Efficacy and Complications after Trabeculectomy with Mitomycin C in Normal Tension Glaucoma.

ผลและภาวะแทรกซ้อนหลังการผ่าตัดรักษาต้อหินในผู้ป่วยต้อหินชนิดความดันนูนปกติ

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ABSTRACT

Purpose: To evaluate the efficacy and complications after trabeculectomy with mitomycin C (MMC) in Japanese normal tension glaucoma (NTG) patients using the Kaplan-Meier life table method.

Methods: Clinical records of 39 NTG patients who underwent trabeculectomy with 0.04% MMC and having postoperative follow-up period of 4 years or more were retrospectively reviewed. Postoperative 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 (mean ± SD) preoperatively to 8-11 mmHg throughout the postoperative follow-up period (P < 0.0001). The life table analysis in which failures of IOP control was defined as when IOPs exceeding 30% or 20% lower than the preoperative IOP were obtained for 3 consecutive visits showed the 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 hypotony were 74.7 ± 6.3% at 4 years after surgery. Postoperative complications observed were shallow anterior chamber (6 eyes), choroidal detachment (9 eyes), hypotonous maculopathy (7 eyes), bleb leak (1 eye), cataract development (3 eyes), and blebitis (2 eyes). No eyes developed endophthalmitis.

Conclusions: In NTG patients, trabeculectomy with MMC showed significant IOP reducing efficacy up to 4 years after surgery. Since risks of postoperative complications are unavoidable, the indication of the surgery should be carefully decided and careful follow up is necessary to avoid severe postoperative complications.
บททัศนอย

วัตถุประสงค์: เพื่อประเมินผลกระทบการรักษาและการแทรกซ้อนหลังการผ่าตัดคันธันกับการใช้ mitomycin C.

วิธีการ: ศึกษาภาวะสมดุลของผู้ป่วยจากปัญหาที่มีการแทรกซ้อนความดันตาปกติ 39 ราย ซึ่งได้รับการผ่าตัด Trabeculectomy ร่วมกับ mitomycin C, ได้ติดตามผลกระทบระยะยาวต่อเนื่องเป็นเวลา 4 ปี โดยตรวจวัดความดันตาทุก 1-2 เดือน วัดตาลของและลานสายตาทุก 6 เดือน และตรวจเราการแทรกซ้อนหลังการผ่าตัด.

ผลการศึกษา: พบว่าความคืบหน้าการกลับของที่มีความสัมพันธ์กับการผ่าตัดตลอดระยะเวลาที่ได้ตามผล (P < 0.0001) โดยตลอดจาก 15.9 mmHg ก่อนผ่าตัด เหลือ -8 -11 mmHg หลังผ่าตัด การวิเคราะห์ Life table analysis พบว่าผู้ป่วยที่ประสบผลลัพธ์ของการรักษา cumulative survival rate โดยความคืบหน้าการกลับจากก่อนผ่าตัดอย่างน้อย 30% และ 20% ตลอดระยะเวลาที่ศึกษา คิดเป็น 39.4 ± 7.8% (mean ± SEM) และ 41.3 ± 8.9%, ตามลำดับ ผลการตรวจสุขภาพตาหลังการผ่าตัด พบว่า mean deviation ไม่ผลิตจากก่อนผ่าตัดอย่างมีนัยสำคัญ (P > 0.5). ผู้ป่วยไม่เป็นภาวะ hypotony (cumulative survival rate) หลังการผ่าตัด 4 ปี คิดเป็น 74.7 ± 6.3% นอกจากนี้การแทรกซ้อนหลังผ่าตัดได้แก่ shallow anterior chamber 6 ตา choroidal detachment 9 ตา hypotonous maculopathy 7 ตา bleb leak 1 ตา cataract 3 ตา blebitis 2 ตา และไม่พบ endophthalmitis.

สรุป: การผ่าตัด trabeculectomy with mitomycin C ในผู้ป่วยที่มีความคืบหน้าการกลับมันที่มีประสิทธิผลให้ความคืบหน้าการกลับดีมากตลอดเวลา 4 ปีที่ศึกษา และเพราะสภาพหลังการผ่าตัดมีผละโอกาสที่จะเกิดการแทรกซ้อนได้ซึ่งต้องพิจารณาปรับปรุงการผ่าตัดอย่างรอบคอบและเมื่อตรวจดีตามหลังการผ่าตัดเพื่อหลักเหясีและผลแทรกซ้อนที่อาจเกิดขึ้นได้

Normal-tension glaucoma (NTG), also referred to as low-tension glaucoma, has been defined as open-angle glaucoma developing in a 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-third of open angle glaucoma. In an epidemiological report in Japan, the prevalence of NTG reached 2.04% of the 40 and older-year age population and 57.3% of all glaucoma patients found in the study.4

Although NTG should be a multifactorial disease, higher IOP is still the only one identified risk factor not only in high tension glaucoma but also in NTG. Several studies suggested that lowering IOP has beneficial effects to halt or slow progression of NTG. For example, a randomized controlled trial concluded that 30% or more reduction of IOP from the preoperative value had significantly beneficial effect to preserve visual fields in NTG patients.8 Moreover, maintaining lower IOP without remarkable fluctuation through a long period should be crucial in the treatment of open angle glaucoma.11

Introducing intraoperative use of mitomycin C (MMC) has improved the success rate of trabeculectomy. It is, however, known that postoperative complications, such as hypotony, bleb leak, cataract
development, focal bleb infection (i.e. blebitis), and endophthalmitis, have increased after the introduction of the agent.12-15 Since the postoperative target IOP is usually lower in NTG patients compared to high tension glaucoma patients, the NTG patients often face the greater risk of ocular hypotony and the associated complications such as hypotonous maculopathy,11-12 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 the long-term observation also for the postoperative complications.

The purpose of this study is to evaluate long-term results of postoperative IOP control and complications after trabeculectomy with MMC in NTG patients whose postoperative follow-up periods were 4 or more years using a life table analysis.

**Patients and Methods**

Clinical records of 39 NTG patients who underwent initial trabeculectomy (i.e. had no history of previous glaucoma surgery except laser procedures) using intraoperative MMC between April 1993 and October 1995 at the Department of Ophthalmology, University of Tokyo Graduate School of Medicine were retrospectively reviewed. The patients who underwent combined procedure of trabeculectomy and other ocular surgeries such as cataract surgery were not included.

The diagnosis of NTG was made according to 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 using a Goldmann applanation tonometer by multiple observers, and normal IOP was defined as IOP that never exceeded 21 mmHg during the follow-up period including 24-hour fluctuation, which was assessed at 2- or 3-hour intervals during an overnight stay in the hospital. Table 1 describes the characteristics of the patients, all of whom were Japanese. If both eyes of a patient underwent trabeculectomy during the above-mentioned period, data obtained

**Table 1** Patients' Demographics at the Time of Surgery.

<table>
<thead>
<tr>
<th>Number of Eyes</th>
<th>39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>55.2 ± 9.4</td>
</tr>
<tr>
<td>Male / Female</td>
<td>19 / 20</td>
</tr>
<tr>
<td>Preop IOP (mmHg)</td>
<td>15.9 ± 1.9</td>
</tr>
<tr>
<td>Mean deviation (dB)</td>
<td>-17.9 ± 6.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early complications</td>
</tr>
<tr>
<td>Shallow anterior chamber</td>
</tr>
<tr>
<td>Choroidal detachment</td>
</tr>
<tr>
<td>Late complications</td>
</tr>
<tr>
<td>Maculopathy</td>
</tr>
<tr>
<td>Bleb Leak</td>
</tr>
<tr>
<td>Cataract</td>
</tr>
<tr>
<td>Infection (blebitis)</td>
</tr>
</tbody>
</table>
in the eye which underwent surgery first was used.

Trabeculectomy was performed as follows. After local anesthesia, limbal-based conjunctival flap and scleral flap of one-half of thickness of the sclera were produced at the superior temporal quadrant. The shape of the scleral flap was triangular, and the size was approximately 3.5 mm x 3.5 mm and hinged at the corneal limbs. 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 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 2 to 5 monofilament 10-0 nylon sutures with adjustment so that a little leakage around the scleral flap margin was observed without shallowing of the anterior chamber. 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 patients were followed-up for at least 48 months after surgery. The postoperative follow-up schedule involved daily eye examinations during the first 7 to 14 days in hospitalization, once a week for the first month in the out-patient clinic, and once a month thereafter. The follow-up studies involved IOP measurements with Goldmann applanation tonometer, precise slitlamp biomicroscopy and funduscopy. To keep appropriate IOP control, topical glaucoma therapies and/or laser suture lysis or needling procedure for bleb revision were addi-
tionally done when necessary. Visual acuity was measured every 4 months postoperatively. Visual fields were evaluated with the central 30-2 program of Humphrey Visual Field Analyzer (Humphrey Inc., San Leandro, CA) within one month preoperatively and then every 6 month postoperatively. The postoperative complications, such as hypotony, hypotonic maculopathy, blebitis, endophthalmitis, were also carefully checked 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) IOPs exceeding the level 30% lower than the preoperative IOP were obtained for 3 consecutive visits; and 2) IOPs exceeding the level 20% lower than the preoperative IOP were obtained for 3 consecutive visits. Since glaucoma topical medications, laser sutureysis, and 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 deciding the failure of IOP control. Incidence of postoperative hypotony was also evaluated using the same life table method in which endpoint was defined as when IOPs lower than 5 mmHg were obtained for 3 consecutive visits or when the treatments, such as surgical bleb repair, autologous blood injection into the bleb, and so on, were carried out to treat hypotony.

**Results**

Mean IOP decreased from 15.9 ± 1.9 (mean
± SD) mmHg preoperatively to 11.1 ± 1.3 mmHg one 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) (Figure 1). Figure 2 represents the cumulative survival rates determined with the Kaplan-Meier life table method in which the endpoint (i.e. failure) of IOP control was defined as when IOPs exceeding the level 30% lower than the preoperative IOP were obtained for 3 consecutive visits, the cumulative survival rate increased to 41.3 ± 8.9% at 4 years postoperatively as shown in Figure 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, Figure 4).

Figure 5 shows the cumulative survival rate from postoperative hypotony of which the above mentioned endpoint was applied. The cumulative survival rate from hypotony was approximately 74.7 ± 6.3% at 4 year after surgery. All postoperative complications found during the follow up period are set out in Table 2. The 2 most common late-onset complications were those relating to the hypotonic conditions; choroidal detachment in 9 eyes.

![Graph](image_url)

**Fig. 1** Averages in IOPs before and after trabeculectomy with mitomycin C with error bars of standard deviation. *: significantly smaller than the preoperative value (paired t test, P < 0.0001).
Fig. 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 the level 30% lower than the preoperative IOP were obtained for 3 consecutive visits.

Fig. 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 the level 20% lower than the preoperative IOP were obtained for 3 consecutive visits.
Fig. 4 Changes in mean deviation of the visual field results obtained preoperatively and at the last visit postoperatively.

Fig. 5 Cumulative survival rate determined with the Kaplan-Meier life table method in which the endpoint was defined as when IOPs lower than 5 mmHg were obtained for 3 consecutive visits or when the treatments.
Fig. 6 Changes in visual acuity decided preoperatively and at the last visit postoperatively.

(23.6%) and maculopathy in 7 (18.4%). In 3 eyes, cataract development was seen but cataract surgery was not performed. There were 2 infection cases and both of which were local blebitis and successfully cured with local or systemic antibiotics, but no eye developed endophthalmitis. Visual acuity was maintained in all eyes except 3 in which cataract development was seen (Figure 6).

Discussion

Mean IOP in the current 39 NTG patients decreased approximately from 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 (Figure 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 (Figures 2 and 3). In those life table analyses, the endpoint (i.e. failure) of IOP control was defined as when IOPs exceeding the level 30% or 20% lower than the preoperative IOP were obtained for 3 consecutive visits. We adopted those endpoints of IOP control according to the results of a previous randomized control study in which 30 or 20% of IOP reduction showed significantly favorable effects 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 result is consistent with this previous result, and brings further information about the cumulative "survival" rate of IOP control after surgery, which should be as im-
portant as mean IOP change. On the other hand, the postoperative IOP control and the cumulative "survival" rate in the current study looks relatively worse than previous studies in the Western countries. Membrey et al.17 reported that the cumulative survival rate regarding the 25% IOP reduction at 2 years after trabeculectomy with 0.01% MMC, which was lower concentration than the current study (0.04%), in 25 NTG patients was approximately 65%. Although differences in the postoperative follow up periods and those in the preoperative IOP levels should be taken into account, discrepancies in fibrotic reactions after trabeculectomy between Japanese and peoples of Western countries should relate to 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 which needed surgery or endophthalmitis (Table 2). 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 (Figure 5). Compared with the report by Membrey et al.17 the incidence of late hypotony (12% in their report) and that of hypotonous maculopathy (28%) are similar, while that of bleb leak (12%), cataract (needed surgery, 12%) or endophthalmitis (6%) is apparently different. These suggest that aqueous leakage from thin-walled bleb may relate to the development of severer cataract and endophthalmitis.

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

It is essential to have good knowledge about probability of keeping successful IOP control after surgery and that about the risks of postoperative complications. Since this study was done in a retrospective manner, there might be unexpected or uncontrolled conflicted factors. Prospective trials including strictly scheduled follow-up should be necessary to provide definitive evidence of efficacy and risks of trabeculectomy with MMC in NTG patients. Until this evidence becomes available, the current results should be useful when choosing therapeutic options in these patients.

REFERENCES


