## **GLAUCOMA**

# Improvement of fluctuations of intraocular pressure after cataract surgery in primary angle closure glaucoma patients

Naoki Tojo • Mitsuya Otsuka • Akio Miyakoshi • Kazuya Fujita • Atsushi Hayashi

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#### Abstract

*Background* Cataract surgery has been shown to reduce intraocular pressure (IOP) in eyes with primary angle closure glaucoma (PACG). In this study, we examined IOP fluctuations and circadian IOP patterns before and after cataract surgery in PACG patients using the contact lens sensor (CLS) Triggerfish<sup>®</sup>.

*Methods* This was a prospective open-label study. Ten consecutive patients with PACG were included. The patients underwent phacoemulsification and intraocular lens implantation (PEA+IOL) surgery. In each eye, IOP fluctuations over 24 h were measured with the CLS before and at three months after the surgery. Changes in corneal curvatures and anatomic parameters of the anterior chamber were measured by anterior segment optical coherence tomography (AS-OCT).

*Results* The mean IOP was significantly reduced from  $14.7\pm 1.5$  mmHg to  $11.2\pm 2.2$  mmHg at three months after the surgery in PACG patients (*P*=0.002). Although the mean range of 24-h IOP fluctuations was not significantly changed after the surgery (*P*=0.49), the mean range of IOP fluctuations during the nocturnal period was significantly decreased from 246±61 mVeq to 179±64 mVeq after the surgery (*P*=0.02). After the surgery, seven eyes of the ten (70 %) showed the same circadian IOP patterns. AS-OCT showed significant improvements in the anatomic parameters of the anterior chamber after the surgery.

*Conclusions* Cataract surgery decreased IOP fluctuations during the nocturnal period in PACG patients. These effects might partly prevent the progression of PACG. **Keywords** Primary angle closure glaucoma · Contact lens sensor · Fluctuation · Intraocular pressure · Circadian pattern

## Abbreviations

AS-OCT	Anterior segment optical coherence tomography
CLS	Contact lens sensor
IOP	Intraocular pressure
PACG	Primary angle closure glaucoma
PEA+IOL	Phacoemulsification and intraocular lens
POAG	Primary open angle glaucoma

## Background

Glaucoma is a leading cause of irreversible blindness worldwide. It is estimated that primary angle closure glaucoma (PACG) affects 3.9 million people worldwide, has a higher prevalence in Asia and is responsible for half of the blindness from glaucoma [1]. Although PACG accounts for only a quarter of all primary glaucoma cases, it is a severe condition and the number of patients who become blind is almost equal to the number of primary open angle glaucoma (POAG) cases [1]. In addition, the chronic PACG patients have been reported to show more generalized field loss than the POAG patients [2].

It has been speculated that the visual field loss in PACG patients may be related, at least in part, to the elevated fluctuations in circadian IOP in PACG patients [3]. Large fluctuations in circadian IOP are also a significant risk factor for progression of visual field loss in POAG patients [3, 4]. Therefore, it is important to reduce the range of circadian IOP fluctuations for glaucoma treatment. Recently, the SENSEIMED Triggerfish<sup>®</sup> (SENSIMED AG, Lausanne, Switzerland) contact lens sensor (CLS) was made available. This CLS can continuously monitor IOP fluctuations over

N. Tojo · M. Otsuka · A. Miyakoshi · K. Fujita · A. Hayashi (⊠) Department of Ophthalmology, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan e-mail: ganka@med.u-toyama.ac.jp

24 h in an ambulatory setting for patients (habitual IOP fluctuations) [5–7].

As potentially effective treatments for PACG, phacoemulsification and intraocular lens implantation (PEA+IOL) have been studied [8, 9]. Previous studies showed that PEA+IOL not only improved the visual acuity but also reduced IOP and the number of anti-glaucoma medications in PACG patients [9–11].

In this study, we measured IOP fluctuations using a CLS in patients with PACG before and after PEA+IOL and evaluated the effects of PEA+IOL on IOP fluctuations and circadian IOP patterns in PACG patients. To the best of the authors' knowledge, this is the first study to employ 24-h continuous measurement of IOP fluctuations in eyes with PACG before and after PEA+IOL.

## Methods

This was a prospective, open-label study. Ten consecutive patients diagnosed with PACG at Toyama University Hospital were enrolled in this study from November 2012 to February 2013. All patients underwent a comprehensive ophthalmic examination including refraction, static and dynamic Goldmann gonioscopy, Goldmann applanation tonometry (GAT), fundus examination, and swept-source anterior segment optical coherence tomography (AS-OCT) (CASIA SS-1000, Tomey Corporation, Nagoya, Japan), and automated perimetry (Humphrey Field Analyzer; Carl Zeiss Meditec, Inc., Dublin, CA). One glaucoma specialist diagnosed PACG based on the criteria of Foster et al. [12].

A diagnosis of PACG was made if all of the following criteria were satisfied: (1) narrow angles (defined as eyes in which at least 270° of the posterior pigmented trabecular meshwork was not visible in gonioscopy); (2) presence of glaucomatous optic disc neuropathy (a cup/disc ratio of  $\geq$ 0.7, or the presence of notching) accompanied by corresponding visual field defects; (3) a threshold examination of SITA 30–2 showing a glaucoma hemifield test "outside normal limits," and a cluster of three contiguous points on the pattern deviation plot depressed at the P < 5 % level (versus age-matched normal subjects) not crossing the horizontal meridian. We confirmed at least two reproducible results of glaucomatous defects by the visual field tests.

Patients were required to meet all of the following criteria for inclusion in this study: (1) best-corrected visual acuity  $\geq 0.2$ ; (2) spherical equivalent  $\leq -6$  diopters; (3) diagnosis of PACG. Patients with any of the following were excluded: (1) pseudo exfoliation syndrome; (2) neovascular glaucoma; (3) steroid glaucoma; (4) primary open angle glaucoma; (5) history of ocular trauma; (6) retinal disease; (7) post vitrectomy; (8) ocular inflammatory disease; and (9) prior laser trabeculoplasty or other prior glaucoma surgery except for laser iridotomy.

The baseline IOP was the average of the last three readings obtained with GAT at the same time of the day prior to PEA+ IOL in each patient. The postoperative IOP was similarly obtained with GAT at three months after PEA+IOL.

Twenty four-hour IOP fluctuations were monitored in each eye before and after PEA+IOL with a Triggerfish® CLS (SENSIMED AG, Lausanne, Switzerland) as previously described [5]. Preoperative IOP fluctuations were measured within three days before PEA+IOL. Postoperative IOP fluctuations were measured at three months after PEA+IOL. Briefly, the CLS consisted of a highly oxygen-permeable soft contact lens, whose key elements were two sensing-resistive strain gauges that were capable of recording circumferential changes in the area of the corneoscleral junction. The device uses a novel approach to IOP monitoring in which changes in the corneal curvature and circumference are assumed to correspond to changes in IOP [13]. A change in 1 mm Hg (mmHg) of IOP was shown to produce a change in approximately 3 µm of the central corneal curvature radius [14]. The unit used in monitoring IOP with Triggerfish® is not mmHg but millivolt equivalent (mVeq), which is unique to Triggerfish<sup>®</sup>. The spiking increases in IOP monitoring with a CLS caused mainly by eye blinks, and the ocular pulsation frequency according to cardiac activity during sleeping. In addition, other factors such as temperature difference and rapid eye movements during sleeping may lead to peak increases.

We evaluated IOP fluctuations separately in the diurnal period and the nocturnal period as previously described [5, 15]. The nocturnal/sleep period was defined through the observation of blink cessation (identified as short and high amplitude spikes that were displayed by the software) on the CLS signals. We also verified the diurnal/wakefulness period and nocturnal/sleep period within the 24-h period by referring to the logs of the individual patients, in which they were instructed to record the time that they returned home, installed eye drops, went to bed, and woke up. Although antibacterial eye drop and anti-inflammatory eye drop were stopped at three months after PEA+IOL, the eye drops for glaucoma were not changed throughout the study periods.

To analyze the IOP fluctuation, the range was defined as the difference between the maximum and minimum values over 24 h, the diurnal period, and the nocturnal period. The patients were classified into three pattern groups, which were the diurnal acrophase, nocturnal acrophase and no significant acrophase groups [15]. The diurnal acrophase group consisted of patients, for whom the average value (mVeq) in the diurnal period was higher than that in the nocturnal period, and the peak value (mVeq) occurred in the diurnal period. The average values (mVeq) were calculated manually. The nocturnal acrophase group consisted of patients, for whom the average value (mVeq) in the nocturnal period was higher than that in



**Fig. 1** a Image of a PACG eye obtained by anterior segment-optical coherence tomography (AS-OCT).**b** Magnification of the square at the angle in A. The anterior opening distance is the perpendicular distance between the corneal endothelium and the anterior iris surface at 500  $\mu$ m anterior to the scleral spur. The trabecular iris angle is defined as the angle between the line of the corneal endothelium and the line of the anterior iris surface. *CCT* central corneal thickness, *CACD* central anterior chamber depth, *SS* scleral spur

the diurnal period, and the peak value (mVeq) occurred in the nocturnal period. The not significant acrophase group consisted of patients who were not assigned to either the diurnal acrophase or nocturnal acrophase group [15]. To evaluate the patterns of IOP fluctuations for 24 h in each patient, the CLS signals were reconstituted by using the hourly mean value (mVeq).

The central corneal thickness and corneal meridians, which may influence IOP measurement, were measured with AS-OCT before and after 24-h IOP measurement in each eye. We also measured the central anterior chamber depth, lens vault and axial length with AS-OCT in each eye. The algorithm then automatically calculated the lens vault, defined as the perpendicular distance between the anterior pole of the crystalline lens and the horizontal line joining the 2 scleral spurs (Fig. 1a). The anterior opening distance at 500  $\mu$ m from the scleral spur and the trabecular iris angle at 500  $\mu$ m from the scleral spur were measured in the AS-OCT images (Fig. 1b).

A Wilcoxon signed-rank test was used for all statistical analyses. Statistical significance was defined at P < 0.05. The difference of IOP fluctuation range before and after cataract surgery was assumed to be about 50mVeq. A standard deviation was supposed to be 50mVeq. With a power of 80 %, a total of 10 patients was necessary to detect the decrease in the range of IOP fluctuation when conducting a paired *t*-test with two-sided 5 % type I error.

The research protocol was approved by the Institutional Review Board of the University of Toyama and the procedures used conformed to the tenets of the Declaration of Helsinki. After the nature and possible consequences of the study were explained to the patients, written informed consent was obtained from each patient.

## Results

Ophthalmic data and cataract surgery

Table 1 shows the ophthalmic data of the patients. The study was performed on ten eyes of ten patients (one male and nine females: mean age  $72\pm6$  years). No patients took oral Acetazolamide. The average values of the central anterior chamber depth, lens vault, central corneal thickness (CCT), and axial length were  $2.01\pm0.28$  (mm),  $1,057\pm221$  (µm),  $537\pm36$  (µm), and  $22.30\pm0.57$  (mm), respectively. All surgeries were performed successfully and no complications occurred.

The mean visual acuity improved from  $0.036\pm0.13$  (logMAR±standard deviation) before PEA+IOL to  $-0.047\pm$  0.07 after PEA+IOL (*P*=0.003). The mean baseline IOP was 14.6±1.5 mmHg. The mean IOP at 3 months after PEA+IOL was significantly reduced to 11.1±2.2 mmHg, compared to

Table 1 Ophthalmic data of ten patients with primary angle closure glaucoma

Case	Gender	Age (years)	R L	CACD (mm)	Lens vault ( $\mu m$ )	CCT (µm)	LI	Axial length (mm)	preIOP (mmHg)	postIOP (mmHg)
1	F	78	R	1.63	1,246	528	_	22.18	14.7	13
2	F	62	L	2.28	1,203	520	_	22.84	16.3	15
3	F	73	R	2.06	1,338	566	_	21.42	14.3	10
4	F	78	R	1.96	826	519	+	21.53	15	11
5	F	65	L	1.88	893	513	-	22.18	17.7	12
6	F	73	R	2.27	837	553	-	23.05	13	10
7	F	76	L	1.98	1,026	529	+	22.86	13.7	8
8	F	75	R	1.84	936	587	+	22.92	15	12
9	М	62	L	1.9	1,139	606	-	22.24	13	8
10	F	74	L	1.71	1,407	486	-	21.72	13	12

CACD central anterior chamber depth, CCT central corneal thickness, LI history of laser iridotomy, IOP intraocular pressure

Fig. 2 a Diagram of 24-h continuous IOP fluctuations recorded with a Triggerfish® CLS before PEA+IOL. The diagram was redrawn with the mean IOP fluctuations every hour. This was the result of case No.10. b Diagram of continuous IOP fluctuations in the same eye over 24 h recorded with a Triggerfish® CLS after PEA+IOL. The dotted line represents the nocturnal period and the solid line represents the diurnal period. The peak IOP and IOP fluctuations were decreased after PEA+IOL



time 12 13 14 15 16 17 18 19 20 21 22 23 0 1 2 3 4 5 6 7 8 9 10 11

the mean baseline IOP (P=0.002). By analysis of AS-OCT images, the mean anterior opening distance at 500 µm from the scleral spur and the mean trabecular iris angle at 500 µm from the scleral spur before PEA+IOL were  $0.20\pm0.1$  mm and  $16.4\pm8.2^{\circ}$ , respectively. These significantly improved to  $0.47\pm0.14$  mm (P<0.001) and  $40.0\pm11.1^{\circ}$  (P<0.001) after PEA+IOL.

## Circadian IOP patterns

IOP fluctuations over 24 h in each patient were successfully recorded using a CLS. Patients showed no serious complications related to the Triggerfish® CLS. We converted the original IOP fluctuation graphs recorded every 5 min to IOP fluctuation graphs with mean fluctuations of every hour (Fig. 2a, b) and evaluated the circadian patterns of IOP changes. Before PEA+IOL, six of ten eyes showed peak values during the nocturnal period (nocturnal acrophase group) and two eyes showed peak values during the diurnal period (diurnal acrophase group) (Table 2). Two eyes were included in the no significant acrophase group because these two eyes did not show any specific patterns before and after PEA+IOL. At three months after PEA+IOL, eight of the ten eves (80 %) showed the same circadian IOP pattern. One eye changed from the nocturnal acrophase to the diurnal acrophase, and another one eye changed from the diurnal acrophase to the nocturnal acrophase.

### Measurement of IOP fluctuations

The ranges of IOP fluctuations over 24 h before and after PEA+IOL are shown in Table 3. The range of IOP fluctuations over 24 h decreased after PEA+IOL in five of the ten eyes.

The ranges of IOP fluctuations in the nocturnal period were smaller than those in the diurnal period in nine of the ten eyes before PEA+IOL and all eyes after PEA+IOL (Table 3).

As shown in Fig. 3, the mean ranges of preoperative IOP fluctuations were  $425\pm54$  mVeq (24 h),  $407\pm72$  mVeq (diurnal period), and  $241\pm61$  mVeq (nocturnal period). The mean ranges of postoperative IOP fluctuations were  $410\pm$ 73 mVeq (24 h),  $409\pm74$  mVeq (diurnal period), and  $179\pm$ 64 mVeq (nocturnal period). The mean range of IOP fluctuations over 24 h was  $425\pm54$  mVeq before PEA+IOL and  $410\pm73$  mVeq after PEA+IOL (*P*=0.49) (Fig. 3a). During the diurnal period, the mean range of IOP fluctuations was  $407\pm72$  mVeq before PEA+IOL and  $409\pm73$  mVeq after PEA+IOL (*P*=0.92) (Fig. 3b). On the other hand, during

Table 2 Circadian IOP patterns before and after cataract surgery

Case	Pre-op	e	Post-ope		
	Туре	Peak time (o'clock)	Туре	Peak time (o'clock)	
1	Ν	N (23)	Ν	N (3)	
2	D	D (19)	D	D (7)	
3	Ν	N (5)	Ν	N (2)	
4	Ν	N (4)	Ν	N (5)	
5	Ν	N (0)	Ν	N (6)	
6	Ν	N (6)	D	D (6)	
7	Ν	N (5)	Ν	N (6)	
8	NS	D (8)	NS	D (7)	
9	D	D (22)	Ν	N (5)	
10	NS	D (14)	NS	D (15)	

Type; D diurnal acrophase group, N nocturnal acrophase group, NS no significant acrophase group. Peak; time; D the peak in diurnal period, N the peak in nocturnal period

**Table 3** Ranges of IOP fluctua-tions over 24 h, the diurnal period,and the nocturnal period

Case	24-h (mVec	D	Diurnal perio	ods (mVeq)	Nocturnal pe	Nocturnal periods (mVeq)	
	Pre-ope	Post-ope	Pre-ope	Post-ope	Pre-ope	Post-ope	
1	424.9	333.9	375.3	333.9	344.4	138.5	
2	433.6	536.9	433.6	536.9	185.3	237.8	
3	353.6	323.9	339	319.8	309.1	287.8	
4	474.8	476	474.8	476	243.9	149.9	
5	461.3	407.6	434.5	400.2	237.7	224.4	
6	348.1	355.5	266.2	355.5	307.7	211.7	
7	462.5	463.9	462.5	463.9	218.8	171.8	
8	512.2	460	512.2	460	214.7	192.2	
9	390.5	413.7	382.4	413.7	155.3	84.5	
10	386.2	333.5	386.2	333.5	197.1	94.2	

the nocturnal period, PEA+IOL significantly decreased the range of IOP fluctuations from  $241\pm61$  mVeq to  $179\pm64$  mVeq (P=0.02) (Fig. 3c). Nine of the ten eyes decreased the amplitude of IOP fluctuations during the nocturnal period after PEA+IOL (Table 3).

and 44.6 $\pm$ 2.0 D after measurement (*P*=0.59). The average CCT was also unchanged: 540 $\pm$ 33 (µm) before measurement and 547 $\pm$ 38 (µm) after measurement (*P*=0.06).

## Corneal effects of the CLS

Fig. 3 Boxplots of the range of

habitual IOP fluctuations for 24 h

before and after PEA+IOL. Only

the range of IOP fluctuations during the nocturnal periods (c) showed a significant decrease

after PEA+IOL (P=0.02)

We chose a size of the CLS from three types of the CLS according to the base curve of the cornea in each eye. In this study, all patients wore the medium size of the CLS. To examine the effects of the CLS on the cornea, we analyzed corneal changes before and after measurement with the CLS. The average steeper meridian was largely unchanged, being  $45.2\pm1.9$  diopter (D) before measurement and  $45.8\pm2.2$  D after measurement (P=0.07). The average flatter meridian was also basically unchanged:  $44.4\pm1.6$  D before measurement

#### Discussion

Cataract surgery in PACG patients has been shown to improve the anterior chamber depth and aqueous humor outflow, resulting in an improvement of IOP control and visual acuity [8–11, 16]. Similarly to the previous studies [9–11], we also demonstrated that PEA+IOL significantly improved the mean IOP and anatomical parameters of the anterior chamber, such as the lens vault and the mean trabecular iris angle, in the PACG patients.

The reproducibility of the measurement of the circadian IOP pattern with the CLS was proved acceptable [7, 15, 17,



18], and our results supported it because the circadian IOP patterns were the same in eight of the ten eyes before and after PEA+IOL in this study. The CLS is the only method to measure habitual IOP fluctuations for 24 h at present. Mansouri et al., reported that the nocturnal acrophase was seen in 62.9 % of glaucoma patients by analysis with the CLS [15]. Pajic B et al., reported that IOP fluctuations measured by the CLS were flattened by medication in the patients with normal tension glaucoma [18]. Even though the CLS does not measure IOP of mmHg, measurement of IOP fluctuations with the CLS is reproducible and useful to evaluate circadian IOP rhythm and effects on glaucoma treatments.

Cataract surgeries were shown to reduce diurnal IOP fluctuations in patients of pseudo exfoliation with both open and occludable angles as well as in patients with primary open angle glaucoma [19, 20]. Our results showed a significant decrease of IOP fluctuations in the nocturnal period only at three months after PEA+IOL. Further studies are needed to examine long-term effects of cataract surgery on IOP fluctuations in glaucoma patients.

The measurement of IOP with the CLS has some limitations. First, it is not possible to convert the recorded units of mVeq to units of mmHg. Since the values of mVeq recorded with a Triggerfish<sup>®</sup> CLS did not directly show the values of mmHg, we evaluated only relative changes of mVeq. Secondly, artifacts of measurements by the CLS method could have an impact on the results. Changes in the corneal curvatures due to corneal hypoxia may have affected the values of mVeq during the 24-h measurement of IOP fluctuations. In this study, the mean steeper meridian was not significantly increased (P=0.07), but it was reported that central corneal thickness and corneal curvature irregularities slightly increased with the Triggerfish<sup>®</sup> CLS [21].

In conclusion, continuous 24-h IOP monitoring with the CLS appears to be useful in the management of patients with glaucoma. Measurement of IOP fluctuations with the CLS revealed that cataract surgery resulted in a significant reduction of the range of IOP fluctuations during the nocturnal period in PACG patients. These results support the idea that PEA+IOL would contribute to the prevention of visual field loss in PACG patients.

**Conflicts of interest** The authors declare that they have no conflicts of interest that are relevant to the content of this manuscript.

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