Evaluation of Blood-filling Patterns in Schlemm Canal for Trabectome Surgery

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inimally invasive glaucoma surgeries (MIGSs) are safe and effective surgical procedures for decreasing the intraocular pressure (IOP).1–3 The Schlemm canal (SC)-based MIGS enhances the conventional outflow pathway via the trabecular meshwork (TM) and SC.

Major resistance to the aqueous outflow in POAG is located in the juxtacanalicular region of the TM.4 However, a previous study demonstrated that circumferential trabeculotomy eliminated 49% of the resistance to the aqueous outflow in eyes with normal IOP.5 Another study reported that 35% of outflow resistance was eliminated after ablating 1 clock hour of tissue from the outer wall of SC and distal sclera using excimer laser at a perfusion pressure of 10 mm Hg.6 These studies indicate that up to half of the outflow resistance lies distal to the inner wall of SC. Therefore, the outcomes of SC-based MIGSs are likely to be affected by the aqueous outflow system distal to SC. Since there are no standardized clinical measures to assess the function downstream distal to SC, it is challenging to predict the efficacy of MIGS. Although outcome markers have yet to be established, potential biomarkers have been reported.7–13 Grieshaber et al13 assessed the aqueous outflow of POAG patients during ab interno canaloplasty using provocative gonioscopy, which induces blood reflux from the anterior ciliary veins via the collector channels (CCs) into SC. They concluded that the blood filling patterns in SC may predict the outcome of ab interno canuloplasty.

Trabectome surgery (NeoMedix Inc., Tustin, CA), an SC-based MIGS, lowers IOP through ab interno TM ablation via gonioscopic visualization.14–16 Blood reflux from the episcleral venous system into SC can be seen before TM ablation. To the best of our knowledge, however, the relationship between the outcomes of trabectome surgery and blood-filling patterns in SC before TM ablation has not yet been investigated.

This study aimed to evaluate the association between the trabectome surgery outcomes and blood filling patterns in SC before TM ablation and assess if the blood filling patterns in SC could be an outcome marker for trabectome surgery, assuming that blood reflux from CCs into SC serves as an indicator for the patent distal aqueous outflow system.

MATERIALS AND METHODS

Study Design and Subjects

This investigation was a retrospective cohort study of Japanese POAG patients who underwent trabectome surgery (NeoMedix Inc.) combined with phacoemulsification and intraocular lens implantation at Okayama Saiseikai General Hospital between January 2016 and April 2018. All patients underwent a comprehensive ophthalmic examination, including slit-lamp examination, Goldmann applanation tonometry, automated perimetry (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA), and preoperative gonioscopic examination that revealed an open

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angle and identifiable SC. The medical records of all patients were retrospectively reviewed with the approval of the Ethics Committee of Okayama Saiseikai General Hospital and in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants. The following exclusion criteria were applied: (a) eyes with glaucoma except POAG; (b) follow-up for <1 year after trabecome surgery; and (c) eyes that had undergone any previous glaucoma surgery.

**Provocative Gonioscopy**

When the IOP was reduced to being lower than the episcleral venous pressure (EVP), by draining most of the aqueous humor from the anterior chamber, blood reflux was provoked from the CC into SC. A minimal amount of cohesive viscoelastic agent (OPEGAN Hi 0.85; Santen Pharmaceutical, Osaka, Japan) was injected into the anterior chamber through a corneal incision to stabilize the space and prevent contact between the iris and the cornea. The surgical microscope was tilted at 30 to 40 degrees and the patient’s head was tilted at 30 degrees, away from the surgeon. Direct gonioscopy (Ocular Hill Open Access Surgical Gonioprism—Left Hand version, USA) was performed around 1 minute after the viscoelastic agent injection.

The blood-filling-pattern classification was conducted using digital video records by 1 observer (K.S.) who was blinded to the patient data. The observed blood reflux was classified pursuant to previous studies into 3 groups, in accordance with the blood filling patterns in SC: no filling (group 1, Fig. 1A); patchy or irregular filling (group 2, Fig. 1B); and complete filling (group 3, Fig. 1C).

**Surgical Procedure and Follow-up**

All patients in this study underwent trabecome surgery combined with phacoemulsification and intraocular lens implantation. All surgeries were performed by 1 surgeon (A.N.) and were digitally recorded. The trabecome surgery was performed before the cataract surgery. A temporal clear corneal incision was made with a 1.7 mm keratome. Under intracameral anesthesia (0.2 mL of lidocaine 1%, Xylocain; AstraZeneca, Germany), the IOP was reduced to below the EVP by aspiration of aqueous humor from the anterior chamber. Direct gonioscopy was performed after a minimal amount of cohesive viscoelastic agent was injected into the anterior chamber to stabilize the space. After the provocative gonioscopy, the trabecome tip was advanced into the TM and inserted into SC. A 120 to 150 degrees arc of the TM and the SC inner wall was removed with a 0.8 W ablation. Subsequently, the anterior chamber was filled with a dispersive viscoelastic agent (VISCOAT 0.5 Ophthalmic Viscoelastic Substance; Alcon, Tokyo, Japan). Phacoemulsification, aspiration, and implantation of a foldable acrylic intraocular lens were performed through the same clear corneal incision used for the trabecome surgery. The corneal incision was closed with a 10-0 nylon suture.

Follow-up examinations were performed at days 1, 2; weeks 1, 2; and months 1, 3, 6, 9, 12 postoperatively. The eyes were treated with a topical steroid for 3 weeks (betamethasone 0.1% eye drops, 4 times a day for 1 week, and fluorometholone 0.1% eye drops, 4 times a day for the following 2 wk), a topical antibiotic for 2 weeks (levofloxacin 0.5% eye drops, 4 times a day), a topical nonsteroidal anti-inflammatory drug for 2 months (diclofenac 0.1% eye drops, 4 times a day), and pilocarpine 2% eye drops 4 times a day for 2 months, to prevent peripheral anterior synchia.

The resumption of glaucoma medications was permitted when treatment escalation was necessary to achieve the target IOP, which was determined based on the pretreatment IOP and glaucoma stage.

Success was defined as an IOP ≤15 mm Hg and a >20% reduction in IOP, with/without glaucoma medication, and without additional glaucoma surgery after a trabecome surgery combined with phacoemulsification and intraocular lens implantation. The subjects were classified into 3 groups according to the blood filling patterns in SC before TM ablation.

**Main Outcome Measures**

The main outcome measures assessed in this study were the blood-filling patterns in SC before TM ablation, IOP, the percentage reduction in IOP, the surgical success rate, and the number of glaucoma medications.

**Statistical Analyses**

All statistical analyses were performed using SPSS version 22.0 (IBM, Armonk, NY). The Kruskal-Wallis test, Pearson χ² test, and log-rank test were used to compare the 3 groups of blood-filling patterns in SC with respect to the clinical data, including the IOP, percentage IOP reduction, surgical success rate, and the number of glaucoma medications. A power calculation determined that a sample size of 84 would detect the relationship between blood-filling pattern and the factors described above for a medium-sized effect of 0.35 with a power of 80%. The estimated cumulative surgical success rates were obtained by Kaplan-Meier survival analyses. P-value of <0.05 was considered statistically significant.

**RESULTS**

In total, 105 eyes of 84 Japanese POAG patients were included in this study. Table 1 summarizes the characteristics of all eyes. The preoperative mean IOP of 17.1 ± 3.6 mm Hg
TABLE 1. Characteristics of the Eyes Included in the Study

| Eyes (n) | 105 |
|---------|-----|
| Sex (female/male) | 55/50 |
| Age [mean ± SD (range)] (y) | 71.5 ± 7.0 (52-87) |
| Preoperative MD (mean ± SD) (dB) | −11.23 ± 6.57 |
| Preoperative IOP (mean ± SD) (mm Hg) | 17.1 ± 3.6 |
| Preoperative number of glaucoma medications (mean ± SD) (n) | 3.4 ± 1.0 |

IOP indicates intraocular pressure; MD, mean deviation.

decreased significantly by 20.6% ± 18.3% to 13.3 ± 3.0 mm Hg (P < 0.001), and the preoperative mean number of glaucoma medications (3.4 ± 1.0) decreased to 2.9 ± 0.8 (P < 0.001) at 12 months after trabectome surgery combined with cataract surgery. The Kaplan-Meier survival analysis showed that the success rate was 50.5% at 12 months after surgery.

Guided by the provocative gonioscopy results, 24 eyes were assigned to group 1 (no filling in SC), 48 eyes to group 2 (patchy or irregular blood filling in SC), and 33 eyes to group 3 (complete filling in SC). The success rates were 54.2% for group 1, 54.2% for group 2, and 42.4% for group 3 at 12 months postoperatively in the Kaplan-Meier survival analyses (Fig. 2).

Increased EVP can induce blood reflux from the episcleral venous system into SC but can lower the success rate after a trabectome surgery. Regarding diseases that could increase EVP, there were 2 patients with Basedow disease in groups 1 and 3, 1 patient with carotid artery stenosis in group 3, and 1 obese patient in group 2. No additional medications (3.4 ± 1.0) decreased to 2.9 ± 0.8 (P = 0.001) at 12 months compared with the preoperative IOP and IOP at 12 months.

FIGURE 2. Surgical success rates after the trabectome surgery in combination with phacoemulsification. The Kaplan-Meier survival analyses showed 12-month success rates of 54.2% for group 1, 54.2% for group 2, and 42.4% for group 3 (definition of success: IOP ≤ 15 mm Hg and ≥ 20% reduction in IOP with/without glaucoma medication and without additional glaucoma surgery). The log-rank test showed no significant differences among the 3 groups at 12 months (P = 0.540).

DISCUSSION

In this study, no significant association was found between the blood-filling patterns in SC before TM ablation and the surgical outcomes of trabectome surgery, including postoperative IOP, percentage IOP reduction, postoperative number of glaucoma medications, or surgical success rate. Even eyes without blood filling in SC had almost the same surgical outcomes as those with a patchy/irregular or complete blood filling pattern in SC.

Our results suggest that trabectome surgery may revive the CCs that were malfunctioning due to increased IOP by removing a portion of the TM and the inner wall of SC. According to previous studies using electron microscopy,18 confocal microscopy,19 3-dimensional microcomputed tomography,20 and spectral-domain optical coherence tomography,21–23 the configurations of CCs are variable and CC dimensions change pressure-dependently; the size and diameter of CCs are likely to decrease at higher IOP. In addition, a pathohistologic study by Battista et al24 revealed that the lumen of SC collapsed and herniated into the CC ostia as IOP increased. In their study, at elevated IOP, the CC entrance was obstructed by the inner wall tissue of the collapsed SC and juxtacanalicular connective tissue (JCT), at mid-teens levels of IOP, the inner wall tissue of SC and JCT partially herniated into the CC entrance. By contrast, at low levels of IOP, the CC entrance and the SC lumen were entirely open. Since blood filling patterns in SC are likely related to the CC ostia occlusion, a lack of blood filling in SC may indicate CC malfunction as a result of CC entrance obstruction due to IOP elevation. Trabectome surgery may revive malfunctioned CCs by ablating the herniated JCT and inner wall tissue of the collapsed SC, leading to an IOP reduction if the aqueous outflow system distal to CCs is intact.

The results of this study are in line with those of previous studies by Huang et al,25–27 who reported that the malfunctioning aqueous outflow pathway distal to SC may be restored after SC-based MIGS. They demonstrated aqueous angiographic patterns with indocyanine green in living human patients and showed that trabecular microbypass stents initially devoid of indocyanine green signals led to increased aqueous angiographic signals. They also showed that regions with or without initial angiographic signals can decrease or increase through yet unidentified mechanisms in their previous studies with live humans along with living nonhuman primates. Hence, they concluded that the lack of angiographic outflow in regions of the eye is not necessarily permanent and that such regions can be rescued either by the trabecular microbypass stent or through dynamic change.

By contrast, Grieshaber et al13 reported that the grade of blood filling patterns in SC correlated with the level of IOP after ab interno canaloplasty in black African patients with POAG. They suggested that provocative gonioscopy may reflect the function of the outflow pathway and may be useful in predicting the surgical outcomes of ab interno.
canaloplasty. The main differences between their study and ours are as follows: (1) surgical procedures: ab interno canaloplasty versus trabectome surgery; (2) mean preoperative IOP: 41.0 versus 17.2 mm Hg. Both canaloplasty and trabectome surgery are SC-based MIGSs that improve the conventional outflow pathway by opening up the CC ostia as well as SC. Canaloplasty routes aqueous drainage through SC, while trabectome surgery opens a drainage channel by removing a portion of the TM and the inner wall of SC. The mean preoperative IOP in their study was much higher than that in our study. It is likely that long-lasting high IOP not only collapses SC and occludes the CC ostia, but also leads to irreversible disruption of the aqueous outflow system distal to CCs, which may have caused the difference in results between their study and ours. Nevertheless, it is noteworthy that in their study, the preoperative mean IOP of 57.7 mm Hg decreased significantly to 20.5 mm Hg after surgery even in the poor SC blood filling group. That may suggest that the blood filling patterns in SC are not likely to become a feasible outcome marker for MIGS.

Our study assumed that observing blood reflux from CCs into SC is an indicator of the patent distal aqueous outflow system, according to the canaloplasty study by Grieshaber et al. However, even though eyes with a less permeable TM may have lower blood reflux into SC, as the aqueous humor in SC may prevent blood from refluxing into SC through CCs, they may experience a large IOP decrease after the trabectome surgery. Furthermore, we may not obtain a good outcome after trabectome surgery, even after ample blood reflux was observed at the trabectome ablation site because, from the CCs, the aqueous humor passes through the aqueous veins or a tortuous system of passages termed intrascleral venous plexus, which in turn communicates with the episcleral veins. Therefore, blood reflux may not necessarily indicate functioning distal outflow through aqueous veins.

The main limitations of this study include the retrospective study design, small sample size, lack of a control group with phacoemulsification alone, and the shorter observation period. Future prospective studies involving larger sample sizes and control groups are necessary to confirm these findings.

| TABLE 2. Between-group Analyses |
|--------------------------------|
|                          | Group 1 | Group 2 | Group 3 | P  |
| Eyes (n)                | 24      | 48      | 33      |    |
| Sex (female/male)      | 15/9    | 24/24   | 16/17   | 0.523* |
| Age (mean ± SD) (y)    | 73.1 ± 6.8 | 71.4 ± 6.3 | 70.3 ± 8.1 | 0.213† |
| Preoperative MD (mean ± SD) (dB) | -11.6 ± 6.3 | -11.9 ± 7.0 | -10.0 ± 6.0 | 0.505† |
| Preoperative IOP (mean ± SD) (mm Hg) | 16.7 ± 2.9 | 17.3 ± 3.9 | 17.1 ± 3.7 | 0.941† |
| IOP at 12 mo (mean ± SD) (mm Hg) | 13.7 ± 2.3 | 13.0 ± 3.2 | 13.6 ± 3.5 | 0.458† |
| Preoperative number of glaucoma medications (mean ± SD) (n) | 3.3 ± 0.8 | 3.4 ± 1.1 | 3.4 ± 1.1 | 0.805† |
| No. glaucoma medications at 12 mo (mean ± SD) (n) | 2.6 ± 0.8 | 3.1 ± 0.9 | 3.0 ± 0.8 | 0.077† |
| IOP reduction rate at 12 mo (mean ± SD) (%) | 16.9 ± 16.2 | 22.9 ± 20.2 | 19.9 ± 16.7 | 0.256† |

*Pearson χ² test.
†Kruskal-Wallis test.
IOP indicates intraocular pressure; MD, mean deviation.

FIGURE 3. A, Changes in intraocular pressure (IOP) in each group. B, Changes in the number of glaucoma medications in each group. Error bars indicate SE. P values are shown above the plots/bars.

FIGURE 4. Comparison between the preoperative intraocular pressure (IOP) and IOP at 12 months.
numbers of patients, with a control group with phacoemulsification alone, and longer follow-up periods are required to confirm whether blood filling patterns in SC can be an outcome marker for the trabectome surgery. In addition, provocative gonioscopy is an intraoperative test that is not useful for making the choice of MIGS and the classification based on the observation of blood reflux is subjective. Ideally, we would use a classification that evaluated blood reflux in a quantitative manner such as the measurement of the blood volume in SC. In addition, before observing the angle of the eye for classification, we drained most of the aqueous humor from the anterior chamber through a corneal incision to induce blood reflux into SC. However, we were unable to confirm if the IOP had reduced to below the EVP using the tonometry during provocative gonioscopy due to the hypotensive corneal striae and low rigidity of the eye, which may have affected the blood filling patterns in SC. Last, we could not evaluate the function of the downstream distal to SC, including the EVP, even though SC-based MIGSs are likely to be affected by the distal aqueous outflow system. Moreover, because the SC lumen and CC entrances are known to show variations in size and shape,18,19 the obstruction of the SC lumen and CC entrances may also vary depending on the patient, which may have affected the surgical outcomes of trabectome surgery.

In conclusion, although the blood-filling patterns in SC before TM ablation are not a plausible outcome marker for trabectome surgery, this study suggests that a malfunctioning aqueous outflow pathway distal to SC may be recanalized after TM ablation by trabectome surgery. Trabectome surgery, combined with phacoemulsification, is an effective procedure for Japanese patients with mild to moderate POAG, regardless of the blood-filling patterns in SC before TM ablation.

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