

Diurnal Intraocular Pressure Fluctuations with Self-tonometry in Glaucoma Patients and Suspects: A Clinical Trial

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SIGNIFICANCE: This article shows that self-tonometry can provide robust measures of diurnal intraocular pressure (IOP) and also detect changes to IOP in response to treatment within a short period of monitoring. These advances in IOP monitoring may contribute to improved management of glaucoma patients and suspects.

PURPOSE: The aim of this study was to prospectively investigate the utility of rebound self-tonometry performed over several weeks for detecting diurnal IOP fluctuations in glaucoma patients and suspects and also initial response to topical treatment in glaucoma patients.

METHODS: Forty patients were recruited following glaucoma-specific examination. Subsequent to successful training with the iCare HOME tonometer, patients were instructed to measure IOP, in a sitting position, four times a day over 4 to 6 weeks. Date, time, laterality, and IOP downloaded from the tonometer and clinical examination data, including applanation IOP and corneal thickness, were analyzed. A user satisfaction survey was also administered at study completion. *t* Test and analysis of variance were used to compare groups and IOP across days. Pearson correlation was used to compare measurements to Goldmann applanation tonometry and IOP measurements from the first day/s to the overall mean IOP.

RESULTS: Twenty-seven patients (18 suspects and 9 glaucoma patients) completed data collection. Patients self-measured IOP on 118 (± 29) occasions for 40 (± 7.4) days. Two dominant patterns of fluctuation were revealed: peak IOP upon awakening ($n = 11$) and at midday ($n = 13$). Diurnal IOP measured in the first 7 days showed strong correlation to diurnal IOP across the entire study period ($r^2 = 0.82$, $P < .0001$). Within 24 hours of treatment commencement (latanoprost 0.005% ophthalmic solution), IOP reduced from 23.9 (± 5.2) to 16.1 (± 2.6) mmHg. Overall, patients rated the instrument as easy to use, although difficulties with correct alignment were expressed.

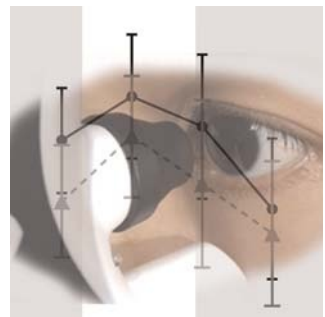
CONCLUSIONS: Rebound self-tonometry demonstrated utility for measuring diurnal IOP fluctuations in most patients, hence enhancing management of patient with or at risk of developing glaucoma.

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Measurement of intraocular pressure is integral to the diagnosis and management of glaucoma.^{1,2} Elevated intraocular pressure is a well-established risk factor for glaucoma progression, and current treatments to prevent progressive optic neuropathy and visual field loss are targeted at reducing intraocular pressure.^{3,4} Evidence for short- and long-term intraocular pressure fluctuations, however, is inconclusive. Long-term fluctuations, defined as the standard deviation (SD) of intraocular pressure measurements across multiple visits, were found to be associated with glaucoma progression in a subgroup of advanced glaucoma patients with low mean intraocular pressure, but not in patients with early glaucoma or ocular hypertension.^{5–7} On the other hand, short-term intraocular pressure fluctuations, defined as the maximum change in intraocular pressure within a 24-hour period or less, are generally greater in patients with glaucoma (5.7 to 5.8 mmHg) and ocular hypertension (5.6 to 6.8 mmHg) compared with healthy patients (4.0 to 5.0 mmHg).^{8–10} Short-term intraocular pressure fluctuations can result from circadian or diurnal variation, and while the extents of fluctuations differ across diagnosis groups, it still remains unclear whether these fluctuations constitute a risk factor for glaucoma progression.^{11–13}

Regardless, measurement of diurnal intraocular pressure forms an important part of glaucoma diagnosis and management.^{1,2} Because of diurnal variation, measurements taken at different times may not be directly comparable, and single in-office measurements will miss the peak or highest intraocular pressure in 69 to 75% of patients.^{14,15}

As a major risk factor and primary treatment outcome, precise determination of a patient's intraocular pressure including fluctuations is essential. Currently, the criterion standard for these measurements is Goldmann applanation tonometry, typically performed in a clinical setting by a trained health care professional and requiring instillation of topical anaesthetic. To establish a diurnal or 24-hour curve, repeated intraocular pressure measurements over multiple visits or an overnight hospital stay are required.¹⁶ Although 24-hour monitoring provides the most comprehensive picture of intraocular pressure fluctuations, it is often too expensive or impractical for integration into standard clinical practice.¹⁷ Technological advances have resulted in the development of a contact lens pressure sensor, which allows continuous 24-hour monitoring; however, the measurements obtained are currently limited

in their clinical utility as they are expressed in units that do not easily translate to mmHg.^{18,19} Furthermore, Moodie et al.²⁰ found that 24-hour monitoring confers only little advantage over daytime phasing of intraocular pressure for identification of intraocular pressure fluctuations or peaks in patients, suggesting that daytime phasing between 8 AM and 6 PM is likely more cost-effective than 24-hour phasing.

In recent years, self-administered rebound tonometry performed without topical anaesthesia has been investigated for use in diurnal intraocular pressure monitoring.^{21,22} First, the iCare ONE and more recently the iCare HOME (iCare Finland Oy, Vantaa, Finland) have demonstrated good repeatability and correlation with Goldmann applanation tonometry in both healthy persons and glaucoma patients.^{23–26} With appropriate training and instruction, most patients were able to successfully perform self-tonometry with the advantage of obtaining intraocular pressure measurements in the patient's habitual environment and fewer visits to the health practitioner's office.^{24,25} Previous reports investigating diurnal intraocular pressure with rebound self-tonometry have demonstrated high intraindividual variation across consecutive days, with participants exhibiting different diurnal curve patterns from day to day.^{21,22} However, no studies to date have investigated diurnal curve fluctuations with iCare HOME for more than a week.

In this prospective study, we investigated the utility of the iCare HOME in identifying diurnal intraocular pressure fluctuations including the extent and patterns of intraocular pressure fluctuations observed in patients with newly diagnosed glaucoma (commencing treatment) and also untreated glaucoma suspects. We hypothesize that surveillance over several weeks can better reveal an individual's diurnal intraocular pressure patterns. In addition, as patient noncompliance with glaucoma therapy is reportedly as high as 80%, it is unclear whether performing self-tonometry, multiple times a day over several weeks, would be acceptable to patients.²⁷ Therefore, we also investigated patient compliance with the instructed measurement regimen (four times per day) and satisfaction with using the instrument in their habitual environment over a minimum period of 4 weeks.

METHODS

This was a prospective study approved by the University of New South Wales Human Research Ethics Committee and registered with the Australia New Zealand Clinical Trials Registry (trial ID ACTRN12615001274561). Written informed consent was obtained from all study participants in accordance with the tenets of the Declaration of Helsinki.

Study Participants

Eligible treatment-naïve glaucoma patients or suspects attending the Centre for Eye Health (University of New South Wales, Sydney, Australia) between February and December 2016 for glaucoma-specific examination were invited to participate in the study. Each patient underwent a standard battery of glaucoma-specific testing by clinical staff prior to recruitment including measurements of visual acuity, automated blood pressure, applanation intraocular pressure, central corneal thickness with ultrasonic pachymetry, corneal curvature with autokeratometry, examination of the anterior and posterior eye with slit-lamp biomicroscopy, gonioscopy and funduscopy, optic nerve and macula imaging with optical coherence tomography (Cirrus HD-OCT; Carl Zeiss Meditec Inc., Dublin, CA), and visual field central threshold 24-2 testing (Humphrey HFA II-i or 3; Carl Zeiss Meditec Inc.). Patients with

the following attributes were excluded: active ocular surface disease, current contact lens wear, high corneal astigmatism (>3-diopter cylinder), keratoconus, significant corneal scarring, history of incisional glaucoma or corneal surgery, poor or eccentric fixation, nystagmus, functionally monocular patients, those with sensory or motor deficits that may affect their ability to undergo training and perform self-handling of the instrument, and use of systemic β -blocker medication. Inclusion criteria required patients 40 years or older, a diagnosis of either glaucoma or glaucoma suspect with open angles, and no risk factors for secondary glaucomas. Diagnosis of glaucoma suspect was based on a previously published classification system.²⁸ In short, suspects were defined as individuals with suspicious optic nerve appearance (e.g., neuroretinal rim thinning or notching), retinal nerve fibre layer defect, or visual field defect but insufficient for glaucoma diagnosis. Suspects with intraocular pressure of 21 mmHg or greater with applanation tonometry at baseline were diagnosed as having ocular hypertension. Diagnosis of glaucoma was confirmed by a glaucoma subspecialist and based on the presence of optic nerve or retinal nerve fiber layer abnormalities with corresponding visual field defect or elevated intraocular pressure, in the absence of other causes. All included glaucoma patients were treated with topical prostaglandin analog (latanoprost 0.005% ophthalmic solution) in either one eye ($n = 3$) due to asymmetric presentation or both eyes ($n = 6$), as recommended by the treating ophthalmologist.

Baseline Visit: Safety and Certification

Prior to patient recruitment, research staff (BZ and JH) completed training and certification in the use of the rebound tonometer, iCare HOME, as per manufacturer's instructions. Research staff conducted training sessions, approximately 30 minutes in duration, with study patients. Patients were orientated to the instrument and measurement procedure, specifically the preparation of the instrument, insertion of a disposable probe, correct positioning, obtaining and checking that measurements were taken, and disposal of the probe upon conclusion. All measurements were obtained in sitting position, as per the instrument design. Following a demonstration by research staff, patients verified their understanding by independently replicating the procedure under supervision. Prior to and following training, patients' corneas were graded for corneal staining with sodium fluorescein, and patients were also asked to grade their ocular comfort on a scale from 1 to 100. Certification was achieved if the patient demonstrated appropriate positioning of the instrument and was able to independently obtain three reliable iCare HOME measurements following a minimum 10-minute interval after the demonstration by research staff.

Data Collection

Patients were asked to perform self-tonometry four times a day (upon awakening, before lunch, before dinner, and before bed) over a 4- to 6-week period, dependent on their scheduled review date as determined by the examining clinician. Glaucoma patients were asked to record the time and date that topical treatment was initiated and to perform self-tonometry prior to instillation of medication, if administered consecutively. The instrument automatically recorded the intraocular pressure, time, date, ordinal number, and laterality of each measurement. During the study period, patients had no access to collected intraocular pressure data, as it is not displayed on the instrument. Data were accessible only after connecting the device to a computer with the iCare LINK software (iCare Finland Oy) installed. Patient demographical and

clinical data such as applanation intraocular pressure, central corneal thickness, diagnosis, prescribed treatment, and review period were collected from clinical examination records.

Follow-up Visit: Review and User Satisfaction Survey

At the follow-up visit, iCare HOME instruments were returned, and intraocular pressure data were downloaded. Corneas were reexamined with sodium fluorescein, and patients were asked to complete a survey, developed by the manufacturers, rating their experience with the instrument on a 5-point Likert scale. With respect to aspects of instrument use, possible responses included easy, somewhat easy, neutral, somewhat difficult, and difficult.

Data Analysis

Data were exported from iCare LINK software for analysis in Microsoft Excel (Microsoft Corp., Redmond, WA), IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, NY), and GraphPad Prism version 7.03 for Windows (GraphPad Software, La Jolla, CA). One eye of each patient was included for the group analysis to avoid between-eye correlation bias.²⁹ For patients undergoing monocular topical treatment, the treated eye was included; otherwise, an eye was randomly selected. For patients who completed training and certification for both eyes and had data that met the inclusion criteria, a post hoc subanalysis was also performed to examine the correlation between eyes. If multiple measurements were recorded at one time ($n = 161$ [4.25%]), only the last consecutive measurement was included for analysis because of specific instructions to patients to repeat measurements only, if the original measurement was not performed correctly. Measurements outside the iCare HOME's range were recorded by the instrument as “<5” and “>50” mmHg and excluded from analysis ($n = 92$ [2.43%]), as well as outliers ($n = 6$ [0.16%]) identified as outside $2.2\times$ the interquartile range for individual patients.³⁰ Patients with an insufficient number of measurements were excluded from the analysis ($n \leq 39$ over the study period and $n \leq 14$ in any week).

Descriptive statistics were used to report the demographic characteristics of the study population and patient-reported instrument usability. Data were presented as mean and SD unless otherwise indicated. Intraocular pressure data were binned into time intervals using (1) local clock time and (2) time of the patient's first measurement (waking time) as reference. Binning was optimized to provide even distribution of intraocular pressure measurements across time intervals and minimize variability within individual bins. To calculate diurnal intraocular pressure fluctuation, each patient's intraocular pressure data were individually analyzed to obtain mean intraocular pressure for each binned time interval. The difference between mean values was defined as the diurnal IOP fluctuation. Patient compliance was calculated by dividing the number of measurements successfully recorded (and included for analysis) by the number of measurements possible if protocol was followed (i.e., four times per day).

Shapiro-Wilk normality test was used to confirm the distribution of continuous data. For normally distributed data including age, baseline, and mean intraocular pressure, the independent t test was used to compare glaucoma and glaucoma suspect groups. Paired and unpaired t tests were applied to compare intraocular pressure variance between the two methods of binning stated above (clock time vs. patient waking time), for five-hourly and two-hourly intervals, respectively. To examine changes in intraocular pressure on consecutive days following treatment, analysis of variance and Tukey multiple-comparisons test were applied. For

non-normally distributed data such as the extent of diurnal intraocular pressure fluctuations, Mann-Whitney U test was used to compare differences between groups. Comparison of categorical data including sex and ethnicity was performed with the χ^2 test. Pearson correlation was calculated between diurnal intraocular pressure (within binned time intervals) measured in the first day/s compared with overall mean diurnal intraocular pressure (of all measurements obtained over the study period). It was also used to examine the relationship between changes in intraocular pressure measured by applanation tonometry and iCare HOME following glaucoma treatment and the effect of central corneal thickness on these measurements. Analysis of variance was applied to test the effect of laterality on the variability of the IOP measurements. In a subanalysis of patients with intraocular pressure data from both eyes, we examined intraclass correlation of intraocular pressure measurements between eyes and also performed paired t test to compare the variability of right and left eye measurements within patients.

RESULTS

Study Participants

Of 40 patients enrolled in the study, 27 reached completion, comprising 9 patients with newly diagnosed glaucoma and 18 suspects. Of the remainder, eight patients could not be certified because they were unsuccessful in performing self-tonometry despite repeated assistance during the training session; three patients did not obtain a sufficient number of measurements during the study period, and another two patients withdrew prior to the minimum 4-week study period. No adverse events were found by the research staff or reported by the patients throughout the study. Patient demographic and characteristics (Table 1) showed no significant differences in age, sex, or ethnicity between the glaucoma and suspect groups with the exception of baseline applanation intraocular pressure. In addition, there were no significant differences between patients who successfully completed training to become certified and those who did not. Over the study period, included patients measured their intraocular pressure on 118 (± 29) occasions for 40 (± 7.4) days. Mean intraocular pressure recorded with iCare HOME was 14.3 (± 1.7) mmHg for treated glaucoma patients and 14.7 (± 3.7) mmHg for suspects, which was not significantly different (t test, $P = .66$). Mean central corneal thickness was also not significantly different (t test, $P = .29$) between the groups at 547 (± 24) μm for the glaucoma patients and 561 (± 33) μm for the suspects.

Patterns and Extent of Intraocular Pressure Fluctuation

To investigate the effect of circadian rhythms (i.e., timing of waking and sleeping hours), binning of intraocular pressure according to local clock time was compared with binning adjusted to the patient's first measurement of the day (i.e., upon awakening). Because this adjustment did not result in significant differences for both two- and five-hourly intervals (t test, $P > .05$), all subsequent analyses were based on local clock time. To illustrate average diurnal patterns of the two investigated groups (18 suspects and 9 treated glaucoma patients), measurements were divided into two-hourly intervals from 6:00 AM to midnight, resulting in nine bins, indicating generally higher intraocular pressure in the morning and early afternoon with a slight and gradual decrease at night (Fig. 1A).

TABLE 1. Patient demographic and baseline characteristics

	Certified		<i>P</i> *	Certified <i>n</i> = 27	Noncertified <i>n</i> = 8	<i>P</i> †
	Suspect <i>n</i> = 18	Glaucoma <i>n</i> = 9				
Age, mean ± SD (y)	62.3 ± 8.3	60.8 ± 9.3	.66‡	61.8 ± 8.5	64.6 ± 10.1	.44‡
Sex, male:female (n)	12:6	6:3	.999§	18:9	5:3	.83§
Ethnicity, EU:AS:AF (n)	16:4:0	5:2:0	.64§	21:6:0	5:2:1	N/A
Handedness, R:L (n)	16:2	9:0	N/A	25:2	7:1	.65§
IOP , mean ± SD (mmHg)	17.3 ± 3.5	22.9 ± 4.5	.006‡	19.1 ± 4.7	—	—

*Certified suspect versus certified glaucoma. †Certified versus noncertified. Comparison of patient groups were performed using unpaired *t* test‡ and χ^2 test§. ||Applanation IOP. AF = African; AS = Asian; EU = European; IOP = intraocular pressure; L = left or ambidextrous; N/A = no answer; R = right.

Individual diurnal patterns were analyzed according to the four daily measurements represented by four 5-hourly intervals starting at 5:00 AM, 10:00 AM, 3:00 PM, and 8:00 PM and corresponding to 26.2, 22.7, 22, and 26.4% of the measurements, respectively. The remaining 2.7% of measurements, recorded between 1:00 and 5:00 AM, were not included for analysis. Across all subjects, diurnal intraocular pressure fluctuation ranged from 2 to 11 mmHg, with a mode of 3 mmHg (Fig. 1B). Extent of diurnal intraocular pressure fluctuation was not significantly different between the groups (Mann-Whitney *U*, *P* = .14) with a median (interquartile range) of 4.9 (3.3 to 7.5) mmHg and 3.3 (2.6 to 5.6) mmHg for treated glaucoma and suspect groups, respectively. Analysis of the individual patterns of intraocular pressure change across the five-hourly binned intervals revealed two major patterns of diurnal intraocular pressure fluctuation (Fig. 2 and Appendix Fig. A1, available at <http://links.lww.com/ALN/B600>). One pattern observed in 11 patients (40.7%; eight glaucoma suspects and three treated glaucoma patients) showed their highest intraocular pressure between 5:00 and 10:00 AM, which decreased into the night (Fig. 2A). Another 13 patients (48.1%; eight glaucoma suspects

including one with ocular hypertension and five treated glaucoma patients) reached their highest intraocular pressure between 10:00 AM and 3:00 PM (Fig. 2B). A possible third pattern was identified in two patients (7.4%; one glaucoma suspect, one treated glaucoma patient), whereby intraocular pressure was highest at night, between 8:00 PM and 1:00 AM (Fig. 2C).

To calculate the minimum observation period possible to predict the diurnal patterns observed over the complete study period (4 to 6 weeks) with reasonable certainty, mean intraocular pressures in each of the five-hourly time intervals (diurnal intraocular pressures) obtained across the entire study period were compared with measurements obtained from day 1. Subsequently, this calculation was repeated by adding measurements from consecutive days (e.g., day 2, then day 3 and so on). Although moderate correlation was observed after measuring for only a single day ($r^2 = 0.55$, $P < .0001$), the correlation increased with each additional day, reaching $r^2 = 0.67$ ($P < .0001$) after 3 days and resulting in a strong correlation after 7 days with $r^2 = 0.82$ ($P < .0001$). After the first week, additional days provided only small increases in the observed correlation with $r^2 = 0.85$

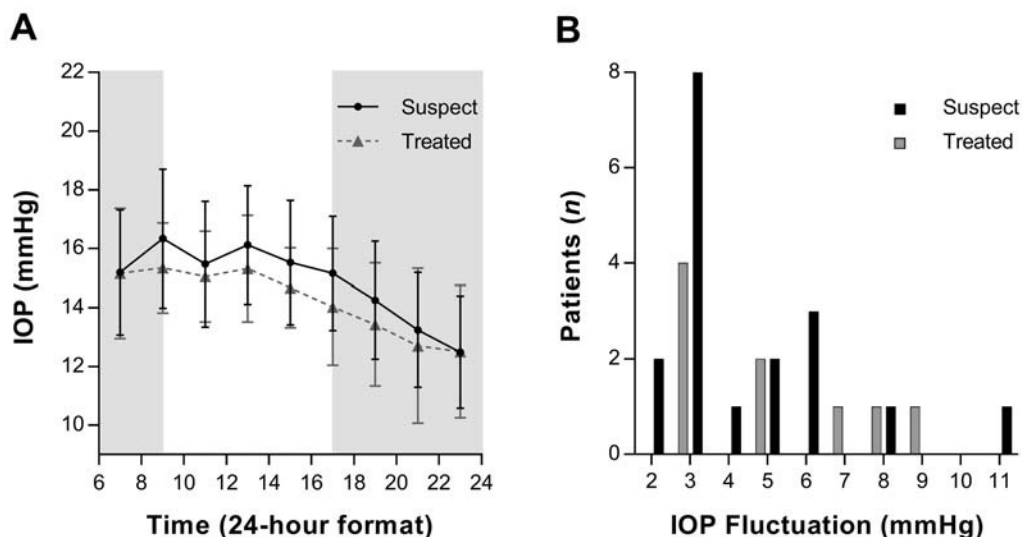


FIGURE 1. (A) Illustration of average diurnal intraocular pressure (IOP) between clock hours of 6:00 AM to midnight for glaucoma suspects (*n* = 18) and treated glaucoma patients (*n* = 9) using a rebound self-tonometer over 4 to 6 weeks. Mean diurnal IOP was higher in the morning and lower at night for both groups. Symbol: mean, error bars: 95% confidence interval, unshaded areas: office hours, that is, 9:00 AM to 5:00 PM. (B) Frequency histogram of diurnal IOP fluctuation (difference between the highest and lowest mean IOPs) had a mode of 3 mmHg and ranged from 2 to 11 mmHg.

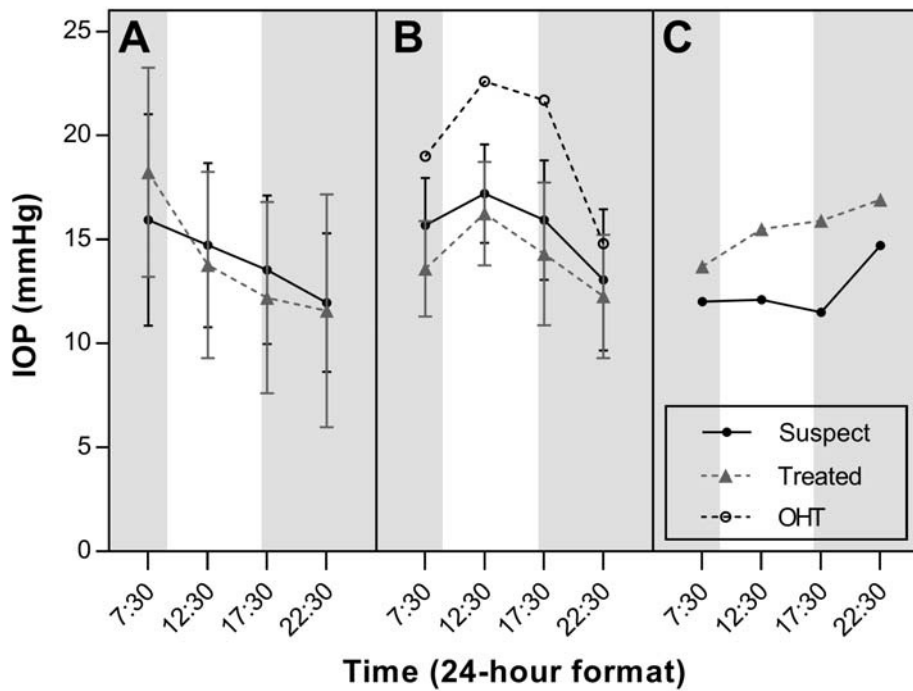


FIGURE 2. Three diurnal intraocular pressure (IOP) patterns demonstrated by glaucoma suspects and patients with rebound self-tonometry monitoring over 4 to 6 weeks based on four daily measurements. Time shown on the x axis represents the center of the 5-hour interval plotted (e.g., 7:30 represents 5:00 to 10:00 AM). (A) Pattern 1: highest IOP at the first measurement of the day (5:00 to 10:00 AM) (n = 11, eight glaucoma suspects, three treated glaucoma patients). (B) Pattern 2: highest IOP at the second measurement (10:00 AM to 3:00 PM) (n = 13, eight glaucoma suspects including one with ocular hypertension, five treated glaucoma patients). (C) Pattern 3: highest IOP at the last measurement (8:00 PM to 1:00 AM) (n = 2, one suspect, one treated). Symbol: mean, error bars: 95% confidence interval. OHT = ocular hypertension. Unshaded areas: office hours (9:00 AM to 5:00 PM).

($P < .0001$) after 10 days (see Appendix Fig. A2, available at <http://links.lww.com/ALN/B601>).

Correlation between Eyes

The correlation of measurements between the eyes of individual patients was examined in a subanalysis of additional data from contralateral eyes (not included in our main analysis). Seventeen patients (7 treated glaucoma patients and 10 glaucoma suspects) had data from their contralateral eye that met the inclusion criteria. Intraocular pressure measurements were highly correlated between the eyes (intraclass correlation coefficient, 0.834; 95% confidence interval, 0.730 to 0.897; $P < .0001$). Variance of intraocular pressure measurements was not significantly different between the right and left eyes within patients (paired t test, $P = .71$). The pattern of diurnal intraocular pressure fluctuation, described above, was consistent between eyes in 88% of the patients (15/17); the two patients with inconsistent patterns were glaucoma suspects.

Measuring the Effect of Glaucoma Treatment

Prior to treatment, baseline measurements for the glaucoma group (n = 9) with applanation tonometry was 22.9 (± 4.5) mmHg compared with 25.5 (± 6.0) mmHg with iCare HOME, obtained during in-office training. Following 4 to 6 weeks of treatment, applanation intraocular pressures were 15.4 (± 3.8) mmHg and 14.6 (± 3.6) mmHg with iCare HOME during the equivalent binned time interval. This corresponded to a measured therapeutic effect

of 32 and 40%, respectively. Although on average the reduction in intraocular pressure and resulting therapeutic effects were comparable using the two measurement methods, there was no significant correlation in the therapeutic effect (% change in intraocular pressure) measured by applanation tonometry compared with iCare HOME ($r^2 = 0.007$, $P = .83$). In addition, central corneal thickness was not significantly correlated with the measured differences in intraocular pressure with applanation tonometry compared with iCare HOME ($r^2 = 0.08$, $P = .45$).

Mean untreated iCare HOME intraocular pressure across all time points, including baseline, on day 0 was 23.9 (± 5.2) mmHg for the glaucoma group and following a single dose of treatment reduced to 16.1 (± 2.6) mmHg on day 1, this difference was statistically significant (Tukey multiple-comparisons test, $P = .0001$) (Fig. 3). Subsequently, on day 2 (14.8 \pm 3.0 mmHg) and day 3 (14.7 \pm 3.0), there was a small but nonsignificant further reduction compared with day 1 ($P = .92$ and $P = .88$). There were also no significant differences between the intraocular pressure measured on days 1, 2, and 3 compared with the mean intraocular pressure (14.3 \pm 1.7 mmHg) across the entire study period ($P = .76$, $P > .99$, and $P > .99$).

Patient Satisfaction and Compliance

Overall, patients rated the iCare HOME instrument as easy to use (Fig. 4). Although most aspects of instrument use were rated “easy,” correct positioning of the instrument on the eye showed

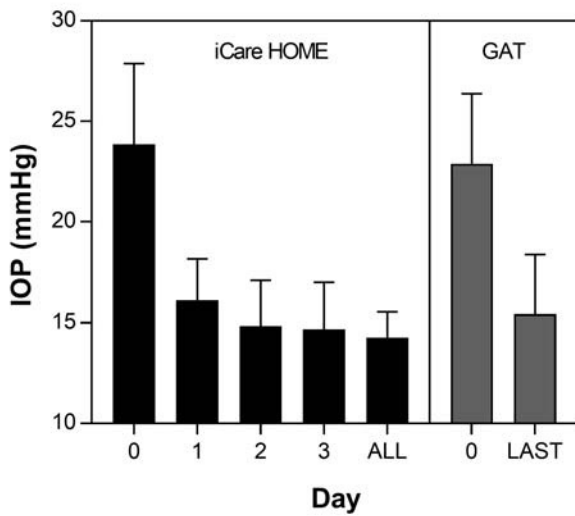


FIGURE 3. Comparison of untreated baseline intraocular pressure (IOP) to treated IOP (latanoprost 0.005% ophthalmic solution) using iCare HOME and applanation tonometry (GAT) in glaucoma patients (n = 9). With iCare HOME, IOP showed a significant reduction following treatment on day 1 compared with baseline (day 0); on subsequent days (days 2 and 3), no further significant IOP reduction was observed. Applanation tonometry (GAT) demonstrated a similar significant reduction at the follow-up visit (last day) compared with the baseline (day 0). Error bars: 95% confidence interval.

measurements per day over 7 days can provide a robust estimation of these intraocular pressure patterns that would otherwise require several weeks of monitoring.

As with previous studies with Goldmann applanation tonometry and the iCare ONE (the precedent model of iCare HOME), our study confirmed that diurnal intraocular pressure is generally highest in the morning then gradually decreases into the evening, a pattern that has been demonstrated in patients with primary open and closed angle glaucomas, ocular hypertension and also normal patients.^{8,10,35} Although on average this may be the case, our data highlighted the individual variations. Two dominant patterns were identified, the first showing peak intraocular pressure in the morning (5:00 to 10:00 AM) and the latter peaking in the late morning to afternoon (10:00 AM to 3:00 PM). These individual patterns likely contributed to the two small peaks observed in the mean diurnal curves (Fig. 1). Additionally, two patients (7.5%) exhibited a third pattern, with intraocular pressure higher in the evening, estimated to be present in up to 35% of glaucoma patients by Chen et al.²¹ Importantly, without establishing diurnal intraocular pressure patterns for individual patients, it is not possible to predict the timing of their peak intraocular pressure.¹⁴ Alternatively, in patients with established patterns, clinicians are able to schedule appointments that increase the chance of measuring peak applanation intraocular pressure. Thus, diurnal intraocular pressure measurements are essential to understanding the full extent of individual intraocular pressure fluctuation, which may lead to changes in diagnosis and management, and may be particularly important for patients who exhibit glaucomatous progression despite acceptable in-office intraocular pressure.^{5,15,36,37}

the highest variability in responses, with 10 patients rating this parameter as either “neutral” or “somewhat difficult.” Three patients rated measuring the left eye as “somewhat difficult,” although as reported previously, the variance of measurements between the right and left eyes was not significantly different for patients with bilateral measurements. Furthermore, across the entire cohort, there was no significant difference in the variance of measurements between the included 15 right and 12 left eyes ($P = .06$). In accordance to the prescribed schedule of four measurements per day, compliance was calculated at 76% ($\pm 16\%$), with the treated glaucoma group significantly more compliant than the suspect group (84 ± 12 vs. $72 \pm 17\%$, t test, $P = .04$).

DISCUSSION

This study provides unique results on diurnal intraocular pressure fluctuations measured over a minimum period of 4 weeks. Previous studies have suggested that diurnal intraocular pressure patterns are inconsistent across days.^{21,22,31–34} Diurnal intraocular pressure changes measured with Goldmann applanation tonometry across 2 separate days in normal and glaucoma patients were poorly correlated across the day.^{31,32} Similarly, diurnal intraocular pressure patterns obtained with rebound self-tonometry on 2 consecutive days showed inconsistency in 47 to 63% of patients.^{21,22} Hence, it was concluded that performing intraocular pressure phasing for a single day incompletely characterizes an individual’s diurnal variations.^{31,32,34} Examining intraocular pressure over several weeks allowed us to observe individual intraocular pressure diurnal patterns and more importantly establish that four

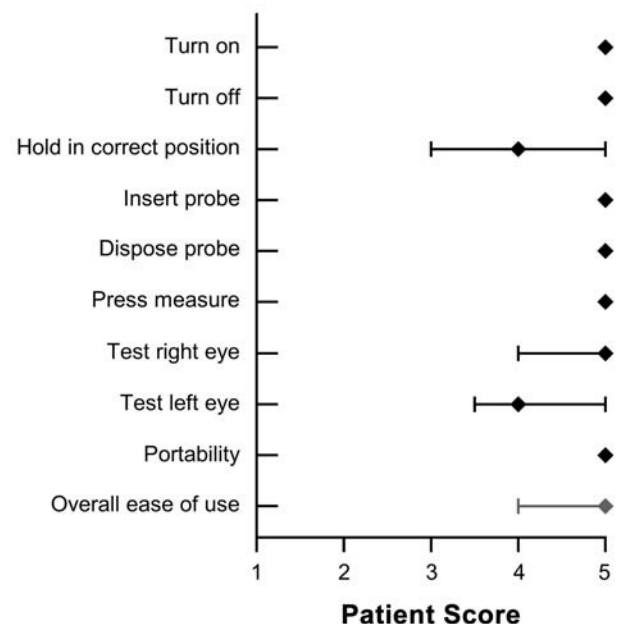


FIGURE 4. Patient usability scoring of the iCare HOME self-tonometer (n = 27). The Likert scale survey was administered at the follow-up visit. On the x axis: 1 = difficult, 2 = somewhat difficult, 3 = neutral, 4 = somewhat easy, and 5 = easy. Overall, patients rated the instrument as easy to use. All aspects were rated “easy” except for holding the tonometer in the correct position and testing the left eye. Symbol: median, error bars: interquartile range.

In glaucoma patients, the iCare HOME allowed detection of changes to intraocular pressure following initiation of treatment with a prostaglandin analog. Cho et al.³⁸ investigated the effect of once-daily treatment with tafluprost 0.0015% ophthalmic solution on patients with primary open angle glaucoma, with iCare ONE self-tonometry, and found that intraocular pressure was significantly reduced following 2 weeks of treatment. This study suggests that intraocular pressure reduction and hence treatment effect could be measured following only a single day of treatment, with a slight further reduction on the second day. This is not surprising, as a single dose of latanoprost 0.005% ophthalmic solution has been shown to reduce intraocular pressure within 24 hours of instillation, with maximal effect at 12 hours.³⁹ However, self-tonometry has the potential to assist clinicians in assessing effectiveness of treatment earlier than the standard clinical review period of 2 to 4 weeks, hence preventing delays to effective lowering of intraocular pressure for patients initiating treatment.⁴⁰

Despite the demonstrated benefits of self-tonometry and high correlation with Goldmann applanation tonometry, the measurements obtained by the two methods are not directly comparable.^{23–26} A potential limitation in rebound self-tonometry was found in our results, specifically that the measured therapeutic effect (% change in intraocular pressure) showed poor correlation with applanation tonometry ($r^2 = 0.007$). This may relate to previous findings that rebound self-tonometry tended to overestimate higher intraocular pressures and underestimate lower intraocular pressures compared with applanation tonometry.^{23,41} Furthermore, others have observed greater discrepancies for corneal thicknesses of less than 500 μm and greater than 600 μm .⁴² A potential source of error observed by our research staff was a tendency for patients to decenter the probe onto the inferior cornea during measurements. Although research staff rectified this prior to the conclusion of training, it is not known how it may have affected unsupervised measurements performed at home. Decentered iCare measurements have been shown to underestimate measurements correctly taken at the central cornea; in particular, measurements at the inferior cornea showed the poorest correlation with intraocular pressure measured with applanation to-

nometry.^{43,44} Difficulty centering the instrument on the cornea was also reflected in the patient feedback obtained in this study. Further improvements to the iCare HOME instrument design may help to reduce the variability of intraocular pressure measurements obtained.

Evidence for short-term intraocular pressure fluctuations contributing to the risk of glaucoma progression remains inconclusive. Results from this study further highlight considerable individual variability in intraocular pressure across the day (see Appendix Fig. A1, available at <http://links.lww.com/ALN/B600>). As glaucoma progression often takes many years to confirm, future longitudinal studies incorporating the use of self-tonometry would help to further investigate these relationships. It may take up to 5 years to establish these fluctuations as an independent risk factor.^{11–13} A significant limitation to use, however, is the relatively high number of patients failing certification, ranging from 20% in the current study to 26% in other studies, which may in part be magnified by age.^{24,25,42} We also observed greater difficulty for patients to obtain measurements for the left eye compared with the right; although the exact reasons require further investigation, eye and hand dominance may be contributing factors. Nonetheless, if training and certification are successfully completed, patients generally perceived the iCare HOME as either acceptable or easy to use in concurrence with previous studies.^{42,45}

In conclusion, the iCare HOME is a valuable clinical tool for establishing diurnal intraocular pressure variations. For clinicians, it can support diagnosis and management of patients at risk of glaucoma by determination of peak intraocular pressure, as well as the extent and patterns fluctuations following 7 days of patient self-monitoring. In addition, in patients with newly diagnosed glaucoma initiating topical prostaglandin analog treatment, it can assist in rapid confirmation of treatment effects. For most patients, self-tonometry could be performed, although design modifications may improve the accuracy and also the ease of correct self-alignment, enabling more patients to use this technology. In the future, longitudinal studies utilizing rebound self-tonometry could help uncover the association between diurnal intraocular pressure fluctuations and glaucoma conversion and progression.

ARTICLE INFORMATION

Supplemental Digital Content: Appendix Figure A1, available at <http://links.lww.com/ALN/B600> shows mean intraocular pressure measured with rebound self-tonometry over 4 to 6 weeks of monitoring. Each color indicates one individual patient. Time shown on the x-axis represents the centre of the 5-hour interval plotted (e.g., 7:30 represents 5:00 to 10:00). (A) Pattern 1: highest IOP at the first measurement of the day (5:00 to 10:00), (n = 11, 8 glaucoma suspect, 3 treated glaucoma). (B) Pattern 2: highest IOP at the second measurement (10:00 to 15:00), (n = 13, 8 glaucoma suspect including 1 with ocular hypertension (OHT), 5 treated glaucoma). (C) Pattern 3: highest IOP at the last measurement (20:00 to 1:00), (n = 2, 1 suspect, 1 treated). Error bars show standard deviation.

Appendix Figure A2, available at <http://links.lww.com/ALN/B601> shows correlation of diurnal IOP measurements across the cohort (n = 27) as a function of the

number of measurements taken and number of days of monitoring. Correlation was calculated by comparing mean IOP measurements (4 per day for each patient) obtained across the entire study period (4–6 weeks) to IOP measurements from Day 1, then with subsequent consecutive days (i.e., Days 1–2, 1–3 and so on). Correlation increases with more days and measurements observed, at Day 7 (dotted vertical line) $r^2 = 0.82$ ($P < .0001$) with only an incremental increase after this. Symbols: Days 1 to 7, then 10, 14, 21, 28 and 42.

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