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ARTICLE

Comparison of outflow facility before and after the microhook ab interno trabeculotomy

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Abstract

Purposes To elucidate the mechanism of intraocular pressure (IOP) reduction by microhook ab interno trabeculotomy (μLOT), the aqueous humour outflow facility was compared preoperatively and post-operatively.

Methods Fifty-one eyes (37 patients; mean age, 67.2 ± 11.8 years) were included. The IOP, number of medications and outflow facility coefficient (*C*) estimated by pneumatonography were compared preoperatively and post-operatively using the paired *t* test. Linear regression analysis was performed to identify possible correlations between the *C* value and IOP or number of medications. To adjust for biases from including both eyes of a patient and differences in background, the preoperative and post-operative *C* values were compared using a mixed effects regression model.

Results The mean preoperative IOP (18.2 mmHg) and mean number of medications (2.8) decreased significantly post-operatively by 26% and 18%, respectively, to 13.5 mmHg and 2.3 ($p < 0.0001$, for both comparisons). The preoperative *C* value of 0.27 μl/min/mmHg increased significantly ($p < 0.0001$) by 89% to 0.51 μl/min/mmHg post-operatively. Linear regression analysis indicated that higher IOP was associated with lower *C* values (estimate, −0.01/mmHg, $p = 0.0107$); medication numbers were not associated with the *C* value (estimate, −0.04/medication, $p = 0.1739$). Mixed effects regression analysis showed that the post-operative measurement (estimate, 0.11/preoperative measurement, $p < 0.0001$) was associated with a higher *C* value, while age, sex, μLOT procedure, IOP and medication numbers were not.

Conclusion Outflow facility assessed by the tonographic *C* value increased significantly after μLOT. Increased conventional outflow by elimination of the outflow resistance at the trabecular meshwork is the main mechanism of IOP reduction after μLOT.

Introduction

Trabeculotomy is performed to reduce intraocular pressure (IOP) in patients with glaucoma. In a new technique, i.e. the ab interno approach, for performing trabeculotomy, the trabecular meshwork (TM) is incised or excised using specialised devices under direct observation of the anterior-chamber angle structure [1]. Microhook ab interno trabeculotomy (μLOT), a minimally invasive glaucoma surgery (MIGS), uses a small metal hook to incise the TM [2–4]. The mechanism of IOP reduction by μLOT is theorised to be via elimination of aqueous flow resistance by cleavage of the TM and inner walls of Schlemm's canal (SC) at the point of outflow resistance of the aqueous humour. To evaluate this theory, we measured the aqueous humour outflow facility before and after μLOT.

Subjects and methods

Subjects

This retrospective study adhered to the tenets of the Declaration of Helsinki; the institutional review board of Shimane University Hospital reviewed and approved the research. Based on the approval, written informed consent from each subject was waived; instead, the study protocol was posted at the study institutions to notify participants about the study. Among the subjects who visited the glaucoma clinic from April to December 2018, a review of the medical charts identified 59 eyes of 39 subjects who underwent pneumatonography before and after μLOT. By reviewing the tonographic curves, eight eyes of six subjects were excluded because the *C* values could not be calculated due to the low

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quality of the obtained tonography curves. As result, 51 eyes of 37 subjects (19 men, 18 women; mean age, 67.2 ± 11.8 years) were included. Tonography was performed a mean of 69 ± 19 days (range, 48–132) post-operatively. The IOP values measured by Goldmann applanation tonometry and the number of antiglaucoma medications preoperatively and post-operatively were collected during a chart review. Eyes recorded with surgical complications that possibly affect the outflow facility such as posterior capsule rapture or vitreous collapse were not included. All the subjects included were Japanese.

Surgical procedure

The surgical procedure was performed through two corneal side ports as reported previously [5]. Briefly, using spatula-shaped microhooks (M-2215S, 2215R and 2215L, Inami, Tokyo, Japan) that had been designed specifically for use during μLOT, the inner wall of SC and TM was incised over 3 clock hours in the nasal and temporal angles; accordingly, the LOT extended more than half of the circumference. Microhooks were inserted into the anterior chamber through the corneal port created at the 2–3 and 9 to 10 o'clock positions. μLOT was performed under observation using a Swan-Jacob gonioprism lens (Ocular Instruments, Bellevue, WA, USA). In combined surgery cases, phacoemulsification cataract surgery was performed before μLOT through a 2.2-mm-wide clear corneal incision created at the 9 to 10 o'clock position (i.e. temporal incision for the right eye and nasal incision for the left eye); a one-piece soft acrylic intraocular lens was inserted into the capsular bag through the same clear corneal incision. Fourteen eyes (27%) underwent solo μLOT procedures and 37 eyes (73%) underwent combined μLOT and cataract surgeries. At the end of surgery, a steroid (2 mg of betamethasone sodium phosphate (Rinderone, Shionogi Pharmaceutical, Osaka, Japan) was injected subconjunctivally and 0.3% ofloxacin ointment (Tarivid, Santen Pharmaceutical) was applied. Finally, 1.5% levofloxacin (Nipro, Osaka Japan) and 0.1% betamethasone (Sanbetason, Santen Pharmaceutical) were applied topically four times daily for 3–4 weeks (i.e. 1 bottle/eye) post-operatively in all cases. Topical non-steroidal anti-inflammatory drugs were not used. Postsurgical medications use was equivalent between solo and combined procedures.

Tonography

To assess the outflow facility, tonography was conducted using a pneumatonometer (Model 30 Classic, Reichert Technologies, Depew, NY, USA). Before tonography, the IOP was measured with the patients in the supine position. A pneumatonometer probe (tip diameter, 5.3 mm) with an added 10 g weight then was placed on the centre of the cornea and held perpendicular to the corneal surface. The tonographic curve was obtained by recording the IOP for 2 min (Fig. 1A). The obtained tonographic curve printed was digitised by scanning at a resolution of 96 pixels/inch using black-and-white mode and saved as a jpeg image file. The image files were opened with image processing software (Photoshop CS5.1, Adobe, San Jose, California, USA), and nonspecific spikes were removed from the tonographic curve using an eraser tool. The curve in the image file then was converted into numerical data using graph digitiser software (CurveSnap version 1.0, https://curvesnap.en.softonic.com/) (Fig. 1B) [6]. The obtained data were opened with statistical analyses software (JMP Pro version 14.2, SAS Institute, Inc., Cary, NC, USA), and a second-order polynomial equation was obtained by fitting the data [6]. From the obtained equation, the IOPs at 0 (*P1*) and 2 (*P2*) min were calculated.

The outflow facility coefficient (*C*, μl/min/mmHg) was calculated using Grant's Eq. (1) [7].

$$C = \frac{\Delta Vs + \Delta Vc}{\Delta P \times t} \tag{1}$$

where, ΔVs (μl) is the IOP change from relaxation of the tension in the sclera and corresponding to the IOP change during tonography, ΔVc (μl) is the change in intraocular volume by corneal indentation, and t is the duration of tonography ($t = 2$ min in this study). ΔP, a value derived from the IOP change during tonography, is obtained by Eq. (2)

$$\Delta P = \frac{P2 - P1}{2} - (P0 + Pc) \tag{2}$$

where Pc is the correction of the steady-state pressure and equal to −4 mmHg for pneumatonography based on the estimation by Langham et al. [8].

ΔVs and ΔVc are obtained by Eqs. (3) and (4), respectively.

$$\Delta Vs = initial\ Vs - final\ Vs \tag{3}$$

$$\Delta Vc = final\ Vc - initial\ Vc \tag{4}$$

Although Langham et al. [8] tabulated the *Vs* (IOP range of 10–50 mmHg) and *Vc* (IOP range, 15–42 mmHg) at each IOP level, to obtain the *Vs* and *Vc* outside of the tabulated IOPs, the formulas to calculate the *Vs* (5) (Fig. 1C) and *Vc* (6) (Fig. 1D) were obtained by fitting the tabulated data

$$Vs = -0.314856 + 1.2378221 \times P - 0.0127178 \times (P - 30)^2 + 0.0006375 \times (P - 30)^3 - 0.00001 \times (P - 30)^4 \tag{5}$$

$$Vc = e^{(4.0937105 - 0.0563311 \times P)} \tag{6}$$

where *P* is *P1* for the calculation of the *initial Vs* or *Vc* and *P2* to calculate the *final Vs* or *Vc*.

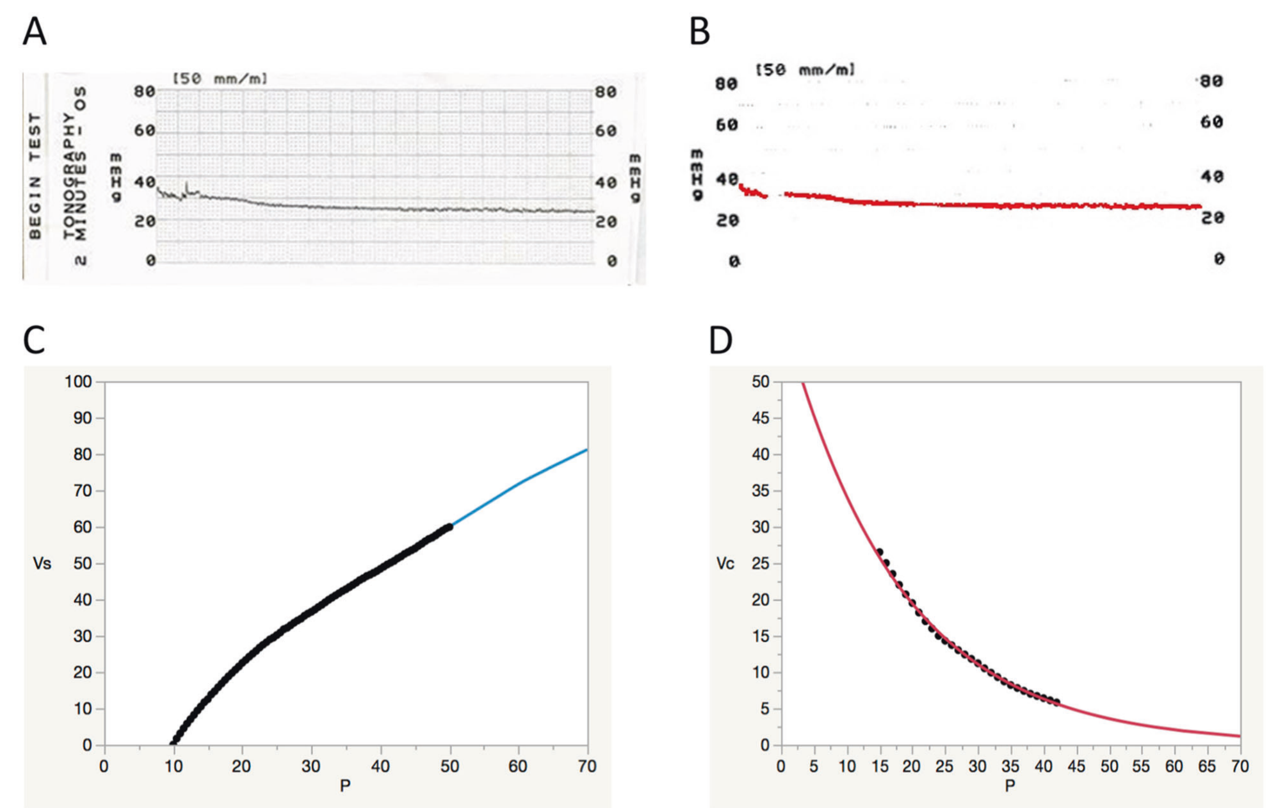

Fig. 1 The methods of pneumatonography and calculation of outflow facility. A The tonographic curve obtained by recording of the IOP for 2 min. **B** The red line indicates the curve to be digitised and converted into numerical data. **C** The fitted curve (blue line) for calculation of the change in the intraocular volume by IOP (*Vs*). **D** The fitted curve (red line) for calculation of the volume of corneal deformation at each IOP level (*Vc*).

Statistical analysis

The preoperative and post-operative IOP values, number of medications, and *C* values were compared using the paired *t* test. Linear regression analysis was performed to identify possible correlations between the *C* value and IOP or number of medications. To adjust for possible biases derived from the inclusion of both eyes of a patient and differences in their backgrounds, the preoperative and post-operative *C* values were compared using a mixed effects regression model in which each patient's identification number was regarded as a random effect and the time period, age, sex, surgical procedure, IOP and medication as fixed effects. All continuous data were expressed as the mean ± standard deviation (SD). All statistical analyses were performed using the JMP Pro version 14.2 statistical software. $P < 0.05$ was considered statistically significant.

Results

The mean preoperative IOP of 18.2 mmHg and mean number of medications of 2.8 decreased significantly to 13.5 mmHg and 2.3 medications, respectively ($p < 0.0001$ for both comparisons) (Table 1). The *C* value of 0.27 µl/min/mmHg preoperatively increased significantly to 0.51 µl/min/mmHg post-operatively ($p < 0.0001$) (Table 1). Significant changes in IOP, number of medications and *C* value

Table 1 Preoperative and post-operative IOP, medications and *C* values.

	Preoperative	Post-operative	*p* value
IOP, mmHg			
Mean ± SD	18.2 ± 5.8	13.5 ± 3.5	<0.0001
95% CI	16.6–19.8	12.5–14.5	
Medication			
Mean ± SD	2.8 ± 1.2	2.3 ± 1.0	<0.0001
95% CI	2.5–3.2	2.1–2.6	
C value, µl/min/mmHg			
Mean ± SD	0.27 ± 0.21	0.51 ± 0.33	<0.0001
95% CI	0.21–0.33	0.41–0.60	

The *p* values are calculated using the paired *t* test between preoperative and post-operative values.

IOP intraocular pressure, *C* value outflow coefficient, *SD* standard deviation, *CI* confidence interval.

Table 2 Preoperative and post-operative IOP, medications and *C* values in each surgical procedure.

	Solo procedure ($N = 14$)			Combined procedure ($N = 37$)		
	Preoperative	Post-operative	*p* value	Preoperative	Post-operative	*p* value
IOP, mmHg						
Mean ± SD	19.6 ± 5.9	14.9 ± 3.0	0.0139	17.7 ± 5.7	12.9 ± 3.6	<0.0001
95% CI	16.2–23.1	13.2–16.7		15.8–19.6	11.8–14.1	
Medication						
Mean ± SD	3.5 ± 0.9	2.9 ± 1.1	0.0142	2.6 ± 1.3	2.1 ± 0.9	<0.0001
95% CI	3.0–4.0	2.3–3.5		2.2–3.0	1.8–2.4	
C value, μl/min/mmHg						
Mean ± SD	0.26 ± 0.20	0.49 ± 0.32	0.0324	0.27 ± 0.22	0.52 ± 0.34	<0.0001
95% CI	0.15–0.38	0.31–0.68		0.20–0.34	0.40–0.52	

The *p* values are calculated using the paired *t* test between preoperative and post-operative values.

IOP intraocular pressure, *C* value outflow coefficient, *SD* standard deviation, *CI* confidence interval.

Table 3 Pre- and post-operative medication classes.

	Preoperative	Post-operative	*p* value
Prostaglandin	51 (100)	49 (96)	0.4950
β blocker	38 (75)	37 (73)	1.0000
CAI	28 (55)	27 (53)	1.0000
α2 stimulator	23 (45)	2 (4)	<0.0001
others	5 (10)	2 (4)	0.4364

Data are expressed as *N* (%). *P* values are calculated between pre- and post-operative groups by Fishers exact probability test.

CAI carbonic anhydrase inhibitor.

between pre- and post-operatively were observed in both solo and combined procedure groups (Table 2). Among the classes of glaucoma medications, compared with pre-operatively, number of α2 stimulator users was significantly reduced post-operatively, while users of other classes of medication including prostaglandin analogues, β blockers, carbonic anhydrase inhibitors, and others unchanged (Table 3). As early post-operative complications, layered hyphema in ten eyes (19.6%), transient IOP elevation more than 30 mmHg in four eyes (7.8%), fibrin reaction in one eye (2.0%) and anterior synechia in one eye (2.0%) were recorded before the post-operative tonography. None of post-operative IOP, number of medications, and *C* value were significantly different between eyes with and without complications (data not shown).

Linear regression analysis showed that higher IOPs were associated with lower *C* values (estimate, −0.01/mmHg, $p = 0.0107$); the numbers of medications were not associated with the *C* values (estimate, −0.04/medication, $p = 0.1739$). Mixed effects regression analysis showed that the post-operative measurement (estimates, 0.11/preoperative measurement, $p < 0.0001$) was associated with higher *C* values, while age, sex, μLOT procedure, IOP and number of medication were not associated with the *C* value (Table 4).

Discussion

After μLOT, the mean IOP decreased by a mean of 4.7 mmHg (26%), the mean number of medications decreased by 0.5 (18%) and the *C* value increased by a mean of 0.24 μl/min/mmHg (89%). Based on the Goldmann Eq. (7) [9], aqueous production (*Q*) is balanced by the sum of the conventional and unconventional (*U*) outflow; conventional outflow is determined by the IOP, episcleral venous pressure (*Pe*), and *C*.

$$Q = (IOP - Pe)C + U \quad (7)$$

If the *Pe* is assumed to be 8.7 mmHg, a value derived from Japanese subjects treated with a topical beta blocker [10], and if μLOT does not affect the unconventional outflow, the change in the observed *C* value should yield a post-operative IOP of 13.7 mmHg. This is close to the actual observation of a post-operative IOP of 13.5 mmHg. The assumption of *Pe* in the range of 8–10 mmHg yields an expected IOP range of 13.4–14.3 mmHg. Accordingly, based on that observation, a large part of the IOP reduction after μLOT can be explained by the increased outflow from SC.

Previous studies have reported that β blockers decrease the *Q* and may increase the *U* [10], prostaglandin analogues increase both the *C* and *U* [11], α2 stimulators decrease the *Q* and *Pe* and increase the *C* [12], and Rho kinase inhibitors increase the *C* and decrease the *Pe* [13]. Although the numbers of medication were not associated directly with the *C* value based on multivariate analyses, the estimation of the *C* value under use of various medications might make interpretation of our results complex. We performed tonography during the early post-operative period. Thus, reduction of the *Q* due to surgical damage and post-operative inflammation might still exist during this period. If this assumption is true, the post-operative IOP should be lower than the observed post-operative IOP. The possible explanation is that we observed a small but significant

Table 4 Multivariate analyses for the association of each parameter on the outflow coefficient.

	Estimate	Lower 95% CI	Upper 95% CI	p value
Age (/year)	0.004	−0.004	0.013	0.3048
Sex (female/male)	0.03	−0.04	0.11	0.4054
Procedure (μLOT/combined)	0.04	−0.07	0.15	0.4234
IOP (/mmHg)	−0.005	−0.019	0.009	0.4714
Number medications	−0.01	−0.09	0.07	0.7959
Period (postop/preop)	0.11	0.05	0.16	0.0003

The p values are calculated by mixed effects regression models to adjust for the interaction among the various backgrounds and cancel the bias resulting from inclusion of both eyes of a subject.

μLOT microhook ab interno trabeculotomy, *IOP* intraocular pressure, *postop* conducted tonography post-operatively, *preop* conducted tonography preoperatively, *CI* confidence interval.

reduction of medications (0.5 medication decrease; most were responsible for post-operative reduction in α2 stimulator users) after μLOT, that might balance the surgically induced reduction of the Q.

A previous study reported that small-incision cataract surgery increased the C value 0.04 (7%) μl/min/mmHg 3 months post-operatively compared with preoperatively [14]; although post-operative inflammation may decrease Q. Our previous study showed that combined cataract surgery yielded an additional IOP reduction over that of ab externo trabeculotomy [15]. In the current study, multivariate analysis did not detect the effect of combined cataract surgery on the C value; post-operative increase of the C value was 0.23 μl/min/mmHg and 0.24 μl/min/mmHg in solo and combined procedure groups, respectively ($p = 0.9055$ by un-paired t test). Masking of the effect of cataract surgery on the C value by a larger effect of μLOT may explain the discrepancy.

By using anterior-segment optical coherence tomography (AS-OCT), Akagi et al. reported that a ciliochoroidal detachment (CCD) was observed in 14 of 33 eyes (42%) 3 days after a Trabectome procedure; the CCD persisted in four eyes (12%) at 1 month and resolved by 3 months [16]. Sato et al. reported that CCDs detected by AS-OCT developed in 21 of 44 eyes (48%) within 7 days after 360-degree suture LOT; the CCDs resolved in 19 eyes within 1 month and in two eyes by 3 months [17]. We previously reported four cases of hypotony that persisted from the early post-operative periods [18]. Thus, CCDs generally are not rare events after MIGS surgery and seem to be associated with IOP reductions immediately post-operatively [18]. CCDs can affect the Q, C, and U [19]. Accordingly, although no marked hypotony was observed in the current patients, we did not assess CCDs in this study, which can be considered a limitation. The retrospective study design, relatively small number of subjects, lack of a control group, absence of medication wash-out and short but various follow-up periods are other study limitations. The C value of 0.27 μl/min/mmHg preoperatively in this study was close to the C values of 0.29 μl/min/mmHg by Schiøtz tonography and 0.24 μl/min/mmHg by pneumatonography estimated in the non-glaucomatous subjects [6]; normal range IOP preoperatively explains the relatively high C value for glaucoma subjects in our study. Inclusions of normal tension glaucoma and eyes under use of multiple antiglaucoma medications can be another explanation. IOP reductions have been seen without the SC opening into the anterior chamber after ab externo [20] and ab interno [21] LOT or after 360-degree suture LOT [22]. Thus, creation of another unconventional outflow pathway can be another mechanism of IOP reduction after LOT procedures; however, the current study did not provide any conclusive information regarding this speculation.

In conclusion, outflow facility assessed by the tonographic C value significantly increased after μLOT, suggesting that increased conventional outflow with elimination of the outflow resistance at the TM and inner wall of SC are the primary mechanisms of IOP reduction after this procedure. The effects of μLOT on unconventional outflow and longer follow-up period should be determined.

Summary

What was known before

- μLOT, a MIGS is theorised to reduce IOP via elimination of aqueous flow resistance by cleavage of the TM and inner walls of SC.

What this study adds

- The change in outflow facility assessed by tonography largely explains the IOP reduction observed after μLOT.

Author contributions MT conceived and designed the study. AT, KM and MM performed the tonography and collected the demographic data. MT calculated the outflow coefficient and performed statistical analyses and data interpretation. MT drafted the paper, and AT, KM and MM approved the final version of the paper.

Compliance with ethical standards

Conflict of interest The microhooks used were co-developed by MT and Inami & Co., Ltd, Tokyo, Japan, and provided by Inami & Co., Ltd. MT receives royalties from Inami & Co., Ltd. The other authors have no competing interests in this study.

Informed consent The institutional review board of Shimane University Hospital approved the study, which did not require that each patient provide written informed consent; instead the protocol was posted at the study institutions to notify participants about the study.

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