Jpn J Ophthalmol 2005;49:223–227
DOI 10.1007/s10384-004-0181-9

CLINICAL INVESTIGATION

Efficacy and Complications After Trabeculectomy with Mitomycin C in Normal-Tension Glaucoma

Boonphen Jongsareejit[1], Atsuo Tomidokoro[1], Tatsuya Mimura[1], Goji Tomita[1], Shiroaki Shirato[2], and Makoto Araie[1]

[1] Department of Ophthalmology, University of Tokyo School of Medicine, Tokyo, Japan;
[2] Department of Ophthalmology, Tokyo Medical University Hachioji Medical Center, Tokyo, Japan

Abstract

Purpose: To evaluate the efficacy of and complications after trabeculectomy using mitomycin C (MMC) in Japanese normal-tension glaucoma (NTG) patients by a retrospective analysis based on the Kaplan-Meier life table method.

Methods: Clinical records of 39 NTG patients who underwent trabeculectomy with 0.04% MMC and had postoperative follow-up periods of 3 years or more (50.5 ± 8.4 months, mean ± SD) were reviewed. Postoperative intraocular pressure (IOP) at every 1 or 2 months, complications, visual acuity, and visual field at every 6 months were recorded.

Results: IOP significantly decreased from 15.9 ± 1.9 preoperatively to 8–11 mmHg throughout the postoperative follow-up period ($P < 0.0001$). The life table analysis, in which failure of IOP control was defined as an IOP above a level either 30% or 20% lower than the preoperative IOP at three consecutive visits, showed a cumulative survival rate of 39.4 ± 7.8% (mean ± SEM) or 41.3 ± 8.9%, respectively, at 4 years after surgery. Mean deviation of the visual field results did not significantly change ($P > 0.5$). The cumulative survival rate from postoperative late-onset hypotony was 74.7 ± 6.3% at 4 years after surgery. Postoperative complications observed were shallow anterior chamber (six eyes), choroidal detachment (nine eyes), hypotonous maculopathy (seven eyes), bleb leak (one eye), cataract development (three eyes), and blebitis (two eyes). No eyes developed endophthalmitis.

Conclusions: In NTG patients, trabeculectomy with MMC showed significant efficacy in reducing IOP up to 4 years after surgery. Since risks of postoperative complications are unavoidable, indications for surgery should be carefully considered, and careful follow-up is necessary to avoid severe postoperative complications. **Jpn J Ophthalmol** 2005;49:223–227 © Japanese Ophthalmological Society 2005

Key Words: complications, intraocular pressure, Kaplan-Meier life table method, mitomycin C, normal-tension glaucoma, trabeculectomy

Introduction

Normal-tension glaucoma (NTG), also referred to as low-tension glaucoma, has been defined as open-angle glaucoma developing in an eye with normal intraocular pressure (IOP) but having some level of glaucomatous optic nerve damage with the corresponding visual field defects. In various countries, the prevalence of NTG has been reported as one-third to two-thirds of open-angle glaucoma patients.[1–4] In an epidemiological report from Japan, the prevalence of NTG reached 2.04% of the 40-and-older population, which was 57.3% of all glaucoma patients in the study.[4]

Although NTG should be a multifactorial disease, high IOP is still the only identified risk factor, not only for high-tension glaucoma but also for NTG. Several studies have suggested that lowering the IOP has the beneficial effect of halting or slowing the progression of NTG.[5–10] For example, a randomized controlled trial showed that a 30% or larger reduction of IOP from the preoperative value had

Received: April 1, 2004 / Accepted: October 15, 2004
Correspondence and reprint requests to: Atsuo Tomidokoro, Department of Ophthalmology, University of Tokyo School of Medicine, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
e-mail: tomidokoro-tky@umin.ac.jp

Jpn J Ophthalmol
Vol 49: 223–227, 2005

a significantly beneficial effect of preserving visual fields in NTG patients.[8] Moreover, maintaining a lower IOP without remarkable fluctuation through a long period is crucial in the treatment of open-angle glaucoma.[11]

The introduction of the intraoperative use of mitomycin C (MMC) has improved the success rate of trabeculectomy for primary open-angle glaucoma patients.[12–15] However, there has been no study on IOP control and complications after trabeculectomy with MMC in NTG patients, except for a few studies with small numbers of subjects (25 or fewer).[6,16,17] Moreover, since the postoperative target IOP is definitely lower in NTG patients compared with primary open-angle glaucoma patients, the NTG patients often face a greater risk of ocular hypotony and its associated complications, such as hypotonous maculopathy, choroidal detachment, and cataract development.[16,17] These complications occur not only in the early postoperative period but also during the long-term follow-up after surgery. Therefore, the outcome of trabeculectomy should be evaluated based on long-term observations also for postoperative complications.

The purpose of this study was to evaluate long-term results of postoperative IOP control and complications after trabeculectomy with MMC in a relatively greater number of NTG patients whose postoperative follow-up periods were 3 or more years by using a life table analysis.

Patients and Methods

Clinical records were reviewed of 39 consecutive NTG patients who underwent initial trabeculectomy (i.e., who had no history of previous glaucoma surgery except laser procedures) using intraoperative MMC at the Department of Ophthalmology, University of Tokyo Graduate School of Medicine, and on whom postoperative follow-up was successfully carried out for 3 or more years. The postoperative follow-up period averaged 50.5 ± 8.4 (mean ± SD) months. Patients who underwent a combined procedure of trabeculectomy and other ocular surgeries such as cataract surgery were not included.

The diagnosis of NTG was made according to evidence of typical glaucomatous optic disc cupping and visual field damage in eyes with normal IOP, open angles, and the absence of any contributing ocular or specific systemic disorders. IOP was measured by multiple observers using a Goldmann applanation tonometer, and normal IOP was defined as IOP that never exceeded 21 mmHg during the follow-up period, including 24-h fluctuation, which was assessed at 2- or 3-h intervals during an overnight stay in the hospital. Table 1 describes the characteristics of the patients, all of whom were Japanese. In general, the indication for trabeculectomy was progression of visual field damage when the maximum tolerable medication had already been prescribed or when there was risk of visual field loss threatening fixation, and surgery was performed only with the patient's informed consent. If both eyes of a patient underwent trabeculectomy during the above-mentioned period, data obtained for the eye that underwent surgery first was used.

Table 1. Patient demographics at the time of surgery

Number of eyes	39
Age[a] (years)	55.2 ± 9.4
Male/Female	19/20
Preop IOP[a] (mmHg)	15.9 ± 1.9
Mean deviation[a] (dB)	–17.9 ± 6.8

IOP, intraocular pressure.
[a] mean ± SD.

Trabeculectomy was performed as follows. After local anesthesia, a limbal-based conjunctival flap and a scleral flap one-half the thickness of the sclera were produced at the superior temporal quadrant. The shape of the scleral flap was triangular, and its size was approximately 3.5 mm × 3.5 mm. It was hinged at the corneal limbus. Small pieces of surgical sponges soaked in 0.04% MMC were placed under the conjunctival flap for 3 min. After the sponges were removed, the area was irrigated with a balanced salt solution. At the edge of the corneoscleral bed, a block of clear corneal and trabecular meshwork tissue was removed and peripheral iridectomy was performed. The scleral flap was sutured with three to five monofilament 10-0 nylon sutures, adjusted so that a little leakage around the scleral flap margin could be observed without shallowing of the anterior chamber. The conjunctiva and Tenon's capsule were closed using a 10-0 nylon running suture. The anterior chamber and filtering bleb were reformed with balanced salt solution to verify that the conjunctival wound was watertight.

The postoperative follow-up schedule involved daily eye examinations during the first 7 to 14 days of hospitalization, once a week for the first month in the outpatient clinic, and once a month thereafter. The follow-up studies involved IOP measurements with Goldmann applanation tonometer, precise slit-lamp biomicroscopy, and funduscopy. To keep appropriate IOP control, topical glaucoma therapy and/or laser suture lysis, or a needling procedure for bleb revision were also carried out when necessary. Visual acuity was measured every 4 months postoperatively. Visual fields were evaluated with the central 30-2 program of the Humphrey visual field analyzer (Humphrey, San Leandro, CA, USA) within 1 month preoperatively and then every 6 months postoperatively. The development of postoperative complications, such as hypotony, hypotonous maculopathy, blebitis, and endophthalmitis, was also carefully checked for at every visit.

To evaluate IOP control and the incidence of hypotonic complications during the postoperative follow-up period, the Kaplan-Meier life table method was used. Two different definitions of the endpoint (i.e., failure) of IOP control were separately applied: (1) when IOPs exceeding a level 30% lower than the preoperative IOP were obtained at three consecutive visits; and (2) when IOPs exceeding a level 20% lower than the preoperative IOP were obtained at three consecutive visits. Since glaucoma topical medications, laser

suture lysis, or the needling procedure were optionally carried out according to the doctor's decision during the postoperative follow-up period, the execution of those procedures was not taken into account when the failure of IOP control was decided. The incidence of postoperative late-onset hypotony was also evaluated using the same life table method, in which the endpoint was defined as when an IOP lower than 5 mmHg was obtained at three consecutive visits, except during the first postoperative month or when a treatment such as surgical bleb repair or autologous blood injection into the bleb had been performed to treat hypotony.

Results

Mean IOP decreased from 15.9 ± 1.9 mmHg preoperatively to 11.1 ± 1.3 mmHg 1 week after surgery ($P < 0.0001$, paired t test), and the significant reduction continued throughout the follow-up period up to 4 years postoperatively ($P < 0.0001$) (Fig. 1). Prior to surgery, the number of topical antiglaucomatous eye drops used averaged 1.0 ± 0.9 (range, 0–3), and oral acetazolamide 500 mg/day was prescribed for two patients. At the latest examination after surgery, the number of topical eye drops was reduced to 0.2 ± 0.5 (range, 0–2), and oral acetazolamide was not used by any patient. Laser suture lysis and the needling procedure were performed in 22 and 5 eyes, respectively, in the follow-up period. Figure 2 shows the cumulative survival rates determined by the Kaplan-Meier life table method, in which the endpoint (i.e., failure) of IOP control was defined as when an IOP more than 30% lower than the preoperative IOP was obtained at three consecutive visits. The cumulative survival rates at 1, 2, 3, and 4 years postoperatively were 58.7 ± 7.1 (mean ± SEM), 39.4 ± 7.8, 39.4 ± 7.8, and 39.4 ± 7.8%, respectively. When the endpoint of IOP control was defined as an IOP exceeding a level 20% lower than the preoperative IOP was obtained at 3 consecutive visits, the cumulative survival rate increased to 41.3 ± 8.9% at 4 years postoperatively (Fig. 3).

There was no significant difference in mean deviation of the visual field results between the preoperative value (–17.9 ± 6.8 dB) and the last obtained value (–17.4 ± 6.9 dB) ($P > 0.5$, Fig. 4).

Figure 5 shows the cumulative survival rate from postoperative late-onset hypotony, to which the above-mentioned endpoint was applied. The cumulative survival rate from hypotony was approximately 74.7 ± 6.3% at 4 years after surgery. All postoperative complications found

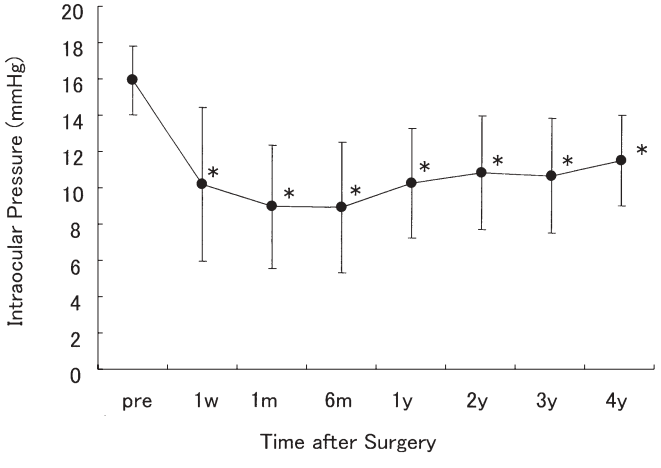

Figure 1. Averages of intraocular pressures (IOPs) before and after trabeculectomy with mitomycin C. Error bars show SD. *significantly smaller than the preoperative value (paired t test, $P < 0.0001$).

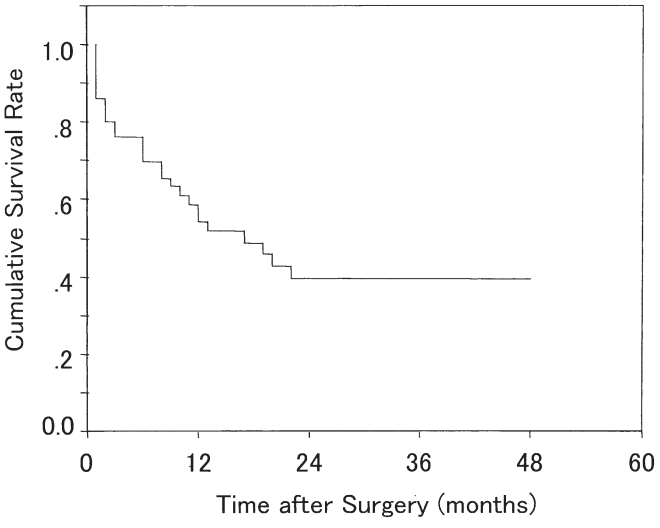

Figure 2. Cumulative survival rate determined with the Kaplan-Meier life table method, in which the endpoint (i.e., failure) of IOP control was defined as when IOPs exceeding a level 30% lower than the preoperative IOP were obtained at three consecutive visits.

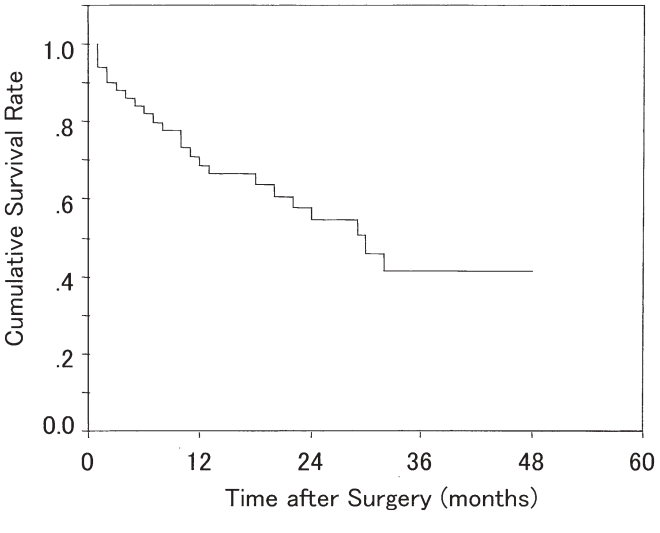

Figure 3. Cumulative survival rate determined with the Kaplan-Meier life table method, in which the endpoint (i.e., failure) of IOP control was defined as when IOPs exceeding a level 20% lower than the preoperative IOP were obtained at three consecutive visits.

Jpn J Ophthalmol
Vol 49: 223–227, 2005

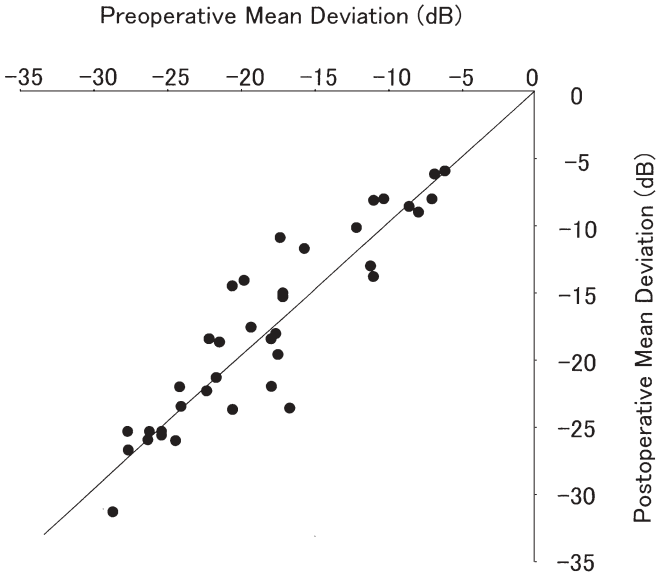

Figure 4. Changes in mean deviation of the visual field results obtained preoperatively and at the last postoperative visit.

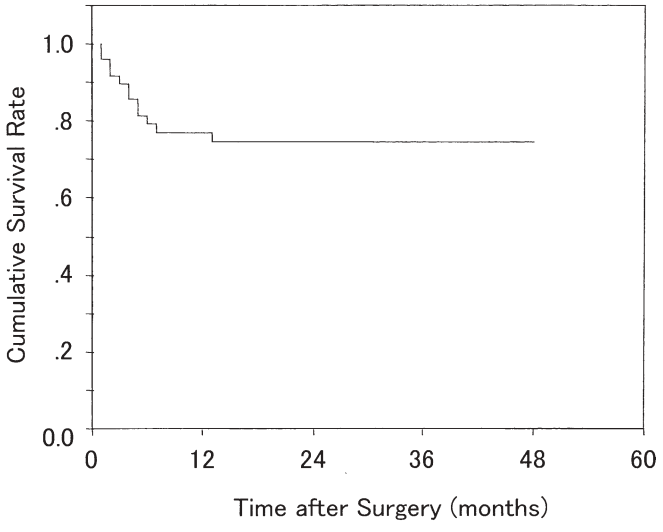

Figure 5. Cumulative survival rate from late-onset hypotony determined with the Kaplan-Meier life table method, in which the endpoint was defined as when IOPs lower than 5 mmHg were obtained at three consecutive visits or when the treatments were started to treat hypotony.

during the follow-up period are listed in Table 2. The two most common late-onset complications were those relating to the hypotonic conditions: choroidal detachment in nine eyes (23.6%) and maculopathy in seven (18.4%). In three eyes, cataract development was seen, but it was not necessary to perform cataract surgery. There were two infection cases; both were local blebitis and were successfully cured with local or systemic antibiotics. No eye developed endophthalmitis. Visual acuity was maintained in all eyes

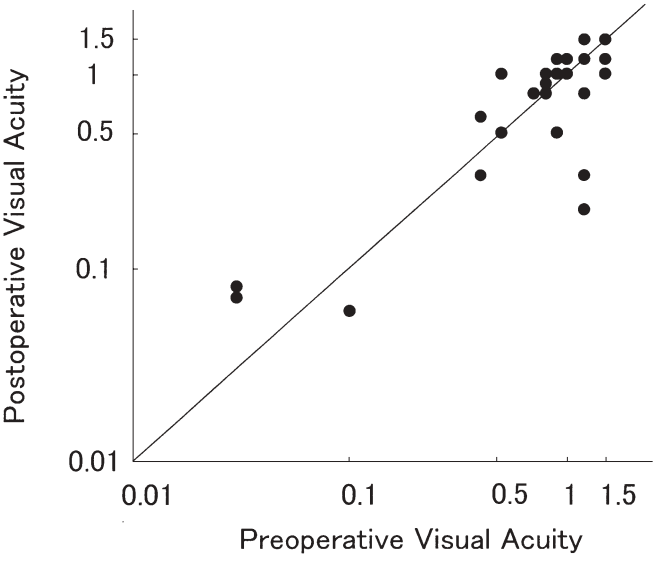

Figure 6. Changes in visual acuity decided preoperatively and at the last postoperative visit.

Table 2. Postoperative complications

	Number of eyes
Early complications	
Shallow anterior chamber	6
Choroidal detachment	9
Late complications	
Maculopathy	7
Bleb leak	1
Cataract	3
Infection (blebitis)	2

except the three in which cataract development was seen (Fig. 6).

Discussion

Mean IOP in 39 NTG patients decreased from approximately 15.9 ± 1.9 mmHg preoperatively to 11.1 ± 1.3 mmHg after trabeculectomy with MMC, and the significant IOP reduction continued up to 4 years (Fig. 1). However, when the outcome was analyzed using the life table method, only about 40% of the patients maintained successful IOP control 4 years after surgery (Figs. 2 and 3). In those life table analyses, the endpoint (i.e., failure) of IOP control was defined as when IOPs exceeding a level 30% or 20% lower than the preoperative IOP were obtained at three consecutive visits. We adopted those endpoints of IOP control in accordance with the results of a previous randomized control study in which an IOP reduction of 30% or 20% had a significantly favorable effect on the retardation of visual field defects in NTG patients.[8]

Hagiwara et al.[16] reported that IOP decreased from 14.8 ± 1.8 mmHg preoperatively to 9.6 ± 3.9 mmHg at one time

point between 2 and 7 years after trabeculectomy with MMC in 21 Japanese NTG patients. The current results shown by the 39 NTG patients included in this study are similar, and provide further information about the cumulative "survival" rate of IOP control after surgery, which should be considered as important as mean IOP change. On the other hand, the postoperative IOP control in the current study seems to be worse relative to the results of previous studies in Western countries. Membrey et al.[17] reported that the cumulative survival rate, regarded as a 25% IOP reduction at 2 years after trabeculectomy with 0.01% MMC, which was a lower concentration than used in the current study (0.04%), in 25 NTG patients was approximately 65%. Although differences in the postoperative follow-up periods and in the preoperative IOP levels should be taken into account, discrepancies in fibrotic reactions after trabeculectomy between Japanese and peoples of Western countries should account for the differences in IOP "survival" rates after trabeculectomy with MMC.

In the current study, we found several cases with late-onset postoperative complications, including hypotonous maculopathy (7/39 eyes, 18%), bleb leak (1/39 eyes, 3%), cataract (3 eyes, 8%), and blebitis (2 eyes, 5%), while no eyes developed cataract requiring surgery or endophthalmitis (Table 2). The life table analysis was used only to assess the incidence of hypotonous maculopathy. Since complications other than hypotonous maculopathy occurred in only a few patients, the life table method was not used for them. According to the life table analysis of the current results, the cumulative survival rate from postoperative hypotony was calculated as 75% at the 4-year follow-up (Fig. 5). Compared with the results reported by Membrey et al.,[17] the incidence of late hypotony (12% in their report) and that of hypotonous maculopathy (28%) are similar in our patients, while those of bleb leak (12%), cataract (surgery needed in 12%), and endophthalmitis (8%) are apparently different. These data suggest that aqueous leakage from thin-walled blebs may be associated with the development of more severe cataract and endophthalmitis.

Trabeculectomy using MMC has been a standard surgical procedure to reduce IOP in open-angle glaucoma patients. However, in patients who show a lower preoperative IOP, the amount of surgical IOP reduction should be smaller and the risk of postoperative complications should be greater or similar. If these points are taken into consideration, neither a case that does not show apparent progression in visual field damage, nor one in which baseline IOP is quite low has a good indication for surgery.

It is essential to have reliable information about the probability of maintaining successful IOP control after surgery and avoiding the risks of postoperative complications. Since this study was done in a retrospective manner, there might have been unexpected, uncontrolled, or conflicting factors. Prospective trials including strictly scheduled follow-up are necessary to provide definitive evidence of the efficacy and risks of trabeculectomy with MMC in NTG patients. Until this evidence becomes available, the results of this study should be helpful when therapeutic options are chosen for NTG patients.

References

1. Hollows FC, Graham PA. Intra-ocular pressure, glaucoma, and glaucoma suspects in a defined population. Br J Ophthalmol 1966; 50:570–586.
2. Bengtsson B. The prevalence of glaucoma. Br J Ophthalmol 1981; 65:46–49.
3. Klein BE, Klein R, Sponsel WE, et al. Prevalence of glaucoma. The Beaver Dam Eye Study. Ophthalmology 1992;99:1499–1504.
4. Shiose Y, Kitazawa Y, Tsukahara S, et al. Epidemiology of glaucoma in Japan—a nationwide glaucoma survey. Jpn J Ophthalmol 1991; 35:133–155.
5. Abedin S, Simmons RJ, Grant WM. Progressive low-tension glaucoma: treatment to stop glaucomatous cupping and field loss when these progress despite normal intraocular pressure. Ophthalmology 1982;89:1–6.
6. Hitchings RA, Wu J, Poinoosawmy D, et al. Surgery for normal tension glaucoma. Br J Ophthalmol 1995;79:402–406.
7. Koseki N, Araie M, Shirato S, et al. Effect of trabeculectomy on visual field performance in central 30 degrees field in progressive normal-tension glaucoma. Ophthalmology 1997;104:197–201.
8. Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol 1998;126:487–497.
9. Daugeliene L, Yamamoto T, Kitazawa Y. Effect of trabeculectomy on visual field in progressive normal-tension glaucoma. Jpn J Ophthalmol 1998;42:286–292.
10. Shigeeda T, Tomidokoro A, Araie M, et al. Long-term follow-up of visual field progression after trabeculectomy in progressive normal-tension glaucoma. Ophthalmology 2002;109:766–770.
11. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS). 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol 2000;130: 429–440.
12. Shields MB, Scroggs MW, Sloop CM, et al. Clinical and histopathologic observations concerning hypotony after trabeculectomy with adjunctive mitomycin C. Am J Ophthalmol 1993;116:673–683.
13. Greenfield DS, Parrish RK II. Bleb rupture following filtering surgery with mitomycin-C: clinicopathologic correlations. Ophthalmic Surg Lasers 1996;27:876–877.
14. Belyea DA, Dan JA, Stamper RL, et al. Late onset of sequential multifocal bleb leaks after glaucoma filtration surgery with 5-fluorouracil and mitomycin C. Am J Ophthalmol 1997;124:40–45.
15. Sihota R, Dada T, Gupta SD, et al. Conjunctival dysfunction and mitomycin C-induced hypotony. J Glaucoma 2000;9:392–397.
16. Hagiwara Y, Yamamoto T, Kitazawa Y. The effect of mitomycin C trabeculectomy on the progression of visual field defect in normal-tension glaucoma. Graefes Arch Clin Exp Ophthalmol 2000;238: 232–236.
17. Membrey WL, Poinoosawmy DP, Bunce C, et al. Glaucoma surgery with or without adjunctive antiproliferatives in normal tension glaucoma. 1. Intraocular pressure control and complications. Br J Ophthalmol 2000;84:586–590.