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Effect of Trabeculectomy on Visual Field in Progressive Normal-Tension Glaucoma

Lina Daugeliene, Tetsuya Yamamoto and Yoshiaki Kitazawa

Department of Ophthalmology, Gifu University School of Medicine, 40 Tsukasa-machi, Gifu-shi 500-8705, Japan

Abstract: The purpose of this study was to investigate the effectiveness of surgical treatment on the visual field in normal-tension glaucoma (NTG) eyes, and associated factors for visual field progression. Thirty-two patients (32 eyes) were enrolled in this retrospective study. Stepwise regression analysis was performed to correlate the visual field change with several clinical factors, such as intraocular pressure (IOP), and several IOP-unrelated parameters. Surgical reduction of IOP helps in preventing the progression of visual field damage in NTG eyes. The stepwise analysis revealed that better visual field prognosis was associated with higher preoperative IOP ($P = 0.006$) and the absence of diabetes mellitus ($P = 0.04$). The functional outcome in the lower IOP group was better when the patients were using Ca^{2+}-channel blockers ($P = 0.08$); it was worse if disc hemorrhage appeared ($P = 0.02$). In conclusion, both IOP-related and unrelated factors are associated with visual field damage progression in NTG eyes. The functional prognosis in the eyes with low IOP depends on IOP-unrelated factors. **Jpn J Ophthalmol 1998;42:286–292** © 1998 Japanese Ophthalmological Society

Key Words: Normal-tension glaucoma, trabeculectomy, visual field.

Introduction

Normal-tension glaucoma (NTG), characterized by glaucomatous optic neuropathy with corresponding visual field defect without elevated intraocular pressure, is a frequently encountered type of glaucoma in the Japanese population.[1] The etiology of NTG remains to be elucidated: It is induced by vascular pathology or by relatively high intraocular pressure (IOP) and other yet to be identified factors. Normal-tension glaucoma patients are more likely to have systemic microvascular or circulatory abnormalities, such as migraine, exaggerated vasospastic response to cold recovery test, higher incidence of cerebral vascular ischemia, systemic hypertension or hypotension, or other vascular abnormalities like disc hemorrhage and peripapillary atrophy.[2–8] Many investigators believe that IOP is still responsible for glaucomatous optic nerve damage even in NTG eyes,[9] and favorable effects on visual field progression could be achieved in NTG eyes after IOP reduction below the low teens.[10–14] Several studies, on the other hand, reported the beneficial effect of Ca^{2+}-channel blockers on the visual field of NTG eyes, which might be attributable to the increase in blood supply to the optic nerve.[15,16]

The purpose of this study was to investigate the effect of surgical treatment on the visual field in NTG eyes with progressive visual field damage, and to determine the factors associated with the progression of this damage in NTG eyes.

Materials and Methods

Of the total of 46 NTG patients who underwent trabeculectomy at Gifu University Hospital between 1991 and 1994, we enrolled 32 patients (32 NTG eyes) who met the following selection criteria: diagnosis of NTG, preoperative follow-up period of at least 12 months, postoperative period of at least 24 months, and more than five preoperative and three postoperative perimetric test results using a Hum-

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Address correspondence and reprint requests to: Lina DAUGELIENE, MD, Department of Ophthalmology, Gifu University School of Medicine, 40 Tsukasa-machi, Gifu-shi 500-8705, Japan

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phrey Field Analyzer (Program 30-2, Zeiss-Humphrey Instruments, Inc., San Leandro, CA, USA), (ie, $<$20% fixation loss and $<$33% false-positive or false-negative answers), abnormal glaucoma hemifield test result, the mean deviation (MD) better than $-$20.00 dB at the time of surgery, and the best corrected visual acuity better than or equal to 20/40. If both eyes were compatible for enrollment criteria, the eye with the worse initial MD was studied. The diagnosis of NTG was made when untreated peak IOP was $\leq$ 21 mm Hg at all times, including 24-hour phasing (IOP measured every 2 hours), a normal open-angle, presence of typical glaucomatous optic nerve and visual field changes, and no ocular, rhinologic, neurological, or systemic disorders responsible for the optic nerve damage. Excluded from the study were patients with previous or postoperative intraocular surgeries and patients with clinically significant cataract development to hamper correct interpretation of the visual field.

The age at the time of surgery averaged 56.9 years (range: 38.0–77.0 years). Seventeen patients were women and 15 men. The preoperative follow-up period averaged 3.8 $\pm$ 2.7 years (range: 1.0–15.0 years). The mean postoperative follow-up was 4.5 $\pm$ 1.1 years (range: from 2.0–6.0 years). Three patients had non-insulin–dependent diabetes mellitus with a duration of more than 5 years.

The number of preoperative ocular hypotensive medications averaged 1.5 $\pm$ 0.7. Ten patients were taking oral Ca^{2+}-channel blockers. The indication for the use of Ca^{2+}-channel blockers was based on individual ophthalmic and systemic conditions, such as IOP, severity of optic neuropathy, and result of cold recovery test.

The indication for surgery was progressive visual field defect with maximum tolerable medical treatment. The indication for the study subjects was classified into the following three categories: (a) MD/year slope over $-$0.50 dB/year (19 eyes), (b) depression of at least 15.00 dB at two contiguous points developed outside of the central 5-degree area (4 eyes), and (c) depression of at least 15 dB confirmed twice in the central 5-degree area (9 eyes).

All surgeries were performed according to a modification of Cairns' technique: a limbal-based conjunctival flap and a 4 $\times$ 4-mm half-layer scleral flap were made, then mitomycin C was applied as described elsewhere.[17] After 5 minutes, the wound was irrigated with 250 mL of balanced salt solution. Then a 0.5 $\times$ 3-mm limbal block was dissected and a peripheral iridectomy was performed. The scleral flap was snugly closed with interrupted 10-0 nylon sutures; the anterior chamber was reformed by injecting balanced salt solution. The conjunctival wound was closed with a continuous 10-0 nylon shoelace suture.

Postoperative follow-up for all patients was performed at the Department of Ophthalmology, Gifu University School of Medicine, Japan. All patients were seen at least twice a year. At each visit all patients had visual acuity testing, biomicroscopy, and IOP measurements with a Goldmann applanation tonometer. The optic disc and peripapillary area (β zone) were evaluated by direct ophthalmoscopy or stereophotographically. Blood pressure was measured at or about the first visit and before surgery. The vasospastic component was measured as reactivity of peripheral vessels and was estimated as described elsewhere.[16] In short, a baseline skin temperature was recorded until a steady baseline reading was achieved. One hand of the patient was then immersed in ice-cold water (4°C) for 10 seconds, and skin temperature was monitored every minute for the next 10 minutes. The temporal change in the skin temperature after immersion in cold water was expressed as a percentage recovery from the lowest to the baseline temperature at each measurement. The visual field was examined at least twice a year using the Central 30-2 program of the Humphrey Field Analyzer. The significance of changes over time was evaluated using Statpac 2 of the Humphrey Field Analyzer. The MD/year slopes for preoperative and postoperative periods were calculated. As a baseline for the latter, the latest two preoperative visual fields were used.

To investigate the effect of the surgery on the visual field, the preoperative and postoperative MD change/year was correlated with an emphasis on IOP reduction in the whole group and also in the two subgroups divided by a preoperative IOP level of 15 mm Hg.

We then performed several multivariate analyses to investigate the association of preoperative and postoperative visual field changes (MD change/year), as well as the difference in visual field changes between preoperative and postoperative periods with several clinical factors. A stepwise regression analysis with a 0.15 significance level was performed using the PC-SAS software[18] to correlate the preoperative MD change per year with several clinical factors. They included preoperative mean and maximal IOPs, mean diurnal IOP, initial MD, presence of disc hemorrhage, peripapillary atrophy (β zone $>$ 50% of optic disc area), refractive error (spherical equivalent), use of Ca^{2+}-channel blockers, use of ocular hypotensive medications, percent recovery in the cold

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Table 1. Patient Backgrounds

Parameter	Preoperative	Postoperative	*P* value
IOP[a] (mmHg)	14.7 ± 1.6 (11.8–20.6)	8.7 ± 2.4 (4.3–13.1)	<.0001
MD change[a] (dB/year)	−0.97 ± 1.07 (+0.27–−3.54)	−0.32 ± 0.61 (+0.49–−1.57)	.003
Disc hemorrhage[b]	14	4	.003
Follow-up[a] (years)	3.8 ± 2.7 (1.0–15.0)	4.5 ± 1.1 (2.0–6.0)	

IOP: intraocular pressure; MD: mean deviation.
[a]Mean ± standard deviation, (range). *P* value calculated by Wilcoxon signed-rank test.
[b]Number of cases developed. *P* value calculated by Fisher's direct probability test.

test at 4 minutes, mean blood pressure (ie: diastolic blood pressure + [systolic blood pressure − diastolic blood pressure]/3), age, and history of diabetes mellitus.

Stepwise regression analysis was performed to correlate the difference of postoperative and preoperative MD change per year with several clinical factors, including difference of preoperative diurnal and postoperative mean IOPs, mean diurnal IOP, mean postoperative IOP, MD at the time of surgery, postoperative presence of disc hemorrhage, peripapillary atrophy, refractive error, use of Ca^{2+}-channel blockers, use of ocular hypotensives, percent recovery in the cold test at 4 minutes, mean blood pressure, age at the time of surgery, and history of diabetes mellitus.

Finally, stepwise regression analyses for MD change/year, using the same independent variables, were also performed in the eyes with a mean diurnal IOP lower than 15 mm Hg, and in the eyes with a mean diurnal IOP higher than or equal to 15 mm Hg.

Results

The preoperative and postoperative backgrounds are shown in Table 1. The preoperative mean diurnal IOP at the 24-hour phasing was 14.4 ± 1.7 mmHg (range: 11.7–18.1 mm Hg) without medications, and the preoperative mean IOP was 14.7 ± 1.6 mmHg (range: 11.8–20.6 mm Hg) with medications. The preoperative MD change/year was −0.97 ± 1.07 dB/year (range: −3.54–0.27 dB/year). The postoperative IOP was 8.7 ± 2.4 mm Hg (range: 4.3–13.1 mmHg) with a mean postoperative IOP reduction of 6.1 ± 3.0 mm Hg (range: 1.2–12.7 mm Hg). Four eyes required additional ocular hypotensive medications

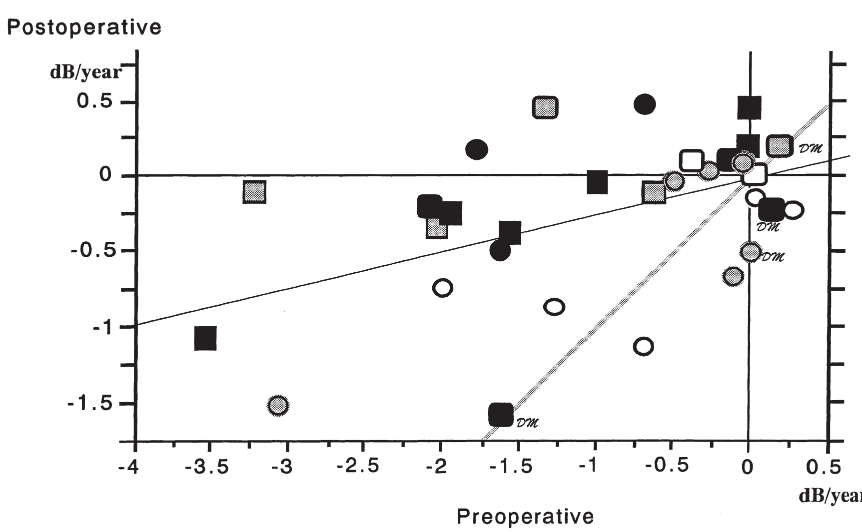

Figure 1. Distrubution of preoperative and postoperative mean deviation (MD) change/year. *Square* denotes case with preoperative mean diurnal intraocular pressure (IOP) above 15 mm Hg. *Round angle square* denotes case with IOP between 14 and 15 mm Hg. *Circle* denotes case with IOP below 14 mm Hg. *White* color indicates IOP reduction less than 3 mm Hg; *gray* color indicates IOP reduction between 3 and below 6 mm Hg; *black* color indicates IOP reduction equal to or more than 6 mm Hg. *Solid gray line* shows no difference in preoperative and postoperative outcome on visual field. DM: diabetes mellitus. The regression line calculated was: Postoperative MD Change/Year = −0.023 + 0.24 × Preoperative MD Change/Year; (R^2 = 0.226).

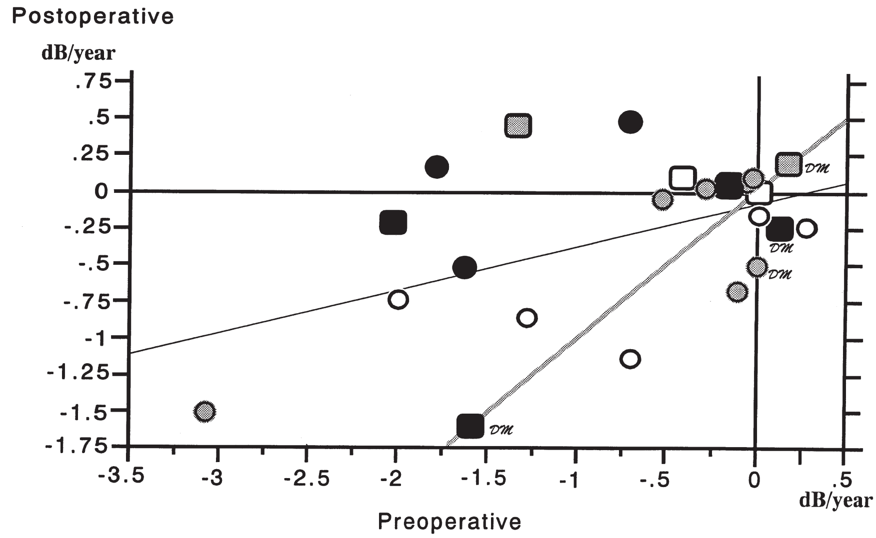

Figure 2. Distribution of preoperative and postoperative mean deviation (MD) change/year in eyes with preoperative mean diurnal intraocular pressure (IOP) below 15 mm Hg. *Round angle square* denotes case with IOP between 14–15 mm Hg. *Circle* denotes case with IOP below 14 mm Hg. *White* color indicates IOP reduction less than 3 mm Hg; *gray* color indicates IOP reduction between 3 and below 6 mm Hg; *black* color indicates IOP reduction equal to or more than 6 mm Hg. *Solid gray line* shows no difference in preoperative and postoperative outcome on visual field. *DM* denotes case with diabetes mellitus. Regression line calculated was: Postoperative MD Change/Year = −0.077 + 0.295 × Preoperative MD Change/Year ($R^2 = 0.221$).

postoperatively, and 2 eyes had bleb revision. Postoperative MD change/year was −0.32 ± 0.61 dB/year (range: 0.49–−1.57 dB/year).

Figure 1 demonstrates the preoperative and postoperative MD change/year with IOP changes. Figures 2 and 3 show a similar relationship in two subgroups of patients divided by a preoperative IOP of 15 mm Hg. In 9 eyes with the preoperative mean diurnal IOP of 15 mm Hg or higher, the postoperative MD/year was improved without exception as compared with the preoperative. It was not the case, however, in the lower IOP group comprised of 23 eyes. Table 2 shows some clinical data of the two subgroups.

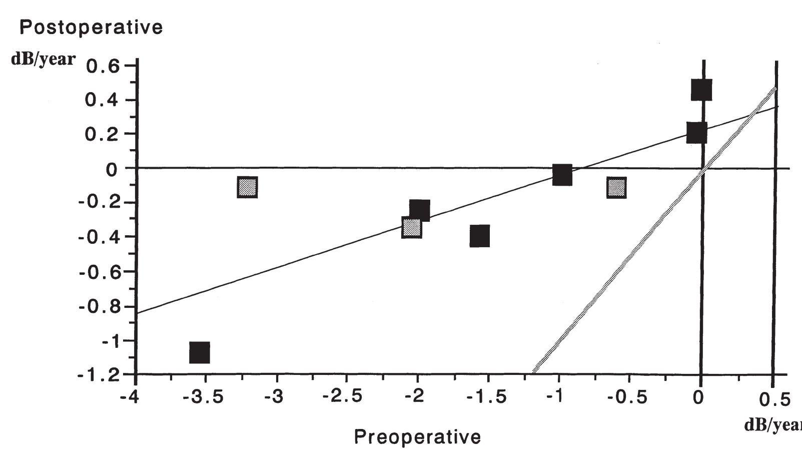

Figure 3. Distribution of preoperative and postoperative mean deviation (MD) change/year in eyes with preoperative mean diurnal intraocular pressure (IOP) equal to or above 15 mm Hg. *Gray* color indicates IOP reduction between 3 and below 6 mm Hg; *black* color indicates IOP reduction equal to or more than 6 mm Hg. *Solid gray line* shows no difference in preoperative and postoperative outcome on visual field. Regression line calculated was: Postoperative MD Change/Year = 0.232 + 0.268 × Preoperative MD Change/Year ($R^2 = 0.635$).

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Table 2. Clinical Data of Cases With "Low" and "High" Preoperative IOPs

	Preoperative IOP < 15 mm Hg		Preoperative IOP ≥ 15 mm Hg		
Parameter	Mean ± SD	Range	Mean ± SD	Range	P value[a]
Preoperative MD change/year	−0.72 ± 0.90	(−3.07–0.27)	−1.56 ± 1.27	(−3.54− −0.01)	.07
Postoperative MD change/year	−0.36 ± 0.66	(−1.57–0.49)	−0.18 ± 0.43	(−1.07–0.46)	NS
MD changes/year deterioration	0.32 ± 0.088	(−0.52–1.96)	1.37 ± 0.97	(0.26–3.11)	.01
Preoperative IOP mean	14.3 ± 1.2	(11.8–16.8)	15.9 ± 2.2	(13.5–20.6)	.02
Postoperative IOP mean	8.7 ± 2.4	(5.4–13.1)	8.5 ± 2.9	(4.3–12.9)	NS
Mean diurnal IOP	13.5 ± 1.0	(11.7–15.0)	16.5 ± 1.0	(15.0–18.1)	<.0001
IOP reduction	4.8 ± 2.6	(−0.6–8.8)	8.1 ± 2.8	(3.9–11.8)	.04
Age	58.0 ± 8.5	(46.0–77.0)	50.7 ± 11.4	(38.0–69.0)	.05
Number of cases	23		9		

IOP: intraocular pressure. MD: mean deviation. NS: not significant.
[a]Calculated by Wilcoxon signed-rank test.

The stepwise regression analysis revealed that negative preoperative visual field change (MD change/year) was highly correlated with several variables, including higher mean of IOP during the phasing (P = .012), history of disc hemorrhages (P = .015), myopic refraction (P = .061), and older age (P = .141) (Table 3).

The amount of postoperative MD change/year deterioration (Postoperative MD change/year minus preoperative MD change/year) was positively correlated with several variables, including high preoperative mean of diurnal IOP (P = .006), absence of diabetes mellitus (P = .04), and myopic refraction (P = .116) (Table 4).

In 23 eyes with the preoperative mean diurnal IOP below 15 mm Hg, the stepwise regression analysis revealed that negative postoperative MD change/year was correlated with both the appearance of disc hemorrhage (P = .02), and nonuse of Ca^{2+}-channel blockers (P = .08); (Table 5). In eyes with higher IOP, the stepwise regression analysis revealed that the most significant factor for the favorable postoperative visual field prognosis was better preoperative MD ($P < .01$) (Table 6).

Discussion

Introduction of mitomycin C into the ophthalmic world, in combination with trabeculectomy, has allowed us to achieve a great IOP reduction in the majority of cases. In the current study, we found that, in general, surgical reduction of IOP favorably affects the visual field progression in NTG eyes. Favorable outcome, however, cannot be expected in all cases. The preoperative IOP value is one critical factor to determine the outcome. When the preoperative mean diurnal IOP was ≥15 mm Hg, our study showed that the surgery helped greatly in preventing the visual field from further deterioration. When the IOP was <15 mm Hg, however, the favorable effect depended upon individual factors. As postulated by some authors,[10–14] reduction of IOP has a favorable effect on

Table 3. Factors Associated With Preoperative Visual Field Damage Progression for Total Cases

Independent Variables	Parameter Estimate	P Value
Mean diurnal IOP	−0.28	.012
Disc hemorrhage	−0.95	.015
Refractive error	0.07	.061
Age	−0.02	.141

IOP: intraocular pressure.
Factors not associated with outcome were: maximal IOP, mean IOP, initial mean deviation (dB), presence of peripapillary atrophy, use of Ca^{2+}-channel blockers, use of ocular hypotensives, percent recovery in cold test (4 minutes), mean blood pressure, and diabetes mellitus.

Table 4. Factors Associated With Difference in MD Change/Year Between Pre- and Postoperative Periods for Total Cases

Independent Variables	Parameter Estimate	P Value
Mean diurnal IOP	0.22	.006
Diabetes mellitus	−0.99	.040
Refractive error	0.05	.116

MD: mean deviation. IOP: intraocular pressure.
Factors not associated with outcome were: mean postoperative IOP, difference of preoperative diurnal and postoperative mean IOPs, MD at time of surgery (dB), presence of peripapillary atrophy, disc hemorrhage, use of Ca^{2+}-channel blockers, use of ocular hypotensives, percent recovery in cold test (4 minutes), mean blood pressure, and age at time of surgery.

Table 5. Factors Associated With Postoperative Outcome on Visual Field in Eyes with Low Preoperative IOP[a]

Independent Variables	Parameter Estimate	*P* Value
Disc hemorrhage	−0.78	.02
Ca^{2+}-channel blockers	0.65	.08

IOP: intraocular pressure.

Factors not associated with outcome were: mean postoperative IOP, diurnal IOP, difference of preoperative diurnal and postoperative mean IOPs, mean deviation at time of surgery (dB), presence of peripapillary atrophy, refractive error, use of ocular hypotensives, percent recovery in cold test (4 minutes), mean blood pressure, age at time of surgery, and diabetes mellitus.

[a]Number of cases: 23.

glaucomatous visual field in NTG eyes and our study supports this. We also found that in the postoperative period, lower preoperative IOP was associated with unfavorable visual field outcome, and postoperative IOP was not selected as an associated factor for visual field prognosis. This may be explained by the theory that IOP has little to do with the visual field deterioration in NTG eyes with lower preoperative IOP. Our stepwise regression analysis of eyes with mean diurnal IOP less than 15 mm Hg supports the theory, although the number of these eyes in our study was small. In the analysis, only factors unrelated to IOP (eg, presence of disc hemorrhage and the use of Ca^{2+}-channel blockers) were found to be associated with the visual prognosis. The effect of surgery on the visual field of NTG eyes was reported by Bhandari and colleagues,[19] where the authors also found that eyes with higher preoperative IOP had better postoperative visual field outcome. Shirai and colleagues,[20] reported that IOP is not a significant factor for visual field damage progression in the eyes with IOP below 15 mm Hg. It is interesting that, postoperatively, neither group in the present study showed a significant difference in postoperative MD change/year or in postoperative mean IOP.

Table 6. Factors Associated With Postsurgical Outcome on Visual Field in Eyes With High Preoperative IOP[a]

Independent Variables	Parameter Estimate	*P* Value
MD during surgery (dB)	0.04	.0087

IOP: intraocular pressure. MD: mean deviation.

Factors not associated with outcome were: mean postoperative IOP, diurnal IOP, difference of preoperative diurnal and postoperative mean IOPs, presence of peripapillary atrophy, disc hemorrhage, refractive error, use of Ca^{2+}-channel blockers, use of ocular hypotensives, percent recovery in cold test (4 minutes), mean blood pressure, age at time of surgery, and diabetes mellitus.

[a]Number of cases = 9.

In the preoperative period both IOP-related and unrelated factors are associated with the visual field outcome of NTG eyes. The effect of IOP was not prominent in the postoperative period, probably because the IOP was reduced sufficiently below 10 mm Hg in most cases. Statistical analysis has found that negative preoperative MD change/year is associated with higher mean diurnal IOP and that the mean diurnal IOP was more closely related to the visual field outcome than was the mean IOP during the follow-up. It is probably because IOP phasing reflects IOP variations more accurately, and because sufficient IOP reduction is hard to achieve medically in NTG eyes. In actuality, the mean IOP with medication was higher than the mean diurnal IOP without medication in the study population.

Disc hemorrhage is known to be associated with progression of glaucomatous visual field.[6,7] It might be that preoperative IOP in some pressure sensitive eyes was high enough to hamper blood circulation of the optic nerve head. Disc hemorrhage was less frequently seen in the postoperative period.

Myopia is a frequently encountered refractive condition in the Japanese population, and more frequent in NTG than in normal eyes.[21] Our study, as was reported by Phelps,[22] also found that myopia is one of the factors associated with more rapid visual field damage progression; myopic eyes showed higher positive response of visual field after surgical reduction of IOP. It might be that myopic alterations in the lamina cribrosa area could make the eye more sensitive to IOP even within the normal range of IOP.

The lowest success candidates for trabeculectomy with mitomycin C with regard to the visual field were patients with diabetes mellitus. Diabetes mellitus is one of the risk factors of glaucoma.[23] This systemic disease, affecting microcirculation, probably adds ischemic damage to the glaucomatous visual field. In some studies, diabetes mellitus was found to be associated with a higher prevalence of retinal ganglion cell death in glaucoma patients.[24,25]

In conclusion, the surgical reduction of IOP helps in preventing visual field deterioration from progressing in NTG eyes. Both IOP-related and unrelated factors are associated with the visual field prognosis. Vascular factors or other IOP-unrelated factors were associated with the prognosis in the eyes with lower preoperative IOP. Surgical reduction of IOP may be the treatment of choice in NTG eyes with progressive visual field loss, especially for eyes with higher IOP.

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