative	6/10	3/31	0.0219
Past history (positive/negative)			
DM	1/15	2/32	> 0.9999
HT	6/10	6/28	0.2386

CF indicates counting fingers; DH, disc hemorrhage; DM, diabetes mellitus; HFA, Humphrey Field Analyzer; HM, hand motion; HT, hypertension.
Values indicate means ± SD (range).

low postoperative IOP groups, we found that in POAG patients, the incidence of disc hemorrhages was 13.6 ± 7.4% (calculated probability ± SE) in the high postoperative IOP group and 1.4 ± 1.4% in the low postoperative IOP group. The life-table analysis demonstrated a significant difference between the two groups ($P = 0.0393$, log-rank test, Fig. 3). On the other hand, the incidence of disc hemorrhages after surgery in NTG patients was 12.4 ± 6.8% in the high postoperative IOP group and 29.2 ± 10.2% in the low postoperative IOP group, revealing no significant difference between the 2 groups ($P = 0.1750$, log-rank test, Fig. 4).

Comparisons of the incidence of disc hemorrhages after surgical intervention between the eyes with or

TABLE 3. Patients' Background and Occurrence of Disc Hemorrhages Both Before and After Trabeculectomy (POAG)

	With DH (Preoperative) (18 Patients)	Without DH (Preoperative) (81 Patients)	*P*
Age (y)	54.8 ± 14.7 (29-83)	56.6 ± 14.7 (27-82)	0.5705
Sex (male/female)	7/11	46/35	0.2632
Follow-up periods (y)			
Preoperative	4.7 ± 2.0 (0.6-7.6)	3.6 ± 3.3 (0.6-14.5)	0.0215
Postoperative	5.3 ± 2.8 (1.7-10.6)	6.4 ± 3.0 (1.3-11.8)	0.0784
Visual acuity			
Preoperative	1.3 ± 0.2 (1.0-1.5)	0.8 ± 0.4 (0.3-1.5)	< 0.0001
At the last visit	0.5 ± 0.4 (LS-1.2)	0.5 ± 0.5 (LS-1.5)	0.7654
IOP (mm Hg)			
Preoperative	17.4 ± 2.0 (13-22)	20.1 ± 4.6 (13-41)	0.0068
Postoperative	11.5 ± 3.5 (5-17)	11.0 ± 4.4 (1-23)	0.4390
HFA program central 30-2 MD (dB)			
Preoperative	− 12.1 ± 4.1 (− 17.8∼ − 0.9)	− 12.2 ± 5.2 (− 19.6∼ − 0.1)	0.7640
Postoperative	− 18.8 ± 7.5 (− 32.0∼ − 6.4)	− 17.9 ± 8.3 (− 31.9∼ − 0.1)	0.4941
DH (positive/negative)			
Postoperative	2/16	2/79	0.1501
Past history (positive/negative)			
DM	1/17	10/71	0.6833
HT	6/12	19/62	0.5649

DH indicates disc hemorrhage; DM, diabetes mellitus; HFA, Humphrey Field Analyzer; HT, hypertension; LS, light sense.
Values indicate means ± SD (range).

TABLE 4. Occurrence of Disc Hemorrhages Both Before and After Trabeculectomy (POAG)

	With DH (Preoperative)	Without DH (Preoperative)	Total
With DH (postoperative)	2	2	4
Without DH (postoperative)	16	79	95
Total	18	81	99

DH indicates disc hemorrhage.

without disc hemorrhages before surgery showed that the cumulative probability of detecting disc hemorrhages in POAG patients was 11.9 ± 7.9% (calculated probability ± SE) or 3.5 ± 2.5%, respectively ($P = 0.0617$, log-rank test, Fig. 5). On the other hand, in NTG patients, incidence of disc hemorrhages was 41.1 ± 13.0% or 8.9 ± 4.9%, respectively, which was a statistically significant difference between the 2 groups ($P = 0.0225$, log-rank test, Fig. 6).

DISCUSSION

In the current study, we demonstrated that IOP reduction via surgical intervention had favorable effects on the detection of disc hemorrhages in glaucoma. We also found that the incidence of disc hemorrhages in the high and low postoperative IOP groups with POAG had a tendency contrary to that with NTG. Furthermore, we revealed that glaucoma (especially NTG) eyes with disc hemorrhage(s) preoperatively still predisposed to their recurrence postoperatively even after marked IOP reduction. Taken together, we speculated that underlying mechanisms except for the raised IOP might be involved in the development or deterioration of glaucomatous optic neuropathy especially in NTG.

Other studies have reported that the incidence of disc hemorrhages was between 2% and 37%[5–10,27–32] in POAG patients, 11% and 42%[4,27,33–35] in NTG patients, and 0.4% and 10%[5,6,8–10,27,29,30] in OH patients. The disc hemorrhages are usually not observed in far-advanced glaucoma in which little remaining neuroretinal rim is preserved.[36] Therefore, we adopted one of the eligible criteria from where calculation of the visual field indices (MD less than −20 dB) can be made. Although it is difficult to compare incidence of disc hemorrhages in glaucoma with previous reports because of the variability of the follow-up periods for each report or the nature of surgical intervention in the present study, the cumulative frequency (POAG 18%, NTG 32%) before surgery observed in the present study was substantially consistent with those of previous reports.

TABLE 5. Occurrence of Disc Hemorrhages Both Before and After Trabeculectomy (NTG)

	With DH (Preoperative)	Without DH (Preoperative)	Total
With DH (postoperative)	6	3	9
Without DH (postoperative)	10	31	41
Total	16	34	50

DH indicates disc hemorrhage.

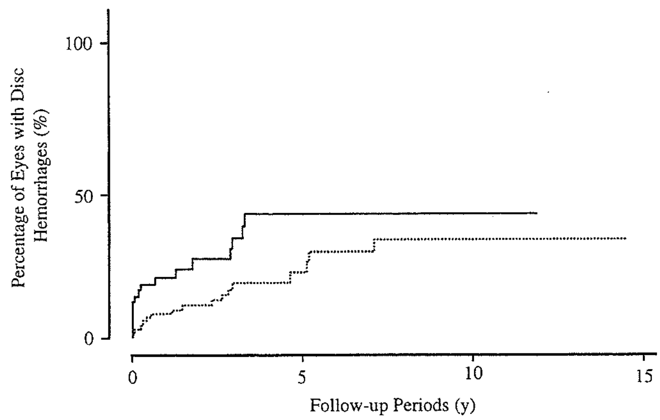

FIGURE 1. The cumulative probability of detecting disc hemorrhages before surgical intervention over time in the NTG and the POAG groups. The solid line indicates NTG and the dotted line represents POAG. The cumulative probability of detecting disc hemorrhages over time in the NTG group was significantly higher than that in the POAG group. The final probability in NTG and POAG was 42.1 ± 8.8% and 33.4 ± 7.8%, respectively (calculated probability ± SE). There was a statistically significant difference between the 2 groups ($P = 0.0341$, log-rank test).

In contrast to a report on the incidence of disc hemorrhages regardless of with and/or without therapy, there are extremely few reports about the alteration of incidence of disc hemorrhages before and after ocular hypotensive therapy. Sonnsjo et al[37] described that ocular hypotensive therapy by pilocarpine or timolol had no effects on the occurrence of disc hemorrhages. Hendrickx

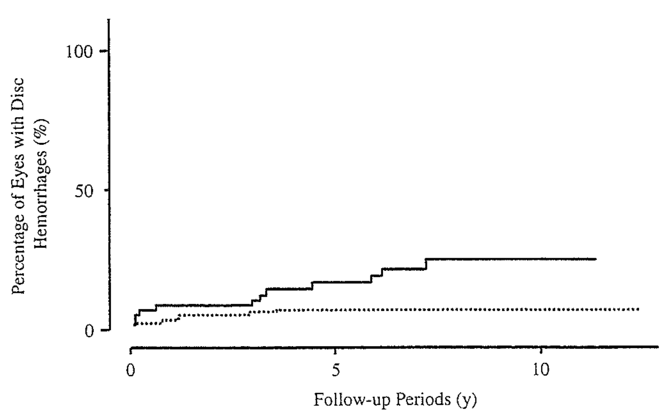

FIGURE 2. The cumulative probability of detecting disc hemorrhages after trabeculectomy over time in the NTG and POAG subgroups by the Kaplan-Meier analysis. The solid line indicates NTG patients and the dotted line represents POAG patients. The final probability of NTG and POAG was 23.1 ± 6.3% and 5.5 ± 2.2%, respectively (calculated probability ± SE). The cumulative probability of detecting disc hemorrhages over time in the NTG group was significantly higher than that in the POAG group ($P = 0.0059$, log-rank test).