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ORIGINAL STUDY

Frequency and Risk Factors for Intraocular Pressure Elevation After Posterior Sub-Tenon Capsule Triamcinolone Acetonide Injection

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Purpose: This study investigated the effects of posterior sub-Tenon capsule (PST) injection of triamcinolone acetonide (TA) on intraocular pressure (IOP) in the human eye.

Methods: The study included 115 patients who received PST injections of 40-mg TA to treat macular edema with diabetic retinopathy (n = 57), branch retinal vein occlusion (n = 35), central retinal vein occlusion (n = 13), or other disorders (n = 10). IOP measurements were performed on the day of injection, and 0.5, 1, 2, 3, 6, 9, and 12 months later.

Results: In 26 (22.6%) of the 115 eyes, an IOP of 24 mm Hg or higher was observed during the 12-month follow-up period after PST TA injection. IOP elevation significantly correlated with young age, but not with past history of diabetes mellitus or systemic hypertension, sex, or type of retinal disease with macular edema. In total, 23 eyes were treated with antiglaucoma medications to control elevated IOP (24 mm Hg or higher). External trabeculotomy was performed in 1 case where medications failed to correct elevated IOP.

Conclusions: PST TA injection is associated with high rates of steroid-induced IOP elevation in eyes with previously normal IOP. However, IOP elevation may be less common after PST injection than after intravitreal injection. Our findings indicate that IOP must be carefully monitored after PST TA injection.

Key Words: glaucoma, corticosteroid, trabeculotomy

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Triamcinolone acetonide (TA) is increasingly used for the treatment of numerous macular disorders that are associated with diabetic retinopathy,[1–6] retinal vein occlusion,[6,7] choroidal neovascularization,[8–10] and uveitis.[11,12] TA is injected into either the vitreous or the sub-Tenon capsule to confine the corticosteroid effects to the ocular tissues, while minimizing the side effects associated with systemic steroid therapy. However, intravitreal injections of TA are associated with increased risks of ocular complications, including vitreous hemorrhage, retinal detachment,[12] and bacterial endophthalmitis,[6,13–16] which can often result in serious visual loss. Nonetheless, many research groups, including our own,[17] have shown that posterior sub-Tenon capsule (PST) injections can effectively reduce macular edema in cases of uveitis[18,19] and diabetic macular edema[20,21] without inducing serious ocular complications.

Intraocular pressure (IOP) elevation is a common side effect of corticosteroid therapy. Although the topical, intravitreal, and systemic corticosteroid administration routes have been reported to cause IOP elevation, the effects of PST injection remain unclear. A few case series of uveitis patients showing IOP elevation after PST injection have been reported previously.[18,19,22,23] However, bearing in mind the large number of patients with macular edema, surprisingly little is known about the frequency, time course, duration, and risk factors of IOP elevation after PST injection. To address this deficit, we carried out a retrospective investigation into the predictive factors of IOP elevation following PST injection of TA.

PATIENTS AND METHODS

Our interventional case series included 115 consecutive eyes from patients with macular edema who underwent PST TA injection, after giving informed consent, at the Kumamoto University Hospital in Japan between June 2003 and January 2004. Patients with macular edema due to uveitis were excluded from the analysis, because treatment with additional corticosteroids and inflammation in the anterior chamber can both affect IOP. Eyes with an IOP of 22 mm Hg or higher were also excluded from the analysis. To avoid biases related to host factors, if both of a patient's eyes were treated with TA, only the eye that first received treatment was included in the analysis. The PST injections were

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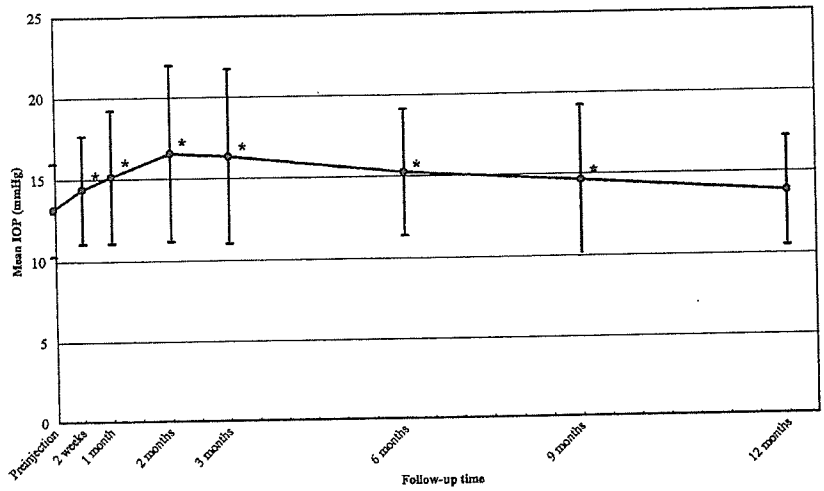

FIGURE 1. The mean IOP at each time point after PST injection of TA. The IOPs at 2 weeks, and 1, 2, 3, 6, and 9 months, were significantly higher than those before the injection. *$P<0.05$; Mann-Whitney U test.

performed using the previously described protocol, with minor modifications.[24] After disinfection with povidone-iodine and topical anesthesia with xylocaine, the conjunctiva and sub-Tenon capsule in the inferotemporal quadrant were incised with scissors. A 25-gauge curved blunt cannula was inserted into the sub-Tenon space to allow the infusion of 40-mg TA (Kenacort; 40 mg/mL; Bristol Pharmaceutical, YK, Tokyo, Japan). At the end of the procedure, the wound was left unsutured and ofloxacin ointment (Tarivid ophthalmic ointment; Santen Pharmaceutical Co, Ltd, Osaka, Japan) was applied to the eye. Each patient was instructed to use 0.5% levofloxacin (Cravit ophthalmic solution; Santen Pharmaceutical Co, Ltd, Osaka, Japan) 4 times per day for 1 week. In addition to these examinations, optical coherence tomography (Humphrey model 2000; Carl Zeiss Meditec International, Germany) was used to measure the central retinal thickness. The IOP was monitored for at least 6 months after the TA injection.

Information on each subject was obtained from a review of their medical records. The IOP measurements were recorded on the day of injection, and 0.5, 1, 2, 3, 6, 9, and 12 months later. All data are presented as the mean (± the standard deviation; along with the range of values). Multiple regression analysis was used to evaluate the effects on IOP of age, sex, lens state (phakic or pseudophakic), vitreous state (vitreous or nonvitreous), systemic diseases, and the number of injections. A Wilcoxon signed-rank test was used to compare the rise in IOP after the first injection with those after subsequent injections. The Spearman rank correlation was used to analyze the relationship between IOP and the thickness of macular edema after the injection. A probability (P) value less than 0.05 was considered statistically significant.

RESULTS

The study population consisted of 115 eyes from a total of 74 males and 41 females, with a mean age of 62.2 (± 12.6; range = 13 to 84) years. The most common retinal diseases accompanying macular edema were diabetic maculopathy (57 eyes; 49.6%), branch retinal vein occlusion (35 eyes; 30.4%), and central retinal vein occlusion (13 eyes; 11.3%). The other disorders present (10 eyes; 8.7%) included exudative age-related macular degeneration, idiopathic focal subretinal neovascularization, polypoidal choroidal vasculopathy, and idiopathic juxtafoveal retinal telangiectasis. The mean follow-up period was 394.9 (± 145.3; range = 180 to 672) days.

The mean IOP before the TA injection was 13.1 (± 2.8; range = 6 to 20) mm Hg, and the mean maximum

TABLE 1. Frequency of Cases of Elevated IOP After PST Injections of 40 mg TA

	No. Cases (%)								
IOP (mm Hg)	Baseline	2 wk	1 mo	2 mo	3 mo	6 mo	9 mo	12 mo	Final
≤21	115/115 (100)	108/112 (96.4)	101/110 (91.8)	88/104 (84.6)	97/113 (85.8)	107/114 (93.9)	81/89 (91.0)	61/62 (98.4)	113/115 (98.3)
22-23	0	3/112 (2.7)	5/110 (4.5)	4/104 (3.8)	5/113 (4.4)	3/114 (2.6)	3/89 (3.4)	1/62 (1.6)	1/115 (0.9)
24-29	0	1/112 (0.9)	4/110 (3.6)	9/104 (8.7)	8/113 (7.1)	3/114 (2.6)	4/89 (4.5)	0	1/115 (0.9)
30-34	0	0	0	1/104 (1.0)	2/113 (1.8)	1/114 (0.9)	0	0	0
35-39	0	0	0	1/104 (1.0)	1/113 (0.9)	0	1/89 (1.1)	0	0
≥40	0	0	0	1/104 (1.0)	0	0	0	0	0
>21	0	4/112 (3.6)	9/110 (7.6)	16/104 (15.4)	16/113 (14.2)	7/114 (6.1)	8/89 (9.0)	1/62 (1.6)	2/115 (1.7)
≥30	0	0	0	3/104 (2.9)	3/113 (2.7)	1/114 (0.9)	1/89 (1.1)	0	0
≥40	0	0	0	1/104 (1.0)	0	0	0	0	0

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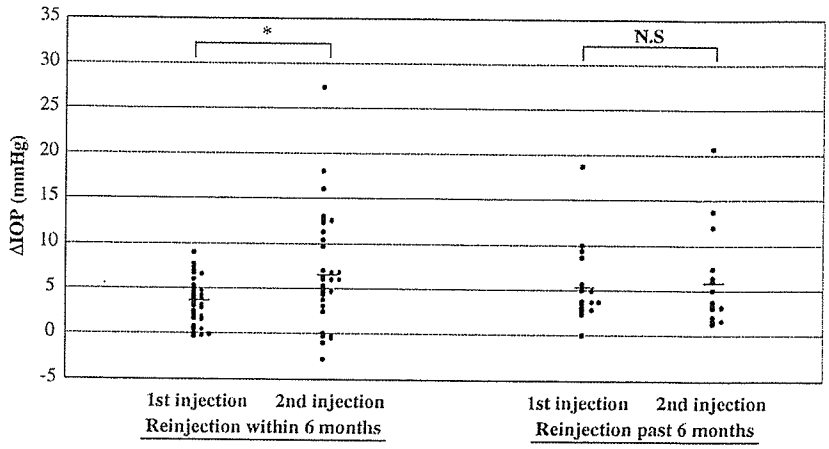

FIGURE 2. IOP elevation augmented by an additional injection of TA after a short time interval. The ΔIOP was calculated for the first and second injections, respectively. When additional injections were performed within 6 months of the first, the ΔIOPs for the second injection were significantly higher than those for the first injection. *P<0.01; Wilcoxon singed-rank test.

IOP after the injection was 19.8 (± 6.3; range = 9 to 42) mm Hg. Thus, the mean rise in IOP was 6.7 mm Hg. The IOPs recorded from 2 weeks to 9 months after the TA injection were significantly higher than those observed before the injection. The mean IOP showed a gradual increase after the injection, peaked at 2 months, and then decreased gradually until reaching a minimum at 12 months (Fig. 1). In addition, 26 (22.6%) of the 115 eyes showed an IOP of 24 mm Hg or higher 1.8 (± 0.8) months after the TA injection. The numbers of eyes with an elevated IOP of 24 mm Hg or higher gradually increased from 2 weeks to 2 months after the TA injection (Table 1), and all such cases were established by 3 months after the injection.

Additional TA injections were performed in 48 (41.7%) of the 115 eyes, because of a recurrence of macular edema after the first injection. For each of the eyes treated with an additional TA injection, we calculated the peak IOP after the injection minus the IOP before the first injection (that is, the ΔIOP). The mean ΔIOP values were 4.1 (± 3.4) mm Hg for the first injection, and 6.4 (± 5.8) mm Hg for the second injection. There was a statistically significant difference between the ΔIOP values for the first and second injections (P < 0.01). Interestingly, when additional injections were performed within 6 months of the first, the ΔIOP values for the second injection were significantly higher than those for the first (P < 0.01). However, there was no statistically significant difference between the ΔIOP values for first and second injections that were performed with more than a 6-month gap between them (Fig. 2).

To investigate the factors affecting IOP elevation after TA injection, multiple regression was used to analyze the relationships between the ΔIOP values (defined as the peak IOP during the total time course minus the preinjection IOP) and the other items. The results demonstrated that age was significantly negatively correlated with ΔIOP. By contrast, there were no significant correlations between ΔIOP and systemic associations of diabetic mellitus or hypertension, or sex (Table 2). In addition, there was no correlation between the ΔIOP and the reduction in relative retinal thickness (RT) calculated using the following formula:

$$RT_{(\text{before the injection})} - RT_{(\text{minimum value after the injection})}/RT_{(\text{before the injection})}$$

Of the 26 eyes that showed an IOP of 24 mm Hg or higher after the TA injection, 19 (73.1%) were administered antiglaucoma ophthalmic drops. The mean maximal number of drops administered during the period of IOP elevation was 1.5 (± 0.7; range = 1 to 3). Oral carbonic anhydrase inhibitors were used in 1 case, which subsequently needed surgical treatment, because the peak IOP reached 35 mm Hg and remained associated with glaucomatous visual field defects, despite treatment with antiglaucoma ophthalmic drops (timolol, latanoprost, and dorzolamide) and oral acetazolamide. External trabeculotomy was performed 10 months after the TA injection in this case, in an attempt to reduce the unresponsive IOP. During the follow-up period after surgical treatment, the IOP in this patient decreased to between 14 mm Hg and 16 mm Hg after treatment with 1 type of antiglaucoma ophthalmic drop (latanoprost).

With regard to TA-related side effects other than IOP elevation, 9 (15.0%) of the 60 phakic eyes showed

TABLE 2. Risk Factors of IOP Elevation After PST Injections of 40 mg TA

	t value (95% CI)		P
Age	−2.32724	(−0.186 to −0.015)	0.022
Sex	−1.41544	(−4.096 to 0.684)	0.160
Laterality of the eye	−0.33899	(−2.431 to 1.721)	0.735
Lens state (phakic or pseudophakic)	0.150151	(−2.448 to 2.849)	0.881
Vitreous state (vitreous or nonvitreous)	−0.35939	(−3.060 to 2.121)	0.720
General disease			
Diabetic mellitus	−1.88658	(−4.460 to 0.111)	0.062
Hypertension	0.54164	(−1.545 to 2.706)	0.589
No. injections	2.193439	(0.170 to 3.363)	0.030

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progression of posterior subcapsular or cortical cataracts. Surgery was performed in 4 of these cases during the follow-up period. An additional complication that was observed in 1 eye (0.9%) after the TA injection was blepharoptosis. Bacterial endophthalmitis, progression of retinopathy, perforation of the eyeball, and orbital fat atrophy were not observed.

DISCUSSION

Although a PST injection of TA delivers a large amount of corticosteroid to the posterior segment of the eye via transscleral absorption, the side effects of this procedure have remained unclear. Our current data show the frequency, time course, duration, and risk factors for IOP elevation after PST TA injection. Several groups previously reported IOP elevation after PST injection of TA in eyes with uveitis. However, the frequency of IOP elevation seemed to vary significantly between the different studies, with values ranging from 1.7% to 36% being reported.[18,19,22,23,25] Corticosteroids other than TA are often simultaneously administered, both topically and orally, for the treatment of uveitis, and these drugs, along with uveitis-associated ocular inflammation, might affect IOP. We therefore excluded eyes with uveitis from our current study, to evaluate the frequency of TA-induced IOP elevation more accurately. In our series, 26 (22.6%) of the 115 eyes showed an elevated IOP of 24 mm Hg or higher. In this study, we considered 24 mm Hg or higher as a level of abnormal IOP, that has been done in previous study.[26] These data were similar to those reported by Okada et al[19] in eyes with uveitis. By contrast, it was previously found that TA injection into the vitreous induced ocular hypertension in 30% to 40% of eyes,[26–29] indicating that IOP elevations might be more common after intravitreal injection than after PST injection. Jonas et al[27] showed that IOP readings higher than 21, 30, and 40 mm Hg were measured in 41.2%, 11.4%, and 1.8%, respectively, after intravitreal injection of approximately 20 mg TA. It indicated that intravitreal injection of TA induces more drastic and frequent IOP elevation than the PST injection does (Table 1). Additionally, the IOP elevation in the present study peaked 2 months after the injection, and then decreased gradually, reaching a minimum after 12 months. Previous reports on intravitreal injection[27] showed that the TA-induced IOP elevation peaked within 3 months of the injection, demonstrating a similar time course to PST injection. Although the pharmacokinetics of TA after PST injection remain unclear,[30,31] the duration of IOP elevation might correspond to the decay time of TA crystals within the ocular tissues. Interestingly, the amount of IOP elevation after the second injection was significantly greater than that after the first injection when the interval between the 2 was 6 months or less. These data suggest that the accumulation of TA in the sub-Tenon capsule might amplify the side effects on IOP. It is not known whether the TA-induced IOP elevations after PST and intravitreal injections are dose-dependent. Further analyses will therefore be needed to verify whether the IOP elevation depends upon the dosage of TA.

The multiple regression analysis showed that younger age was a significant predictive factor for IOP elevation. Younger patients are also reported to be at a higher risk of developing steroid-induced glaucoma through the use of corticosteroid eye-drops.[32] Although it remains unclear why younger patients should experience steroid-induced ocular hypertension more frequently, it is possible that PST injection of TA might induce IOP elevation in younger patients via the same mechanism. In our current analysis, there were no correlations between the frequency of IOP elevation and any factors other than age. Patients with diabetes have been reported to experience a higher incidence of IOP elevation caused by corticosteroid therapy.[33] By contrast, a recent randomized clinical trial demonstrated that diabetes mellitus was not a major risk factor for glaucoma.[34,35] This supports the present finding of a correlation between TA-induced IOP elevation and diabetes mellitus.

With the exception of cases of IOP elevation, cataracts developed in 15% of the patients in the current study after the PST TA injection. The progression of cataracts was previously reported in 24.2% of patients after intravitreal injection,[29] thereby demonstrating a higher incidence than that observed after PST injection. PST injection has previously been linked to complications such as mis-injection-related embolic occlusion of the central retinal artery,[36,37] orbital abscess,[38] and cutaneous hypopigmentation.[39] However, no such complications were encountered in the present study. Blepharoptosis, which was encountered in the present study, is a known complication of PST injection, because the local effects of triamcinolone are thought to be associated with wasting of the lid muscle, and weakening of the tendon, levator muscle, levator aponeurosis, and orbital septum.[40] The intravitreal injection of TA is reportedly associated with bacterial endophthalmitis[6,13–16] at a frequency of 0.87%.[15] On the other hand, there have been no previous reports on endophthalmitis after PST injection. Because this technique does not penetrate the sclera tissue, the risk of endophthalmitis might be much lower for PST injection than for intravitreal injection. However, bacterial endophthalmitis is rare complication in the field of ophthalmic surgery, so future collaboration and pooling of data from other intervention studies will be useful to clarify the safety of PST injection of TA.

Despite the administration of antiglaucoma medication, prolonged IOP elevation was encountered in 1 eye. We therefore performed an external trabeculotomy to correct this uncontrollable elevated IOP. Several other groups have reported using filtering surgeries, such as trabeculectomy, on eyes with IOP elevation induced by TA.[11,18,22,27,41] We previously demonstrated that external trabeculotomy was effective in 14 out of 14 eyes with steroid-induced glaucoma.[42] It has been hypothesized that corticosteroids promote the abnormal accumulation

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of extracellular matrices in the trabecular meshwork, thereby leading to an increased resistance of aqueous outflow.[43–47] Because trabeculotomy reduces the outflow resistance in the trabecular meshwork and the inner wall of Schlemm's canal, we believe that external trabeculotomy is the reasonable surgical choice for controlling elevated IOP in eyes with TA.

In conclusion, PST injection of TA caused an elevated IOP of 24 mm Hg or higher at a frequency of 22.6% within 3 months of the injection. Furthermore, in younger patients, an additional injection within 6 months of the first often caused a further increase in IOP. Our data suggest that IOP should be monitored for at least 3 months after PST TA injection, especially in younger patients or those who are given an additional injection within 6 months.

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Stability of Central Visual Field After Modern Trabeculectomy Techniques in Eyes with Advanced Glaucoma

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Short title: Trabeculectomy for Advanced Glaucoma

Abstract

Purpose: To determine surgical results and complications of trabeculectomy in advanced glaucoma with threatened fixation.

Methods: In this study, trabeculectomy was done with mitomycin C and postoperative laser suturelysis. We reviewed clinical records prior to, and at 2 months after trabeculectomy and long term surgical outcomes in 49 eyes.

Results: At 2 months after surgery, there were no eyes with fixation loss. The chance of visual acuity remaining within two lines of preoperative level was 75%. IOP levels reduced from xx $\pm$ xx mmHg to 11.7 $\pm$ 4.7 mmHg. Kaplan-Meier survival analysis showed that the success rate in achieving intraocular pressures (IOPs) of 15mmHg or lower at 5 years after surgery was 70 %. In 29 of 49 eyes, the visual acuities kept in their pre-operative level at the final visit. But, visual acuity decreased to less than 0.1 in 3 eyes (cataract progression n=2; fixation loss n=1).

Conclusion: Our results suggest that laser suturelysis and step-wise management of IOP levels, which were performed in the modern postoperative management for trabeculectomy decrease the frequency of fixation loss during the early phase after trabeculectomy.

Key words

Hypotony, hypotensive maculopathy, wipe-out, overfiltration

Introduction

Loss of the central visual field (fixation loss) in glaucomatous eyes with advanced visual field defects has been reported by a number of investigators.[1-12] Sudden visual loss during or immediately after trabeculectomy, which is referred to as "wipe-out"[1,2] or "snuff-off",[13] is regarded as one of the most serious complications in trabeculectomy, and results in a decreased quality of life for glaucomatous patients. However, the mechanism and prevention of this serious complication are well unknown although it has been suggested that hypotonic condition may be one of risk factors for fixation loss in advanced glaucoma.[reference]

Recently, the adjunctive use of anti-metabolites such as mitomycin C (MMC) and 5-fluorouracil has dramatically improved filtration efficiency. On the other hand, the occurrence of adverse effects associated with overfiltration such as shallow anterior chamber, choroidal detachment and hypotonic maculopathy have become increased. Therefore, tight sutures for scleral flap, postoperative laser suturelysis and ocular massages are conducted to achieve step-by-step IOP reduction. These modified intraoperative and postoperative managements enable us to decrease postoperative IOP fluctuation during the early postoperative period. Thus, it is likely that these modifications may influence the postoperative complications associated with hypotony including hypotensive maculopathy and fixation loss. Herein, we reviewed postoperative surgical results, complications, and visual prognosis after

modern MMC trabeculectomy techniques in eyes with advanced glaucoma.

Materials and Methods

We retrospectively examined the surgical outcomes for patients with advanced glaucoma who underwent trabeculectomy at Kumamoto University Hospital. Written informed consent about the surgical procedure, the predictive merits and complications were obtained from all the patients. The IRB Committee at Kumamoto University Graduate School of Medical Sciences has approved the retrospective chart review. In a previous report, a generic grading system was devised to grade glaucomatous visual field defects.[14] Visual fields were assessed on the Goldmann perimeter. The classifications were, grade 0 = no visual field defect present; grade I = nasal step or localized paracentral defect; grade II = nasal step and paracentral defect or a single arcuate defect; grade III = two arcuate scotomas or an altitudinal scotoma not encroaching on fixation; grade IV = advanced visual field loss abutting, but not involving, fixation; and grade V = advanced visual field loss with loss of fixation.

To avoid biases related to host factors, when both eyes were included in the criteria, the eye that first received trabeculectomy was included in the study. This study included 49 eyes of 49 patients that were classified as grade IV. Furthermore, we subdivided the visual field defects into three categories, grade IV-1 = visual field loss in one or more hemispheres; grade IV-2 = isolated fixation with visual island(s); grade IV-3 = fixation only (Fig.1). There were 23 eyes with grade IV-1, 8 eyes with grade IV-2, and 18 eyes with grade IV-3. Patients with grades 0, I, II, III and V or

those without reliable visual field data were excluded from the study. In addition, patients with glaucoma secondary to uveitis, trauma, and ischemic retinal diseases were also excluded. Of those included in the current study, there were cases of primary open-angle glaucoma in 27 eyes, primary angle closure glaucoma in 10 eyes, and exfoliative glaucoma in 12 eyes (Table 1). Previous glaucoma surgeries were trabeculectomy in 10 eyes, laser iridotomy in 8 eyes and goniosynechiolysis in 1 eye.

Indications for trabeculectomy were: patients with progressing visual field damage, even with maximally tolerated anti-glaucomatous medications, and/or those treated with oral acetazolamide to control IOP. Trabeculectomy was performed after retrobulbar anesthesia. After the limbal-based conjunctival incision, 4 x 4 mm –square scleral flap was prepared. Then, 0.04% MMC was applied in the conjunctival scleral flaps for three to five minutes. The operative field was washed immediately with 200 ml of balanced saline solution. Sclero-corneal tissue, including the trabecular meshwork, was then excised. Two to ten 10-0 nylon sutures were placed to close the scleral flap, and a shoelace continuous conjunctival suture was placed. After surgery, IOP levels and formation of filtering blebs were followed, and postoperative laser suturelysis and associated ocular massage were conducted in a step-by-step manner until the expected target pressure was achieved. Laser suturelysis was conducted postoperatively when IOP increased and/or the filtering bleb became more localized and flattened. Also, ocular compression (massage) was

added routinely after the laser suturelysis. Postoperative medications included topical corticosteroid and antibiotic drops were administrated for about 3 months.

We compared pre- with post-operative best corrected visual acuities (at 2 months after trabeculectomy), and evaluated IOP and operative complications from patients' records. Operative complications were defined as: choroidal detachment, hyphema, hypotony (IOP of 4 mmHg or lower) for at least 14 days, flattened anterior chamber, hypotensive maculopathy, expulsive hemorrhage, endopthalmitis, cataract progression and fixation loss. Furthermore, we examined the number of scleral sutures during surgery, and the timing and the number of laser suturelysis after surgery. Next, to evaluate long term outcomes of trabeculectomy, Kaplan-Meier analysis using target IOP (20, 15 and 12 mmHg) was used to determine cumulative success probabilities of trabeculectomy. Postoperative visual acuity at long term follow-up was examined at the final visit.

Results

Outcomes of visual acuity and operative complications at early phase after trabeculectomy

There were no eyes with fixation loss at 2 months after surgery. Changes of visual acuity before and after trabeculectomy (at 2 months) in 49 eyes are shown in Fig.2. The chance of visual acuity remaining within two lines of preoperative level was 75% at 2 months after the surgery. Decreased visual acuity with 3 lines or more were encountered in 7 eyes, but visual acuity gradually recovered to the preoperative value in 2 of the 7 eyes. The other 5 eyes were associated with cataract progression (n=3), retinal vein occlusion (n=1) and hyphema (n=1). In the eye with hyphema, hemorrhage in the anterior chamber diffused into the vitreous space because of aphakia. However, the visual acuity recovered to pre-surgical levels when the vitreous blood was absorbed. At 1st day after the surgery, the mean post-operative IOP was 11.4 $\pm$ 7.8 mmHg (range, 1~34). Although IOP levels of 4 mmHg or lower were associated with 7 eyes at 1st day after the surgery, no eyes were associated with prolonged hypotony for 14 days or more. Choroidal detachment was seen in 15 eyes, disappeared in several days after surgery. Hyphema between 3 and 37 days after surgery was seen in 12 eyes. Hypotensive maculopathy, flattened anterior chamber, Endophthalmitis or expulsive hemorrhage were not seen in the current study. The mean number ($\pm$ standard deviation) of scleral flap sutures was 4.5 $\pm$ 1.3 (range, 2~7),

and the mean number of performed suturelysis was 1.6 ± 1.7 (range, 0~6). Laser suturelysis was conducted an average of 7.6 ± 12.1 days (range, 2~65 days) after the surgery.

Long term outcome of trabeculectomy

At the final visit, IOP was reduced to 11.8 ± 4.2mmHg in 49 eyes. Using Kaplan-Meier survival analysis, the success rates for achieving target IOPs of 20, 15 and 12mmHg for 5 years after the surgery were 100, 70 and 25%, respectively (Fig.3). The chance of visual acuity remaining within two lines of preoperative level was 59% (29 eyes) at final visit. Three eyes exhibited a decreased postoperative visual acuity of less than 0.1 (9%), caused by cataract progression in 2 eyes, and fixation loss in 1 eye (Fig. 5). As for the eye with primary open-angle glaucoma associated with fixation loss, the visual field of Grade IV-2 and visual acuity of 1.0 regressed to fixation loss and hand motion level at 3.5 years after surgery, respectively although the IOP levels around 20 mmHg before surgery was controlled to the level of 8 to 11 mmHg until the association of fixation loss.

Discussion

No eyes with advanced glaucoma in our study had sudden postoperative fixation loss at early phase after trabeculectomy. Several previous studies have described about the risk of sudden fixation loss after surgery (Table 2). Kolker et al.[1] and Aggarwal et al.[2] described that loss of fixation was seen in 3 out of 22 eyes (13.6%) and 4 out of 26 eyes (15.4%), respectively, after trabeculectomy in advanced primary open-angle glaucoma. On the other hand, in the 1990s, the frequency of fixation loss has been decreased. Levene,[15] Martinez et al.[16] and Costa et al.[13] reported that loss of fixation after trabeculectomy was encountered in 1 of 96 advanced glaucomatous eyes, no eyes of 54 advanced glaucomatous eyes and 4 of 508 glaucomatous eyes, respectively. The decreased incidence of sudden visual acuity loss after trabeculectomy in eyes with advanced glaucoma is thought to be due to postoperative step-by-step IOP reduction obtained by intraoperative application of antimetabolites and postoperative laser suturelysis. Filtering effect of trabeculectomy has become more drastic during the long postoperative period because wound-healing activities can be inhibited by the adjunctive aid of anti-metabolites such as 5-fluorouracil and MMC. On the other hand, overfiltration has caused higher incidences of hypotonic maculopathy and prolonged choroidal detachment, and can lead to poorer visual result. Costa et al.[13] reported that hypotonic IOP levels between 0 to 2 mmHg were observed in 3 of 4 eyes which encountered fixation loss after the surgery. Thus,

postoperative hypotonic conditions may be regarded as a significant risk factor. With the subsequent introduction of multiple sutures combined with laser suturelysis, it has recently become possible to lower postoperative IOP in a step-by-step manner. In our series, no eyes encountered prolonged hypotony. Our data suggest that the subsequent surgical procedure of trabeculectomy with MMC, tight sutures for scleral flap, postoperative laser suturelysis and ocular massages decreases the risk of fixation loss in eyes with advanced glaucoma because of less frequency of hypotony or excess IOP fluctuation after surgery.

However, one eye encountered fixation loss during the long term follow-up, not at the early phase. The IOP levels of the eyes were controlled between 8 and 11 mmHg. It means that the mechanism of fixation loss at the chronic phase after trabeculectomy may be different from the mechanism in the early phase after trabeculectomy. Recently, it has been suggested that several IOP-independent factors such as circulatory disorder, autoimmunity and glutamate toxicity are associated with the progression of glaucomatous optic neuropathy.[references] Further studies will be required for elucidating the risk factors related to fixation loss during chronic phase after trabeculectomy in eyes with advanced glaucoma.

In conclusion, trabeculectomy with MMC and tight sutures for scleral flap, followed by postoperative laser suturelysis, results in rare incidence in postoperative hypotony demonstrating rare frequency of fixation loss. We suggest that the

procedure may be favorable for IOP lowering in advanced glaucoma.

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