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Surgical Results of Trabeculectomy among Groups Stratified by Prostaglandin-Associated Periorbitopathy Severity

Akiko Ishida, MD,[1] *Takako Miki, MD, PhD,*[2] *Tomoko Naito, MD, PhD,*[2] *Sho Ichioka, MD,*[1] *Yuji Takayanagi, MD,*[1] *Masaki Tanito, MD, PhD*[1]

Purpose: To report the role of prostaglandin-associated periorbitopathy (PAP) severity in the surgical effectiveness of trabeculectomy (LEC).

Design: Retrospective observational case series.

Participants: A total of 139 consecutive eyes of 139 Japanese subjects (74 men, 65 women; mean age ± standard deviation, 65.7 ± 10.6 years) who underwent LEC were included. All had primary open-angle glaucoma (POAG), no history of conjunctival incisional surgery, completed all postoperative visits for 12 months, and information on the PAP severity using the Shimane University PAP Grading System (SU-PAP).

Methods: Data were collected from a medical chart review at 2 hospitals.

Main Outcome Measures: Comparison of surgical success rates among groups stratified by SU-PAP grades 0 to 3 by survival curve analysis using the definitions of failure based on surgical intervention other than laser suture lysis (LSL), intraocular pressure (IOP) reduction below 20%, postoperative IOP exceeding 15 mmHg (definition A) or 12 mmHg (definition B), and a postoperative IOP below 6 mmHg.

Results: Twelve months postoperatively, the success rates of grades 0, 1, 2, and 3 were 86%, 68%, 40%, and 0%, respectively, for definition A ($P < 0.0001$, log-rank test) and 86%, 61%, 36%, and 0%, respectively, for definition B ($P < 0.0001$). Interventions other than LSL ($P < 0.0001$, Cochran-Armitage trend test), IOP reduction less than 20% ($P = 0.010$), and IOP exceeding 15 mmHg ($P = 0.016$) or 12 mmHg ($P < 0.0001$) were associated with surgical failure; IOP under 6 mmHg was not ($P = 0.31$). The proportional hazard model for definition A showed that compared with grade 0, grade 2 (risk ratio [RR], 5.82, $P = 0.0043$) and grade 3 (RR, 12.2, $P = 0.0003$) were associated with surgical failure. For definition B, grade 1 (RR, 3.53, $P = 0.040$), grade 2 (RR, 6.65, $P = 0.0021$), and grade 3 (RR, 12.0, $P = 0.0003$) were associated with surgical failure. Differences in age, gender, preoperative IOP and medications, refractive error, and simultaneous cataract surgery were not associated with surgical failure in both models.

Conclusions: The preoperative presence of severe PAP worsens the 1-year success rate of LEC in patients with POAG. To retain the surgical effectiveness, treating physicians should prevent patients from progressing to severe PAP, an avoidable side effect, by switching or stopping the causative medications.

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Topical prostaglandin F2α–derived prostanoid FP receptor agonists are the most common medical treatment for glaucoma because of their excellent intraocular pressure (IOP)-lowering effect with a lower frequency of eye drop instillation and fewer systemic side effects,[1] although the use of this medication class is associated with local side effects referred to as "prostaglandin-associated periorbitopathy syndrome" (PAP).[2] Hypertrichosis and periocular hyperpigmentation are linked to the FP agonists' effects on hair follicles[3] and melanogenesis[4] or melanocyte proliferation,[5] respectively. However, deepening of the upper eyelid sulcus (DUES) and enophthalmos are linked to inhibition of adipogenesis of orbital fat.[6] Accordingly, each sign of PAP may occur through different mechanisms. A mechanical insult to the eyelids in patients with DUES caused levator dehiscence leading to Müller's muscle degeneration.[7] Thus, further remodeling of the extracellular matrix of the orbital/deeper lid tissue is associated with ptosis and hardening of lid skin.[8] With a deep upper eyelid sulcus and no preseptal fat, lifting a tight lid without applying pressure to the globe is difficult,[9] resulting in difficulty performing Goldmann applanation tonometry (GAT). Therefore, in the presence of ptosis and tight eyelids, PAP is not merely a cosmetic side effect, but it also affects glaucoma management. We use our inhouse grading system, referred to as the "Shimane University PAP Grading System" (SU-PAP), to grade PAP severity based on the underlying mechanisms of PAP. The severity is divided into 4 grades, with grade 0 indicating no PAP, 1 indicating superficial cosmetic

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PAP, 2 indicating deep cosmetic PAP, and 3 indicating tonometric PAP.[10] Using this system, we previously reported a difference in severity of PAP among different FP agonists and the roles of PAP in overestimation of IOP measured by GAT.[10]

A previous study suggested that the presence of DUES was associated with a lower success rate of trabeculectomy (LEC), and presurgical use of bimatoprost was associated with a higher risk of recurrent IOP elevation than other FP agonists for up to 24 months postoperatively.[11] In the current 2-center study, using SU-PAP, we assessed the effect of PAP severity on the surgical effectiveness of LEC in patients with primary open-angle glaucoma (POAG).

Methods

This retrospective observational case series study adhered to the tenets of the Declaration of Helsinki; the Institutional Review Board (IRB) of Shimane University Hospital reviewed and approved the research conducted at both Shimane University Hospital and Grace Eye Clinic (IRB No. 20210908-1; approval date, October 22, 2021). The IRB approval did not require that each patient provide written informed consent for publication; the study protocol was posted at the study institutions to notify participants about the study. All subjects who met the inclusion criteria and did not meet the exclusion criteria were selected from the department database. The inclusion criteria required that eyes underwent LEC or LEC combined with small-incision cataract extraction (LEC-CE) between June 2018 and December 2020 at 1 of the 2 study sites; POAG; no history of previous intraocular surgery except uncomplicated small-incision cataract surgery, ab-interno minimally invasive glaucoma surgery, and any laser therapy; and completion of all postoperative visits at months 1 (range, 2−6 weeks), 3 (1.5−4 months), 6 (5−7 months), 9 (8−10 months), and 12 (11−13 months). The PAP severity graded by SU-PAP was recorded in the medical chart preoperatively or anterior segment photographs that allowed us to determine the SU-PAP grade were obtained preoperatively. The exclusion criteria included the presence of a conjunctival scar, phacodonesis or lensdonesis, vitreous prolapse, and total inability to perform GAT because of PAP. If both eyes were eligible, the eye with the earlier surgical day was included. An institutional database search identified 205 trabeculectomies that were performed to treat POAG during the study period in both hospitals. As a result, 139 consecutive eyes of 139 Japanese subjects (74 men, 65 women; mean age ± standard deviation, 65.7 ± 10.6 years) were included in the study. No eye was excluded from the study because of the inability to perform GAT.

Surgical Procedure

All surgeries were performed under standard sub-Tenon anesthesia using 2% lidocaine. LEC was performed in the superior hemisphere. After creation of a limbal-based conjunctival peritomy of less than 1 quadrant, a half-thickness 3−4 × 3−4-mm scleral flap was created. After the first flap was dissected, 0.04% mitomycin C was applied for 3 minutes followed by rinsing with balanced salt solution. Under the first scleral flap, a four-fifths−thickness second flap was created inside the scleral bed of the first flap, and then the trabecular tissue was excised en bloc in the second scleral flap. After a peripheral iridectomy was performed, the first scleral flap was closed with 5-8 interrupted 10-0 nylon sutures. The conjunctiva was readapted with 10-0 nylon or 10-0 absorbable suture. At the end of surgery, 2 mg of betamethasone sodium phosphate was injected subconjunctivally and 0.3% ofloxacin ointment was applied. For LEC alone, surgeries were performed under miosis induced by topical 1% pilocarpine. When the combined procedure was performed, surgeries were performed under mydriasis included by topical tropicamide and phenylephrine hydrochloride; phacoemulsification cataract surgery was performed before LEC; the cataract surgery was performed through a clear corneal incision, and a 1-piece soft-acrylic intraocular lens was inserted through the same clear corneal incision. Postoperatively, topical antibiotics was applied 4 times daily for 1 to 2 months, and 0.1% betamethasone was applied 4 times daily for 2 to 3 months in all cases. After combined surgery, topical nepafenac was also applied 3 times daily for 2 to 3 months.

SU-PAP Grading System

The SU-PAP grading system classifies the severities of PAP into 4 grades based on the appearance and difficulty performing GAT. The grades were constructed on the basis of the underlying mechanisms of each PAP factor as described previously.[10] Grade 0 (no PAP) was defined as no prostaglandin-associated cosmetic changes by macroscopic or slit-lamp observation; grade 1 (superficial cosmetic PAP) was defined as the presence of eyelid hyperpigmentation or eyelash growth; grade 2 (deep cosmetic PAP) was defined as the presence of at least 1 of DUES, blepharochalasis involution, periorbital fat loss, and enophthalmos; and grade 3 (tonometric PAP) was defined as difficulty performing GAT or reduced reliability of GAT due to the presence of PAP-related DUES, hardening of eyelids, ptosis, or enophthalmos. The difficulty or the reduced reliability was based on the subjective judgement of the examiners. The agreement in the SU-PAP grading between 2 graders (A.I. and M.T.) in 17 random subjects was calculated to be excellent ($\kappa = 0.88$ by Cohen's κ statistics) based on the agreement classification proposed by Altman et al.[12] In this study, 28 eyes had their SU-PAP grade recorded in the medical chart preoperatively, and 111 eyes were determined the SU-PAP grade by using the recorded pictures in combination with the description of medical chart regarding a difficulty in IOP measurement. Each grading was done by consensus between 2 graders (A.I. and M.T. at Shimane University Hospital, and T.M. and T.N. at Grace Eye Clinic) without referring the surgical results.

Data Collection

The following data were collected from the medical charts: age, gender, glaucoma type, best-corrected visual acuity (VA), IOP, medication score, visual field mean deviation (central 30-2 program, Humphrey Visual Field Analyzer, Carl Zeiss Meditec), spherical equivalent refractive error (SERE), use of topical FP-agonist (FPA) or EP2-agonist (EPA), SU-PAP grade, lens status, surgical procedure (i.e., LEC alone or combined LEC-CE), and additional procedures within 12 months. The decimal VA was converted to the logarithm of the minimum angle of resolution. Counting fingers, hand motions, light perception, and no light perception were regarded as decimal VAs of 0.0025, 0.002, 0.0016, and 0.0013, respectively.[13] The IOP was measured using GAT. The medication score was 1 point per topical medication component or per 250-mg oral acetazolamide.

Statistical Analysis

All continuous data are expressed as the mean ± standard deviation with 95% confidence interval. The preoperative and postoperative IOPs, medication scores, and VAs were compared among groups stratified by SU-PAP grades by 1-way analysis of variance. Successful IOP control was assessed by survival curve analysis in which the uncensored date was defined as the postoperative period of longer than 90 days and the day of surgical intervention other

Table 1. Demographic Subject Data

Parameter	Mean ± SD or No. (%)	95% CI or No. (%)
No. eyes	139	
Age, yrs	65.7 ± 10.6	63.9–67.5
Gender	Male, 74 (53)	Female, 65 (47)
VA, logMAR	0.16 ± 0.48	0.1–0.2
Preoperative IOP, mmHg	21.4 ± 8.9	19.9–22.9
Preoperative medication score	3.9 ± 1.2	3.7–4.1
MD, dB	−16.0 ± 7.8	−17.3 to −14.7
SERE, D	−3.2 ± 2.8	−3.7 to −2.8
Prostaglandin use	Yes, 131 (94)	No, 8 (6)
Prostaglandin	Latanoprost, 69 (50)	Tafluprost, 24 (17)
	Travoprost, 19 (14)	Bimatoprost, 16 (11)
	Omidenepag, 3 (2)	
SU-PAP grade	Grade 0, 22 (16)	Grade 1, 66 (47)
	Grade 2, 42 (30)	Grade 3, 9 (6)
Lens status	Phakia, 77 (55)	Pseudophakia, 62 (45)
Surgical procedure	LEC, 116 (83)	LEC-CE, 23 (17)

CE = cataract extraction; CI = confidence interval; D = diopters; dB = decibels; IOP = intraocular pressure; LEC = trabeculectomy; logMAR = logarithm of the minimum angle of resolution; MD = mean deviation; SD = standard deviation; SERE = sphere equivalent refractive error; SU-PAP = Shimane University prostaglandin-associated periorbitopathy grade; VA = visual acuity.

than LSL, IOP reduction of less than 20%, postoperative IOP exceeding 15 mmHg (definition A) or 12 mmHg (definition B), and a postoperative IOP below 6 mmHg. The difference in survival rates among the SU-PAP grades was compared using the log-rank test. The difference in the proportion of categorical variables among the SU-PAP grades was compared using the Cochran-Armitage trend test. Factors associated with surgical success were assessed using a Cox proportional hazard model. All statistical analyses were performed using the JMP Pro version 15.0 statistical software (SAS Institute, Inc). $P < 0.05$ was considered significant.

Results

Table 1 summarizes the demographic subject data including age, gender, preoperative IOP, medication score, visual field mean deviation, and SERE. At the time of surgery, 131 (94%) of 139 eyes were treated with topical FPA or EPA; half of them used latanoprost (50%), followed by tafluprost (17%), travoprost (14%), bimatoprost (11%), and omidenepag (Eybelis, Santen Pharmaceuticals) (2%). Preoperatively, the SU-PAP grades were grade 0 in 22 (16%), grade 1 in 66 (47%), grade 2 in 42 (30%), and grade 3 in 9 (6%). Preoperatively, 45% of eyes were pseudophakic; a combined surgery was performed in 17%.

The IOP, medication score, and VA during the follow-up period are summarized in Table 2. Among groups stratified by the SU-PAP grade, the IOPs differed at 3 ($P = 0.0017$) and 6 months ($P = 0.0040$), and the medication scores differed at 9 ($P = 0.016$) and 12 months ($P = 0.010$), whereas the VAs were similar throughout the follow-up period.

The postoperative interventions are shown in Table 3. The frequencies of needling ($P = 0.039$), bleb revision ($P < 0.0001$), and surgery other than glaucoma ($P = 0.0043$) were significantly higher in the patients with higher SU-PAP grades, whereas the frequencies of LSL, anterior chamber reformation procedure, and

Table 2. Comparisons in Preoperative and Postoperative IOP, Medication Score, and VA among Groups Stratified by SU-PAP grade

	Garde 0		Grade 1		Grade 2		Grade 3		
Parameter	*Mean ± SD*	*95% CI*	*Mean ± SD*	*95% CI*	*Mean ± SD*	*95% CI*	*Mean ± SD*	*95% CI*	**P Value**
IOP, mmHg									
Preoperative	20.5±11.2	15.6–25.5	22.3±9.6	20.0–24.6	20.5±6.1	18.6–22.4	21.8±9.6	14.4–29.2	0.73
1 mo	9.6±3.0	8.3–10.9	9.3±3.1	8.5–10.1	10.9±4.5	9.5–12.3	11.1±3.6	8.3–13.8	0.12
3 mos	9.5±1.7	8.7–10.2	9.4±2.9	8.7–10.2	11.0±3.4	9.9–12.0	11.7±2.0	10.2–13.3	0.0017**
6 mos	9.7±2.1	8.7–10.6	9.6±2.8	8.9–10.3	11.4±3.8	10.2–12.6	12.2±2.3	10.5–14.0	0.0040**
9 mos	9.8±1.8	9.0–10.6	9.8±3.2	9.1–10.6	11.3±3.7	10.2–12.5	11.1±3.4	8.5–13.8	0.09
12 mos	9.7±2.5	8.6–10.8	10.0±3.1	9.2–10.8	11.0±3.4	9.9–12.0	11.3±1.6	10.1–12.5	0.22
Medication score									
Preoperative	3.7±1.2	3.2–4.3	3.9±1.2	3.6–4.2	4.0±1.2	3.7–4.4	4.6±1.8	3.2–5.9	0.35
1 mo	0.0±0.0	0.0–0.0	0.1±0.4	−0.0–0.2	0.0±0.2	−0.0–0.1	0.0±0.0	0.0–0.0	0.78
3 mos	0.1±0.6	−0.1–0.4	0.1±0.5	−0.0–0.2	0.2±0.8	−0.1–0.4	0.0±0.0	0.0–0.0	0.89
6 mos	0.2±0.9	−0.2–0.6	0.2±0.8	0.0–0.4	0.6±1.2	0.2–1.0	0.0±0.0	0.0–0.0	0.07
9 mos	0.2±0.9	−0.2–0.6	0.3±1.0	0.0–0.5	0.9±1.4	0.4–1.3	0.0±0.0	0.0–0.0	0.016**
12 mos	0.4±1.0	−0.1–0.8	0.3±1.0	0.1–0.5	1.0±1.5	0.5–1.5	0.0±0.0	0.0–0.0	0.010**
VA, logMAR									
Preoperative	0.02±0.26	−0.09–0.14	0.19±0.55	0.06–0.33	0.20±0.50	0.05–0.36	0.11±0.23	−0.06–0.29	0.48
1 mo	0.08±0.31	−0.06–0.21	0.31±0.65	0.16–0.47	0.34±0.50	0.18–0.49	0.23±0.26	0.03–0.43	0.29
3 mos	0.09±0.29	−0.04–0.22	0.23±0.56	0.09–0.37	0.25±0.06	0.13–0.38	0.15±0.26	−0.06–0.35	0.55
6 mos	0.05±0.30	−0.08–0.19	0.23±0.62	0.08–0.39	0.23±0.43	0.10–0.37	0.16±0.27	−0.04–0.37	0.49
9 mos	0.05±0.29	−0.08–0.18	0.20±0.56	0.06–0.34	0.25–0.55	0.08–0.43	0.18±0.29	−0.04–0.40	0.49
12 mos	0.02±0.26	−0.10–0.14	0.24±0.65	0.08–0.40	0.19±0.37	0.07–0.31	0.19±0.34	−0.08–0.45	0.38

P values were calculated among SU-PAP groups by 1-way analysis of variance.
CI = confidence interval; IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution; SD = standard deviation; SU-PAP = Shimane University prostaglandin-associated periorbitopathy; VA = visual acuity.
**Significance level of 1%.

Table 3. Postoperative Interventions in Each SU-PAP Grade

Parameter	Grade 0	Grade 1	Grade 2	Grade 3	P Value
LSL	n (%), 21 (95)	58 (88)	39 (93)	9 (100)	0.63
Needling	0 (0)	1 (2)	3 (7)	1 (11)	0.039*
Bleb revision	1 (5)	1 (2)	9 (21)	5 (56)	<0.0001**
AC reform	0 (0)	3 (5)	2 (5)	0 (0)	0.72
Glaucoma surgery	1 (5)	1 (2)	1 (2)	0 (0)	0.55
Other surgery	0 (0)	7 (11)	5 (12)	4 (44)	0.0043**

P values were calculated among SU-PAP groups by Cochran-Armitage trend test.
AC = anterior chamber; LSL = laser suture lysis; SU-PAP = Shimane University prostaglandin-associated periorbitopathy.
*Significance level of 5%.
**Significance level of 1%.

additional glaucoma surgery did not differ among the SU-PAP grades. Surgery other than glaucoma included scleral flap suturing, conjunctival suturing, cataract surgery, and others.

By survival curve analyses, the success rates for IOP control were significantly worse in eyes with higher SU-PAP grades than in eyes with lower grades for both definitions A (Fig 1A, $P < 0.0001$) and B (Fig 1B, $P < 0.0001$). At 12 months postoperatively, the success rates of grade 0, 1, 2, and 3 were 86%, 68%, 40%, and 0%, respectively, for definition A, and 86%, 61%, 36%, and 0%, respectively, for definition B. The reasons for surgical failure in survival curve analyses are summarized in Table 4. Interventions other than LSL ($P < 0.0001$) and IOP reduction less than 20% ($P = 0.010$), IOP exceeding 15 mmHg ($P = 0.016$) or 12 mmHg ($P < 0.0001$) were all associated with surgical failure, whereas IOP under 6 mmHg was not ($P = 0.31$).

Factors associated with surgical failure were assessed using a proportional hazard model for definitions A (Table 5) and B (Table 6). For definition A (IOP < 15 mmHg), compared with SU-PAP grade 0, grade 2 (risk ratio [RR], 5.82, $P = 0.0043$) and grade 3 (RR, 12.2, $P = 0.0003$) were associated with surgical failure. For definition B (IOP < 12 mmHg), grade 1 (RR, 3.53, $P = 0.040$), grade 2 (RR, 6.65, $P = 0.0021$), and grade 3 (RR, 12.0, $P = 0.0003$) were associated with surgical failure. Differences in age, gender, preoperative IOP and medications, SERE, and simultaneous cataract surgery were not associated with surgical failure in either model.

Discussion

Survival curve analyses and proportional hazard models clearly showed that the surgical success of LEC for achieving both middle-teen IOPs (Fig 1A, Table 5) and low-teen IOPs (Fig 1B, Table 6) was affected by the PAP severity. The main reasons for the failure were insufficient reduction of IOP and interventions for treatment of insufficient IOP reduction, rather than over-filtration (Table 4). Previously, various factors including young age, higher preoperative IOP, and simultaneous cataract surgery[14,15] were reported to be risk factors for surgical failure of LEC. In our dataset, except for the SU-PAP grade, any parameters included in the proportional hazard model were associated significantly with surgical failure. This was true if the SU-PAP grade was excluded from the models for definitions A and B (data not shown). Accordingly, the results suggested the strong effect of PAP severity in the surgical effectiveness of LEC.

In this study, the association between SU-PAP grades 2 and 3 and surgical failure was marked. This agreed with the previous study that the presence of DUES was associated with the surgical failure of LEC.[11] Compression of the trabeculectomy site by the tightened and hardened eyelid seen in advanced PAP [8] may be involved in the mechanisms of restricted filtration. We observed some cases of bleb formation by lifting a tight lid during the postoperative slit-lamp examination. Use of antiglaucoma medication induced histopathologic and inflammatory changes in the ocular surface,[16] and both the conjunctival inflammation and long-term use of topical medications were risk factors for failure of LEC.[17] Given that the severity of PAP was associated with FPA use,[18] long use of topical medications reflected by the SU-PAP score may be another explanation for the association of the PAP score and the surgical success, especially for surgical failure of lower SU-PAP grades (i.e., grade 1).

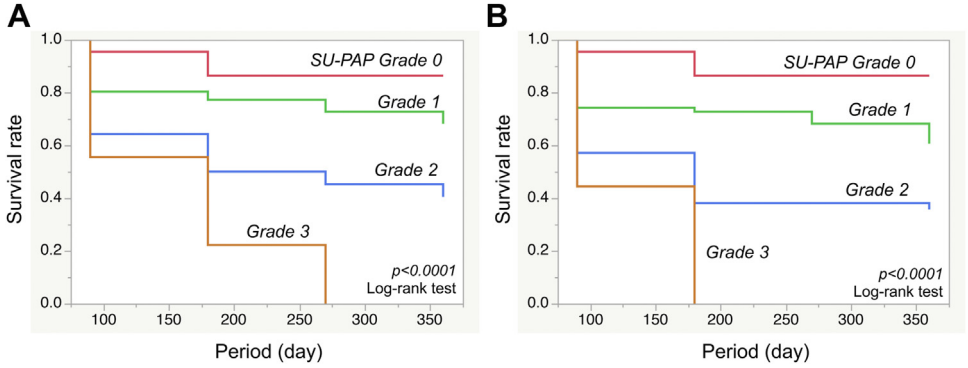

Figure 1. Success rate of intraocular pressure (IOP) control in each SU-PAP grading system grade groups. For the survival curve analysis, the uncensored data were defined as the postoperative period of later than 3 months and the day when the IOP level exceeded 15 mmHg (definition A) **(A)** or 12 mmHg (definition B) **(B)**; IOP reduction of less than 20% irrespective of antiglaucoma medication use, hypotony less than 6 mmHg, or interventions other than laser suture lysis. The cases other than those were regarded as censored cases at the final visit. SU-PAP = Shimane University prostaglandin-associated periorbitopathy.

Table 4. Reasons for Surgical Failure in Each SU-PAP Grade

Parameter	Grade 0	Grade 1	Grade 2	Grade 3	*P* Value
Interventions other than LSL	n (%), 0 (0)	9 (14)	12 (29)	7 (78)	<0.0001**
IOP reduction less than 20%	3 (14)	11 (17)	14 (33)	4 (44)	0.010*
IOP over 15 mmHg	1 (5)	6 (9)	10 (24)	2 (22)	0.016*
IOP over 12 mmHg	2 (9)	14 (21)	19 (45)	6 (67)	<0.0001**
IOP under 6 mmHg	0 (0)	4 (6)	2 (5)	1 (11)	0.31

P values were calculated among the SU-PAP groups by Cochran-Armitage trend test.
IOP = intraocular pressure; LSL = laser suture lysis; SU-PAP = Shimane University prostaglandin-associated periorbitopathy.
*Significance level of 5%.
**Significance level of 1%.

The strongest evidence for protecting the optic nerve and remaining visual field is to maintain the IOP in the low teens or even the upper single digits and to reduce IOP fluctuations.[19] The most effective way of slowing glaucoma progression in a patient with a low IOP is to lower the IOP further, sometimes to a single digit.[20] Although various minimally invasive glaucoma surgical procedures (MIGS) are currently available, we still needed to perform LEC because of the limited effectiveness of MIGS in achieving single-digit IOPs.[21] Compared with latanoprost or tafluprost, bimatoprost and travoprost were associated with a higher risk of deep cosmetic PAP, including DUES, dermatochalasis involution, periorbital fat loss, and enophthalmos.[10,22-26] Switching from latanoprost to bimatoprost induced DUES in 60% of patients after 3 months.[27] Downgrading of the SU-PAP score by switching or stopping the causative medication preoperatively might improve the LEC effectiveness and therefore should be tested in future clinical studies.

Study Limitations

Although we included all subjects who met the inclusion/exclusion criteria, because of the retrospective study design, selection bias may have existed. The absence of a medication history such as duration of prostaglandin agonist use and previous switching of the medication among the prostaglandin agonists were study limitations. Our subjects used other topical medications in addition to prostaglandin agonists. Although other medications are less likely to be associated with PAP, allergic reactions and follicular conjunctivitis are not uncommon side effects of glaucoma medications and might have had some impact on the current results. Different preservatives can stimulate ocular surface inflammation with a different magnitude.[28] Therefore, we cannot exclude the possibility that the preservatives contained in the medications had some roles in the surgical effectiveness of LEC. Because of the definition of SU-PAP, the GAT-measured IOP might be uncertain in subjects with grade 3 SU-PAP. We have previously reported that the grade 3 SU-PAP was associated with overestimation of GAT-measured IOP that compared with rebound tonometer-measured IOP;[10] accordingly, we cannot exclude a possibility that the IOPs reported in this study also were higher than the true IOP. Considering that higher SU-PAP grades were associated with higher frequencies of interventions such as needling and bleb revision, we speculated that the main study results, that is, the worse effectiveness of LEC with higher SU-PAP grades, would remain unchanged if the IOP was measured with another method such as a rebound tonometry.

Table 5. Factors Associated with Survival Rate with Definition A

	Risk Ratio	95% CI	*P* Value
Age, yrs	0.99	0.96–1.02	0.37
Gender (female/male)	1.01	0.58–1.76	0.97
SERE, D	1.02	0.92–1.15	0.97
Preoperative IOP, mmHg	0.97	0.93–1.01	0.11
Preoperative medications medication	1.06	0.85–1.31	0.58
Surgical procedure (LEC-CE/LEC)	0.82	0.40–1.69	0.58
SU-PAP grade (1/0)	2.71	0.80–9.18	0.11
SU-PAP grade (2/0)	5.82	1.74–19.5	0.0043**
SU-PAP grade (3/0)	12.2	3.18–47.0	0.0003**

P values were calculated by the Cox hazard model.
CE = cataract extraction; CI = confidence interval; D = diopters; IOP = intraocular pressure; LEC = trabeculectomy; SERE = spherical equivalent refractive error; SU-PAP = Shimane University prostaglandin-associated periorbitopathy.
*Significance level of 5%.
**Significance level of 1%.

Table 6. Factors Associated with Survival Rate with Definition B

	Risk Ratio	95% CI	*P* Value
Age, yrs	0.99	0.96–1.02	0.43
Gender (female/male)	1.25	0.75–2.11	0.39
SERE, D	0.97	0.88–1.08	0.60
Preoperative IOP, mmHg	0.91	0.20–3.60	0.90
Preoperative medications, medication	1.00	0.81–1.21	>0.99
Surgical procedure (LEC-CE/LEC)	0.97	0.50–1.89	0.94
SU-PAP grade (1/0)	3.53	1.06–11.7	0.040*
SU-PAP grade (2/0)	6.65	1.99–22.2	0.0021**
SU-PAP grade (3/0)	12.0	3.13–45.9	0.0003**

P values were calculated by the Cox hazard model.
CE = cataract extraction; CI = confidence interval; D = diopters; IOP = intraocular pressure; LEC = trabeculectomy; SERE = spherical equivalent refractive error; SU-PAP = Shimane University prostaglandin-associated periorbitopathy.
*Significance level of 5%.
**Significance level of 1%.

Conclusions

The preoperative presence of severe PAP worsened the 1-year success rate of LEC in patients with POAG. To retain the surgical effectiveness, we recommend that treating physicians pay attention to patients with severe PAP, because PAP is an avoidable side effect, by switching or stopping the causative medications.

Footnotes and Disclosures

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[1] Department of Ophthalmology, Shimane University Faculty of Medicine, Izumo, Japan.

[2] Grace Eye Clinic, Okayama, Japan.

Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s):

T.N.: Lecture fees − Santen Pharmaceutical Co, Ltd, Otsuka Pharmaceutical Co, Ltd, Senju Pharmaceutical Co, Ltd, Nitto Medic Co, Ltd, Pfizer Inc., Novartis Inc.

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HUMAN SUBJECTS: Human subjects were included in this study. This retrospective observational case series study adhered to the tenets of the Declaration of Helsinki. The institutional review board of Shimane University Hospital reviewed and approved the research conducted at both Shimane University Hospital and Grace Eye Clinic. The Institutional Review Board approval did not require that each patient provide written informed consent for publication; the study protocol was posted at the study institutions to notify participants about the study.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Naito, Tanito

Data collection: Ishida, Miki, Naito, Ichioka, Takayanagi, Tanito

Analysis and interpretation: Ishida, Miki, Naito, Ichioka, Takayanagi, Tanito

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Overall responsibility: Ishida, Miki, Naito, Ichioka, Takayanagi, Tanito

Abbreviations and Acronyms:
CE = cataract extraction; **DUES** = deepening of upper eyelid sulcus; **GAT** = Goldmann applanation tonometry; **IOP** = intraocular pressure; **IRB** = Institutional Review Board; **LEC** = trabeculectomy; **LSL** = laser suture lysis; **PAP** = prostaglandin-associated periorbitopathy; **POAG** = primary open-angle glaucoma; **RR** = risk ratio; **SERE** = spherical equivalent refractive error; **SU-PAP** = Shimane University PAP Grading System; **VA** = visual acuity.

Keywords:
Adverse effect, Deepening of upper eyelid sulcus, FP agonist, Prostaglandin-associated periorbitopathy, Trabeculectomy.

Correspondence:
Masaki Tanito, MD, PhD, Department of Ophthalmology, Shimane University Faculty of Medicine, 89-1 Enya, Izumo, 793-8501, Shimane, Japan. E-mail: tanito-oph@umin.ac.jp.

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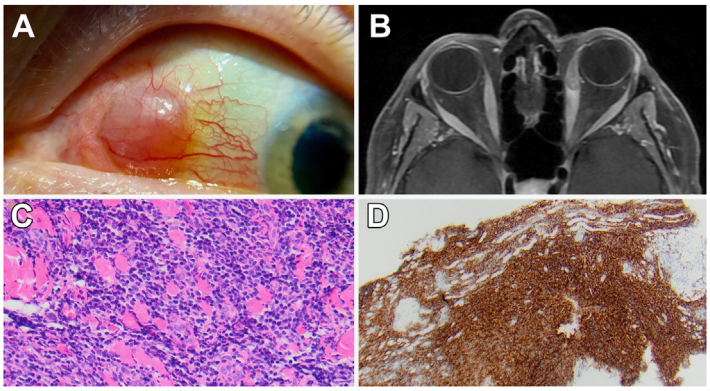
Pictures & Perspectives



Focal Isolated Extraocular Muscle Lymphoma

A 61-year-old woman presented with a painless left subconjunctival nodule (Fig **A**). Magnetic resonance imaging revealed a heterogeneously enhancing mass at the insertion of the left medial rectus muscle on postcontrast T1-weighted images (Fig **B**). Incisional biopsy was performed. Histopathology demonstrated fibrous tissue with atypical lymphoid infiltrate (Fig **C**, Hematoxylin and eosin stain) and positive CD20 (Fig **D**) and BCL-2 staining consistent with extranodal marginal zone lymphoma (EMZL). The patient was treated with external beam radiotherapy with complete remission. Isolated extraocular EMZL is rare and can present in the absence of additional orbital signs and symptoms (Magnified version of Fig **A**-**D** is available online at www.aaojournal.org).

Tamer N. Mansour, MD[1]
Marielle Mahan, MD[2]

[1]The Eye Center, Fairfax, VA/George Washington University, Washington, DC; [2]MedStar Georgetown University Hospital/Washington Hospital Center, Washington, DC