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Outcomes After Combined Deep Sclerectomy and Trabeculotomy to Treat Primary Open-Angle Glaucoma and Exfoliation Glaucoma

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Objective: To compare surgical outcomes after combined deep sclerectomy and trabeculotomy（DS-LOT）between primary open-angle glaucoma（POAG）and exfoliation glaucoma（EXG）. Methods: This retrospective study included 144 consecutive patients with POAG（n=49）or EXG（n=95）who underwent DS-LOT. Surgical failure was defined as the need for additional glaucoma surgeries or two consecutive measurements of postoperative intraocular pressure（IOP）that exceeded the preoperative IOP. The decreases in postoperative IOP and success probabilities were compared in both groups. Results: Both groups had significant IOP decreases at all follow-up visits to 4 years postoperatively. The preoperative and postoperative IOP levels at 3 and 6 months in the EXG group were significantly higher than in the POAG group. Conclusions: The postoperative success probabilities in the EXG group were significantly lower than in the POAG group. More preoperative medication use and the absence of combined cataract surgery, rather than EXG itself, were associated with DS-LOT failure.

Key words: primary open-angle glaucoma, exfoliation glaucoma, glaucoma surgery, deep sclerectomy, trabeculotomy

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INTRODUCTION

Trabeculectomy remains the most common surgical treatment for glaucoma that is refractory to medical treatment. However, the perforating filtering procedure is associated with several severe complications such as bleb leaks, hypotony, a flat anterior chamber, choroidal detachment, and endophthalmitis［1, 2］.

Until now, various nonperforating or nonfiltering procedures, such as sinosotomy, trabeculotomy（LOT）, deep sclerectomy（DS）, viscocanalostomy（VCS）, Trabectome（NeoMedix Corporation, Tustin, CA）implantation, canaloplasty with a microcatheter, micro-bypass stent（iStent, Glaukos, San Clemente, CA）implantation, Gold Micro Shunt（Solx, Sammamish, WA）implantation, Microhook（Inami, Tokyo, Japan）, and use of the Kahook Dual Blade（New World Medical, Rancho Cucamonga, CA）had been developed to avoid these complications instead of trabeculectomy［3-13］. These safer and less invasive procedures compared with traditional incisional surgery are referred to as minimally invasive glaucoma surgery, and there has been an increasing trend toward their use. However, the nonpenetrating glaucoma surgeries are less effective than trabeculectomy for achieving intraocular pressure（IOP）reductions［14-17］. Some nonpenetrating surgeries are more effective such as trabeculotomy in certain scenarios for treating steroid-induced glaucoma, phacoemulsification（PEA）-VCS for treating normal tension glaucoma, and PEA-trabeculotomy for treating primary open-angle glaucoma（POAG）in elderly patients［18-20］.

There has been an increasing trend toward combined procedures to achieve greater IOP reductions compared to a single procedure, because these procedures have different mechanisms of action［21-23］.

Therefore, we expected that combined deep sclerectomy and trabeculotomy (DS-LOT) would achieve good surgical outcomes with IOP reduction. Although Luke et al. reported surgical outcomes after PEA-trabeculotomy plus deep sclerectomy, the combined trabeculotomy and deep sclerectomy surgical procedure has not been studied extensively [22]. The current retrospective study evaluated the IOP effects, surgical success rate, and safety of deep sclerectomy combined with trabeculotomy in Japanese patients with POAG and EXG.

PATIENTS AND METHODS

We retrospectively reviewed the medical records of the Shimane University Faculty of Medicine to identify all patients with POAG or EXG who underwent DS-LOT from February 2007 to March 2011. The current study was part of a study protocol titled "Epidemiologic study in ocular morphology and function," that the Ethics Committee of Shimane University Hospital approved. After excluding patients with a follow-up shorter than 6 months and those with a history of a previous glaucoma surgery except for laser procedures, 144 eyes of 144 patients remained. Patients with a history of uncomplicated cataract surgery, i.e., intracapsular cataract extraction and/or intraocular lens (IOL) suturing, were included in this study. The demographic data are summarized in Table 1. When cataracts affected the visual acuity (VA) at the time of surgery, the crystalline lens was removed by clear corneal incision and replaced by an IOL. If DS-LOT was performed bilaterally, the eye treated first was investigated.

All patients had a history of IOP exceeding 21 mmHg, typical glaucomatous optic disc cupping, visual field damage, open angles, and no contributing ocular or specific systemic disorders. EXG was diagnosed by slit-lamp examination of exfoliation material deposited on the iris and/or lens surface.

SURGICAL PROCEDURES

One surgeon (MT) performed all surgeries. PEA and IOL implantation were performed before DS-LOT in the case of combined glaucoma and cataract surgery. DS-LOT began with a limbal peritomy and radial conjunctival incision at the 7 to 8-o'clock position, and a fornix-based conjunctival flap was created. The conjunctiva and Tenon's tissue were retracted carefully to expose the sclera. After a 5 × 5-mm triangular area was marked, the sclera was incised to half of the scleral depth, and a second 4 × 4-mm four-fifths-thickness scleral flap was created with a razor blade. Schlemm's canal was deroofed and Descemet's membrane and corneal parenchyma were separated during the extension of the deep scleral flap. A Nagata semicircular trabeculotome probe (Inami) was inserted into Schlemm's canal in both directions (right and left) and in-rotated to disrupt the inner wall of the canal and the juxtacanalicular tissue of the trabecular meshwork. The deeper flap then was excised. Apposition of the superficial scleral flap was achieved using 10-0 nylon sutures. The conjunctiva was closed with 9-0 silk sutures.

OUTCOME MEASUREMENTS

The IOP was measured using Goldman applana-

Table 1. Characteristics of the study eyes

	Total (n =144)	POAG (n = 49)	EXG (n = 95)	*p* Value
Age at surgery (years) (mean ± SD)	76.3 ± 8.3	73.0 ± 9.5	78.0 ± 7.2	0.0017[a]
Sex (male/female)	79 / 65	23 / 26	56 / 39	0.2162[b]
With cataract surgery (yes/no)	109/35	40/9	69/26	0.3060[b]
Preoperative IOP (mmHg) (mean ± SD)	25.1 ± 8.9	21.2 ± 7.3	27.2 ± 9.0	<0.0001[a]
Preoperative glaucoma medications (mean ±SD)	2.6 ± 0.9	2.4 ± 1.0	2.7 ± 0.8	0.1026[a]
Follow-up (months) (mean ± SD)	24.6 ± 13.0	26.9 ± 13.2	23.5 ± 12.8	0.1416[a]

Primary open-angle glaucoma: POAG, Exfoliation glaucoma: EXG, standard deviation: SD.

[a]Comparison between POAG and EXG groups by the unpaired t-test.

[b]Comparison between POAG and EXG groups by Fisher's exact probability test.

tion tonometry. The preoperative IOP was measured at the last preoperative visit. The postoperative IOP was measured on the day of each outpatient examination. The preoperative and preoperative IOPs were compared using the paired t-test, and the preoperative and postoperative antiglaucoma medication scores were compared using the paired t-test. The VA results were evaluated at the last follow-up and classified as the presence or absence of a two-line or greater reduction on a decimal VA chart. The frequencies of intraoperative and postoperative complications and the need for additional glaucoma surgeries were demonstrated in both groups. The total surgical success rate and that of both groups were evaluated by three criteria: criterion A, surgical failure was defined as a postoperative IOP of 13 mmHg or higher; criterion B, ≥17 mmHg or higher; and criterion C, 21 mmHg or higher on two consecutive IOP measurements. Surgical failure was defined as a postoperative IOP that was higher than the preoperative IOP and as the need for another glaucoma surgery. IOPs that corresponded to criteria A, B, and C up to 1 month postoperatively were not considered surgical failures because of the occurrence of postoperative IOP elevations after trabeculotomy. The total success probabilities and those of both groups based on the three criteria were estimated by Kaplan-Meier life-table analyses and compared by log-rank tests. To determine potential risk factors for surgical failure of DS-LOT, the following variables were assessed: sex, age, preoperative IOP, preoperative medication score, combined cataract surgery or not, and glaucoma type (POAG or EXG). These factors were analyzed statistically with criteria A, B, and C. Data on postoperative complications also were collected from the medical records.

STATISTICAL ANALYSIS

Data analyses were performed using the Multiple Classification Analysis version 2 (Esumi Co., Ltd., Nakano, Tokyo, Japan). The Kaplan-Meier survival-curve analysis was used to estimate the percentage of eyes satisfying the success criteria or without the need for additional glaucoma surgeries. Cox proportional hazard models were used to investigate the associations between the characteristics of the patients, eye, or surgery and failure of DS-LOT. $P < 0.05$ was considered statistically significant.

RESULTS

We identified 144 persons who underwent DS-LOT and met our inclusion criteria. All eligible patients were Japanese. The preoperative diagnosis was POAG in 49 (34%) eyes and EXG in 95 (66%) eyes. Significant differences were seen between both groups in age and preoperative IOP (Table 1). The postoperative IOP levels and glaucoma medications are shown in Figs. 1 and 2, respectively. Significant IOP reductions were achieved at every follow-up evaluation up to 4 years postoperatively (Fig. 1). The mean postoperative IOPs were 12.8 ± 3.5 mmHg at 12 months (n = 120) and 12.7 ± 3.2 mm Hg at 24 months (n = 69) in all patients (data not shown). The use of antiglaucoma medications also decreased significantly at every follow-up point up to 4 years postoperatively (Fig. 2). The postoperative antiglaucoma medication scores were 1.3 ± 0.8 at 12 months (n = 120) and 1.6 ± 0.9 at 24 months (n = 69) for all patients.

The postoperative IOP levels in the POAG and EXG groups are shown in Fig. 3. In both groups, significant differences are seen preoperatively and 3 and 6 months postoperatively. At any time point,

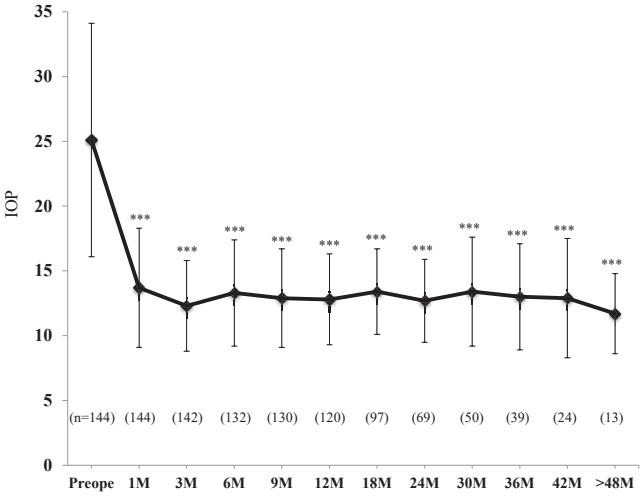

Fig. 1. Preoperative and postoperative levels over 4 years. ***$p < 0.0001$ (paired t-test). The numbers in parentheses indicate numbers of patients. Months: M, intraocular pressure: IOP.

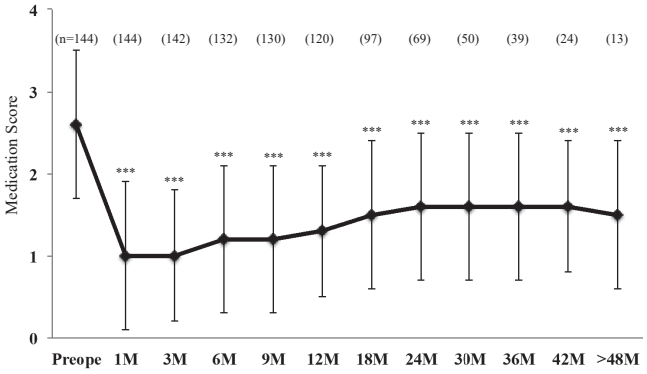

Fig. 2. Preoperative and postoperative medication score over 4 years. ***$p < 0.0001$ (paired t-test). The numbers in parentheses indicate numbers of patients. Months: M.

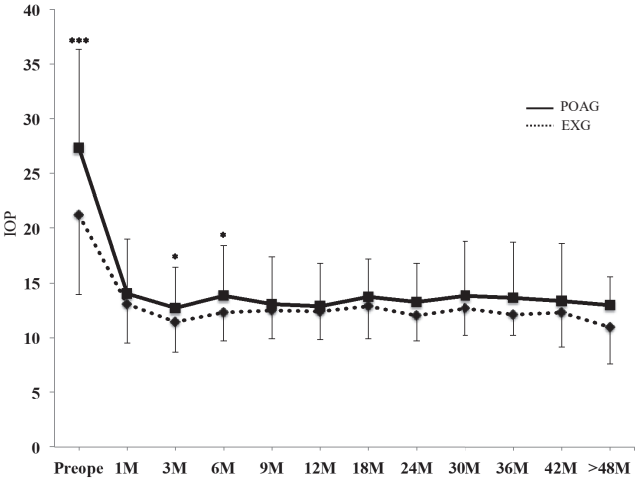

Fig. 3. Preoperative and postoperative intraocular pressure (IOP) over 4 years of primary open angle glaucoma (POAG) and exfoliation glaucoma (EXG). *$p < 0.05$; ***$p < 0.001$ (unpaired t-test). Months: M.

the IOP levels in eyes with EXG were higher than in eyes with POAG. The preoperative IOP levels differed significantly ($p < 0.001$) between both groups.

Table 2 shows the intraoperative and postoperative complications associated with DS-LOT. IOP elevations to more than 30 mmHg within 1 month postoperatively was the most frequently occurring complication in the EXG group (9 eyes). The incidence of IOP elevations in the EXG group was significantly ($p = 0.0282$) higher than in the POAG group. Rupture of Descemet's membrane accompanied by iris prolapse and the need for a peripheral iridectomy occurred in three eyes in the POAG group and four eyes in the EXG group. Prolonged hyphema lasting more than 7 days or requiring anterior chamber washout occurred in one eye in the POAG group and two eyes in the EXG group. A Descemet membrane detachment occurred in two eyes in the POAG group. Cataract surgery-related complications, rupture of the posterior lens capsule, dialysis of the Zinn zonules, incision of the pupillary sphincter, contraction of the continuous circular capsulorrhexis, and after cataract also occurred in both groups, but the incidence rates of any cataract surgery-related complications did not differ significantly between the two groups.

Additional glaucoma surgeries were needed in 10 eyes with EXG, a difference that reached significance ($p = 0.0161$). The details are showed in Table 3. The cause of the need for additional glaucoma surgeries was inadequate IOP control in all 10 cases and progression of visual field loss in five cases (Table 3).

The VA prognoses in both groups are shown in Table 4. At the last follow-up visit, the VA in three of 49 eyes with POAG deteriorated more than two lines because of glaucoma progression (2 eyes) and cataract progression (1 eye). The VA in 18 of 95 eyes with EXG deteriorated more than two lines because of glaucoma progression (11 eyes) and macular degeneration (2 eyes), and cataract progression, macular hemorrhage, postoperative cystoid macular edema, vitreous hemorrhage, and central retinal vein occlusion (1 eye each). The VA reductions by more than two lines in the EXG group differed significantly ($p = 0.0465$) from the POAG group.

The success probabilities related to all postoperative IOPs are shown in Fig. 4. The success probabilities of achieving criteria A, B, and C were 43.1%, 81.6%, and 94.9% at 1 year, respectively, and 27.7%, 76.0%, and 90.2% at 2 years. The success probabilities related to postoperative IOP in the POAG and EXG groups are shown in Fig. 5. The success probabilities of achieving criteria A, B, and C were 54.2%, 91.8%, and 100% at 1 year, respectively, and 35.8%, 89.1%, and 100% at 2 years in the POAG group; the respective percentages were 37.5%, 76.2%, and 92.2% at 1 year and 23.3%, 68.7%, and 84.7% at 2 years in the EXG group. The success probabilities differed significantly ($p =$

Table 2. Intraoperative and postoperative complications and additional surgery

	Total (n = 144)	POAG (n = 49)	EXG (n = 95)	*p* Value
IOP elevation [b]	9 (6.3)	0	9 (9.5)	0.0282[a]
Iris prolapse (iridectomy)	7 (4.9)	3 (6.1)	4 (4.2)	0.6898
Prolonged hyphema [c]	3 (2.1)	1 (2.0)	2 (2.1)	1.0000
Descemet's detachment	2 (1.4)	2 (4.1)	0	0.1142
Cataract surgery related				
Rupture of posterior lens capsule	2 (1.4)	1 (2.0)	1 (1.1)	1.0000
Dialysis of the Zinn zonules	3 (2.1)	0	3 (3.2)	0.5511
Incision of pupillary sphincter	11 (7.6)	1 (2.0)	10 (10.5)	0.0983
Contraction of CCC	3 (2.1)	0	3 (3.2)	0.5511
After cataract	6 (4.2)	4 (8.2)	2 (2.1)	0.1804
Additional surgery				
Trabeculectomy	10 (6.9)	0	10 (10.5)	0.0161[a]

Primary open-angle glaucoma: POAG, Exfoliation glaucoma: EXG, intraocular pressure: IOP, continuous curvilinear capsulotomy: CCC.

[a] Comparison between POAG and EXG groups by Fisher's exact probability test.

[b] ≥ 30 mmHg within 1 month postoperatively.

[c] ≥ 7 days or anterior chamber washout

Values in parentheses are percentages.

Table 3. Characteristics of the cases requiring additional surgery

Total cases, n	10
Sex (male/female)	8/2
Age (years)	77.1 ± 9.8
Type of glaucoma (POAG/EXG)	0/10
Time until second surgery (days)	528 ± 377
Operation type (DS-LOT alone/with cataract surgery)	3/7
Preoperative IOP (mmHg)	32.5 ± 11.1
Preoperative medicine score	3.2 ± 0.9
Cause of second surgery	
Inadequate IOP, n	10
Progression of visual field loss, n	5

Primary open-angle glaucoma: POAG, Exfoliation glaucoma: EXG.
combined deep sclerectomy and trabeculotomy: DS-LOT, intraocular pressure: IOP.

Table 4. Postoperative decrease (2 lines or more) in visual acuity and its cause

	POAG (n = 49)	EXG (n = 95)	*p V*alue
Decrease (2 lines or more)	3	18	0.0465[a]
Cause			
Progression of glaucoma	2	11	0.2193
Progression of cataract	1	1	1.0000
Macular degeneration	0	2	0.5479
Macular hemorrhage	0	1	1.0000
Postoperative CME	0	1	1.0000
Vitreous hemorrhage	0	1	1.0000
CRVO	0	1	1.0000

Primary open-angle glaucoma: POAG, Exfoliation glaucoma: EXG, cystoid macular edema: CME, central retinal vein occlusion: CRVO.

[a] Comparison between POAG and EXG groups by Fisher's exact probability test.

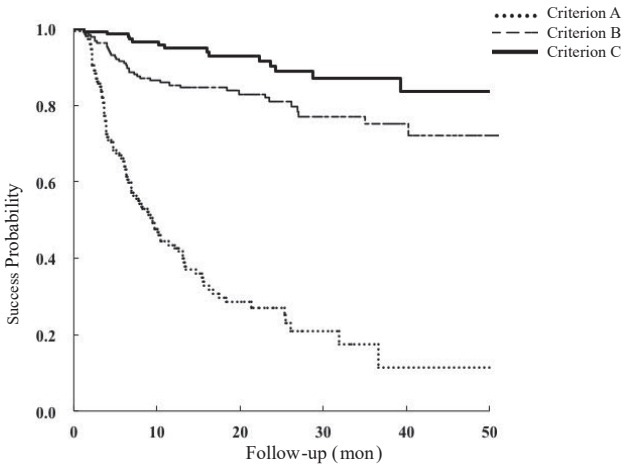

Fig. 4. Kaplan-Meier estimates for surgical success using three success criteria. In this figure, success includes an intraocular pressure criterion and no further glaucoma surgery. mon = months.

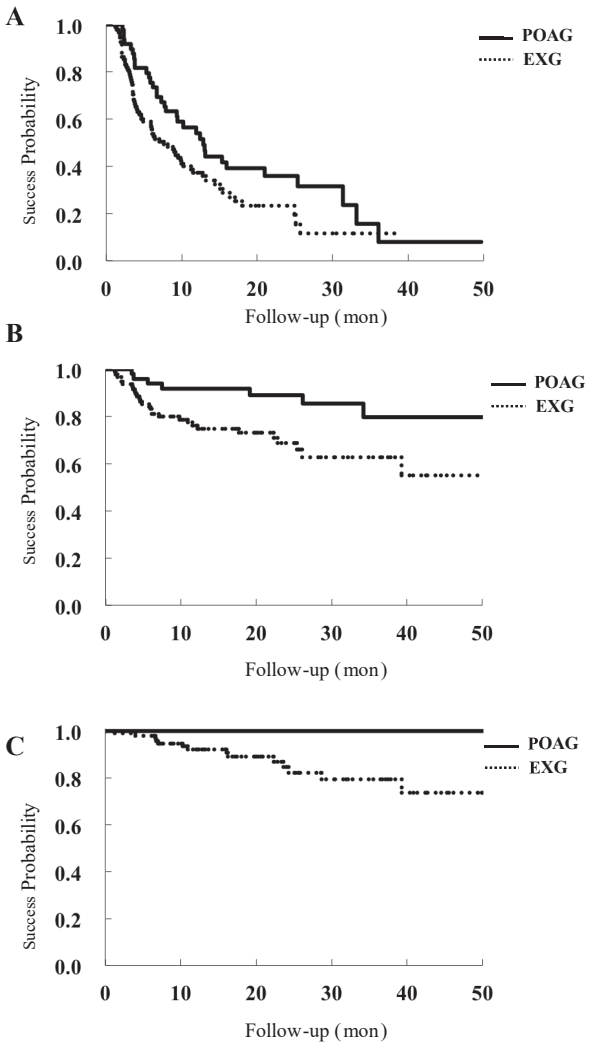

Fig. 5. Kaplan-Meier survival analysis of success rates of intraocular pressure control. (A) Criterion A, (B) criterion B, and (C) criterion C. Primary open-angle glaucoma: POAG, exfoliation glaucoma: EXG, mon = months; intraocular pressure: IOP.

0.0143, $p = 0.0228$, $p = 0.0030$, respectively, for survival curves achieving criteria A, B, and C by the log-rank test) between the groups.

The Cox proportional hazards model showed that prognostic factors for surgical failure were the preoperative medication score (relative risk [RR], 1.632, $p = 0.036$ for criterion B and RR, 2.941, $p = 0.008$ for criterion C), combined cataract surgery (RR = 0.602, $p = 0.036$ for criterion A and RR. 0.254, $p = 0.02$ for criterion C), and female gender (RR. 0.408, $p = 0.023$ for criterion B) (Table 5).

DISCUSSION

We observed significant reductions in the postoperative IOP levels and antiglaucoma medication use compared with the preoperative levels up to 4 years postoperatively (Figs. 1 and 2). The mean postoperative IOPs were 12.8 ± 3.5 mmHg at 1 year and 12.7 ± 3.2 mmHg at 2 years for all patients (data not shown).

We reported previously that the surgical success rates of a group that underwent VCS and a group that underwent LOT to achieve IOP control under 15, 17, and 21 mmHg were, respectively, 32%, 67%, and 95% and 30.0%, 58.7%, and 95.8%, at 1 year [24, 25]. The current results showed that the surgical success rates of DS-LOT were 43.5%, 81.5%, and 94.7% for achieving criteria A, B, and C 1 year postoperatively, and 27.8%, 75.9%, and 89.9% at 2 years postoperatively. These results showed that combined DS-LOT should achieve lower postoperative IOP levels than VCS alone or trabeculotomy alone. Previous studies of PEA-trabeculotomy combined with deep sclerectomy showed mean postoperative IOPs and antiglaucoma medicine scores at 1 year of 14.4 ± 3.1 mmHg and 0.5 ± 0.9 and 13.8 ± 2.6 mmHg and 0.3 ± 0.5, respectively [22 , 26]. The current results showed lower postoperative IOPs and higher antiglaucoma medicine scores at 1 year than those of the previous study.

The current study suggested the efficacy of DS-LOT for reducing IOP. Ellingsen and Grant reported that the mechanism of trabeculotomy in reducing IOP was eliminating the resistance to aqueous outflow by mechanical cleavage of the trabecular meshwork and inner wall of Schlemm's canal [27].

Table 5. Cox proportional hazards models determining likelihood of surgical outcomes

	Criterion A			Criterion B			Criterion C		
Characteristic	RR	95% CI	*p* value	RR	95% CI	*p* value	RR	95% CI	*p* Value
Age (years)	0.986	0.962-1.012	0.284	1.021	0.974-1.070	0.396	1.089	0.990-1.199	0.080
Preoperative IOP (per mmHg)	1.002	0.979-1.025	0.858	1.014	0.977-1.053	0.460	0.998	0.945-1.054	0.939
Preoperative medicine score	1.184	0.916-1.532	0.198	1.632	1.033-2.577	0.036	2.941	1.331-6.498	0.008
Female gender	0.843	0.564-1.258	0.403	0.408	0.188-0.882	0.023	0.347	0.084-1.435	0.144
Combined cataract surgery	0.602	0.374-0.968	0.036	0.513	0.255-1.035	0.063	0.254	0.080-0.805	0.020
Exfoliation glaucoma	1.421	0.892-2.262	0.139	2.076	0.837-5.148	0.115	26473	4.675×10^{-36}-$1.499\times10^{+44}$	0.827

Confidence interval: CI, relative risk: RR, intraocular pressure: IOP.

In deep sclerectomy, the aqueous may ooze into the lake through the attenuated trabeculo-Descemet membrane or microperforations of the juxtacanalicular tissue and migrate from the lake through an ablated and thin scleral bed to the supracilliary space, the subconjunctival space, or both [28]. Park *et al*. reported that the sizes of the lakes and IOP reductions decreased in parallel after VCS [29]. The intrascleral lake also may be related to the IOP reduction after DS-LOT.

The incidence rate of IOP spikes that exceeded 30 mmHg was 6.3%, which was lower than that after trabeculotomy combined with PEA and IOL implantation for POAG and EXG, i.e., 29% and 22%, respectively, reported previously [30-32]. This relatively lower incidence of IOP spikes suggests the efficacy of deep sclerectomy, i.e., aqueous humor outflow from the bleb and lake.

We compared the surgical results between the POAG and EXG groups. The preoperative and postoperative IOP levels at 3 and 6 months in the EXG group were significantly higher than those in the POAG group. Moreover, the life-tables of IOP survival with no more than 12, 16, and 20 mmHg (Fig. 5 A, B, and C, respectively) showed that the success probabilities in the EXG group were significantly (p = 0.0143, p = 0.0228, and p = 0.0030, respectively) lower than those in the POAG group. The incidence rates of IOP elevations to more than 30 mmHg and the need for additional trabeculectomy in the EXG group were significantly (p = 0.0282, p = 0.0161, respectively) higher than in the POAG group (Table 2). All cases that required additional glaucoma surgeries had EXG. The incidence rate of postoperative decreases in the VA of two lines or more in the EXG group was significantly (p = 0.0465) higher than in the POAG group (Table 4). The surgical results in the EXG group were worse than in the POAG group regarding IOP reduction, complications, need for additional surgery, and VA prognosis. When we evaluated the risk factors for surgical failure related to IOP control, we found that EXG was not a risk factor for surgical failure in each criterion (Table 5). The characteristics of the 10 cases that required additional surgery indicated that the preoperative IOP and preoperative medication scores of these 10 cases (32.5 ± 11.1 mmHg and 3.2 ± 0.9, respectively) were comparatively higher than the total EXG group (27.2 ± 9.0 mmHg and 2.7 ± 0.8, respectively). The higher the preoperative IOP levels were, the less likely that the postoperative IOP levels were controllable, similar to trabeculotomy and other nonfiltering surgeries [33,34] . Therefore, additional surgery and VA deterioration in the EXG group might be explained by the higher number of patients with severe progressive glaucoma than in the POAG group.

The Cox multiple regression analyses of criteria A and C indicated that DS-LOT alone (not combined with cataract surgery) was a significant risk factor in IOP control. This agreed with previous reports that the IOP decrease was larger with combined trabeculotomy and cataract surgery than trabeculotomy alone [24, 30, 32, 35-37]. We found that the preoperative medication score was a significant risk factor for failure to achieve IOP control. Our results agreed with the study of Broadway *et al*., which reported that preoperative topical antiglaucoma therapy was a risk factor for filtering surgery because a high preoperative medication score would be recognized as frequent exposure of antiglaucoma medication relative to a low score [38]. In addition, a high

medication score may mean difficulty in reducing the IOP. Female gender was a significant variable for criterion B (RR = 0.408, p = 0.023). Gender is not a risk factor for glaucoma surgical success according to previous studies [39]. A comparison of some surgical results between patients with POAG and EXG showed that the surgical outcomes of EXG were inferior to that of POAG. However, the current Cox multiple regression analysis showed that EXG was not a risk factor for the surgical failure of DS-LOT.

To the best of our knowledge, the current study is the first to compare the surgical efficacy and complications between POAG and EXG treated with DS-LOT.

In conclusion, based on our study, DS-LOT lowers IOP sufficiently in Japanese patients with POAG and EXG. No vision-threatening intraoperative and postoperative complications of DS-LOT developed in the current series.

CONFLICTS OF INTEREST: The authors have nothing to declare.

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