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Original Article

Long-term Reliability of Diurnal Intraocular Pressure Patterns in Healthy Asians

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Purpose: To determine the long-term repeatability of diurnal intraocular pressure (IOP) patterns in healthy Asian subjects without glaucoma.

Methods: Twenty-three eyes in 23 healthy Asian subjects without glaucoma underwent diurnal IOP measurements using Goldmann applanation tonometry every 2 hours from 9 AM to 11 PM during two visits that were 8 weeks apart. To validate repeatability between visits, we calculated intra-class correlation coefficients (ICCs) mean IOP, peak IOP, minimum IOP, and IOP fluctuation at each time point and expressed the results as the difference between peak IOP and minimum IOP or as the standard deviation of all diurnal IOP values in the diurnal IOP curve.

Results: IOP repeatability was excellent at all time points, with ICCs ranging from 0.812 to 0.946 ($p < 0.001$). The 9 AM IOP showed the best repeatability between visits (ICCs, 0.946). Repeatability of mean IOP, peak IOP, and minimum IOP was also excellent (ICCs ranging from 0.899 to 0.929). However, IOP fluctuations showed poor repeatability, with an ICC lower than 0.15.

Conclusions: Long-term repeatability of diurnal IOP patterns in healthy Asian subjects was excellent. These findings suggest that IOP measurements at standardized times of the day will be useful for assessing the effectiveness of glaucoma therapy.

Key Words: Diurnal rhythm, Intraocular pressure, Repeatability

Elevated intraocular pressure (IOP) is the only proven risk factor for the development and progression of glaucoma [1-3]. Therefore, IOP measurements provide important information used to evaluate glaucoma, assess the possibility of progression, and monitor the clinical response to therapy. However, IOP varies throughout the day and has a circadian rhythm in both glaucomatous and non-glaucomatous eyes [4-9]. The reason for diurnal IOP fluctuation is not known exactly but may be partly explained by the body posture changes associated with blood pressure and episcleral venous pressure changes [4,6,10-14], diurnal fluctuations in cortisol level [15-17], aqueous production changes over the day [17,18], environmental light and dark cycle [19-21], and seasonal influence [22,23]. Although

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many scholars have investigated repeatable diurnal IOP variation [24-26], some clinicians still doubt the comparison between pretreatment and posttreatment IOPs and the ability to assess the IOP-lowering effect of glaucoma drugs [27-30].

The repeatability of diurnal IOP has been evaluated previously in both normal subjects [26,27,29] and subjects with ocular hypertension or primary open angle glaucoma [24,25,28]. The reliability of diurnal IOP was variable when comparing values from different days, although few such studies have been performed. Some studies have shown poor to good agreement [27-30] between visits, while several other studies have shown excellent agreement [24-26]. Most of these studies included data from Latino patients [24,25] or non-Hispanic white patients [26,28,29], and the change in diurnal IOP was measured at 1 day [24,25] or 1 week [26,28,29].

There is a wide range of racial variation in the prevalence and type of glaucoma [27-33]. Although there are a large number of Asians worldwide, few studies have explored the long-term repeatability of diurnal IOP patterns in this population. Accordingly, we conducted this prospective study to validate the long-term repeatability of diurnal IOP patterns in healthy Asian subjects without glaucoma.

Materials and Methods

This prospective study was approved by the Institutional Human Experimentation Committee and investigational review board of Kangbuk Samsung Hospital, and all investigations were performed in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants.

We recruited patients who visited our clinic for ocular examination between May 2007 and December 2007. All healthy participants underwent a comprehensive ophthalmic examination including best-corrected visual acuity, manifest refraction, slit-lamp biomicroscopy, IOP measurement using Goldmann applanation tonometry, Zeiss four-mirror gonioscopy, dilated fundus examination using indirect microscopy, stereoscopic optic disc photography, and standard automated perimetry with a 30-2 Swedish Interactive Threshold Algorithm of the Humphrey Visual Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA). Subjects were included only if they had an IOP of 21 mmHg or less, no history of IOP greater than 21 mmHg, open angles, optic discs with a healthy appearance, and normal standard automatic perimetry results. Subjects were excluded if they had glaucomatous optic discs, defined by the presence of neuroretinal rim thinning, excavation, or localized or diffuse retinal nerve fiber layer defects indicative of glaucoma. We also excluded subjects if they had abnormal glaucoma hemifield test results, cataract of Grade II or greater by the Lens Opacities Classification System III [34], previous ocular surgery, a history of systemic or topical medication that might affect IOP, corneal pathologic features that might limit the accuracy of tonometry readings, or if they did not wish to participate in repeated Goldmann applanation tonometry. Finally, 23 eyes in 23 subjects were included in this study. If both eyes in the same patient were eligible, we randomly selected one.

All subjects were admitted to the hospital. General daily activities, diet, physical activity, body position such as supine, prone, or lateral decubitus, and systemic medications that would not influence IOP were not restricted. Diurnal IOP was assessed in the sitting position with a Goldmann applanation tonometer, and the subjects remained in a sitting position for 10 minutes before IOP measurement. We scheduled IOP measurements every 2 hours between 9 AM and 11 PM, and two diurnal IOP assessments were performed 8 weeks apart. Right eyes were measured before left eyes by a well-trained ophthalmologist (KUS) using the same slit-lamp, and the mean of three measurements at each time point was recorded. To minimize bias, prior IOP measurements were not available during the measurement process.

Statistical analysis

To determine the repeatability of diurnal IOP according to time-course profile, we calculated intra-class correlation coefficients (ICCs) at each time point to compare visits 1 and 2, which occurred 8 weeks apart. In addition, to verify the repeatability of diurnal IOP according to trend-course profile, we calculated ICCs for mean IOP, maximum IOP, minimum IOP, fluctuation-IOP (maximum IOP to minimum IOP), and fluctuation-standard deviation (standard deviation of mean IOP) for visits 1 and 2. Poor, fair to good, and excellent agreement were noted when ICCs were less than 0.4, between 0.4 and 0.75, and higher than 0.75,

respectively [35]. Statistical analyses were performed using SPSS software ver. 19.0 (IBM Corp., Armonk, NY, USA). The alpha level (type I error) was set at 0.05.

Results

Among 23 Asian subjects, 12 (52.2%) were female, and the average age was 65.4 ± 13.9 years (range, 21 to 84). Fifteen of the 23 eyes (65.2%) were right eyes.

Reliability at each time profile

The mean IOP and the mean difference between the two visits at each time point are presented in Table 1. The mean difference was less than 1 mmHg, and this difference was not significant ($p > 0.05$, Mann-Whitney *U*-test) at any time-point. The repeatability of IOP measurements was excellent at all time-points, with ICCs ranging from 0.812 to 0.946 ($p < 0.001$). The 9 AM IOP showed the best reliability between visits (ICCs, 0.946).

Reliability at trend profile

Repeatability was excellent for mean IOP, peak IOP, and minimum IOP. Mean IOP showed the best repeatability (ICCs, 0.929), followed by minimum IOP (ICCs, 0.912) and then peak IOP (ICCs, 0.899). IOP fluctuation, expressed as the difference between peak IOP and minimum IOP or as the standard deviation of all diurnal IOP values, showed poor reliability (Table 2).

Discussion

IOP measurement is pivotal in monitoring the clinical response to glaucoma treatment. If diurnal IOP measurements are highly repeatable from day to day, it would provide a basis for comparing IOPs during both pretreatment and posttreatment periods at standardized times of the day and would be useful for assessing the IOP-lowering effect of glaucoma drugs.

In the current study, our results showed excellent long-

Table 1. The intraocular pressure measurements at each time point and visit, and ICCs between the two visits

Time	Visit 1 (mmHg)	Visit 2 (mmHg)	Mean difference* (mmHg)	ICCs† (95% CI)
09:00	12.6 ± 2.6	12.6 ± 3.0	0.0	0.946 (0.873–0.977)
11:00	12.6 ± 2.5	12.5 ± 2.6	0.1	0.888 (0.737–0.953)
13:00	12.2 ± 2.5	12.7 ± 2.6	–0.5	0.813 (0.559–0.921)
15:00	11.9 ± 2.5	12.3 ± 2.7	–0.4	0.841 (0.624–0.932)
17:00	12.3 ± 2.3	12.3 ± 2.4	0.0	0.818 (0.572–0.923)
19:00	12.1 ± 2.5	12.1 ± 2.7	0.0	0.845 (0.634–0.934)
21:00	12.2 ± 2.6	11.5 ± 2.5	0.7	0.845 (0.634–0.934)
23:00	11.9 ± 2.6	11.5 ± 2.4	0.4	0.812 (0.557–0.920)

Values are presented as mean ± standard deviation.
ICCs = intra-class correlation coefficients; CI = confidence interval.
*Mean difference: visit 1 to visit 2. All $p > 0.05$ by Mann-Whitney *U*-tests; †All $p < 0.001$ by ICCs.

Table 2. ICCs for reliability between two diurnal IOP assessments recorded 8 weeks apart

	Visit 1 (mmHg)	Visit 2 (mmHg)	ICCs* (95% CI)
Mean IOP	12.2 ± 2.6	12.2 ± 2.4	0.929 (0.832 to 0.970)
Peak IOP	13.5 ± 2.5	13.9 ± 2.7	0.899 (0.763 to 0.957)
Minimum IOP	10.9 ± 2.4	10.6 ± 2.3	0.912 (0.792 to 0.963)
Fluctuation (peak IOP – minimum IOP)	2.6 ± 0.8	3.2 ± 1.5	0.131 (–1.050 to 0.631)
Fluctuation (SD)†	0.9 ± 0.3	1.2 ± 0.5	0.111 (–1.095 to 0.623)

Values are presented as mean ± SD.
ICCs = intra-class correlation coefficients; IOP = intraocular pressure; CI = confidence interval; SD = standard deviation.
*All $p < 0.001$ by ICCs; †SD of IOP measurements in 1 day.

term repeatability of diurnal IOP measurements in healthy Asian subjects. The most reproducible IOP measurement was that performed at 9 AM. There was also excellent agreement of diurnal IOP with regard to mean IOP, peak IOP, and minimum IOP. However, IOP fluctuation, expressed as the difference between peak IOP and minimum IOP or as the standard deviation of all diurnal IOP values, showed poor reliability. This report encourages clinicians to evaluate IOP and assess the effectiveness of IOP-lowering therapy with confidence.

Our study has some remarkable strengths. First, we evaluated the second IOP measurement 8 weeks following the first measurement in order to validate the long-term repeatability of diurnal IOP measurements. Second, we analyzed the diurnal IOP of a healthy Asian population, which has a higher prevalence of normal-tension glaucoma than other racial groups.

Few studies have shown the repeatability of diurnal IOP in normal subjects [26,27,29,36,37], and their results were variable. Daubs [27] evaluated the diurnal IOP of seven male international airline pilots every hour over a range of 5 to 23 days using a Durham-Langham pneumatic type tonometer, and de Venecia and Davis [36] evaluated the diurnal IOP of 230 eyes in 115 males using Schiøtz tonometry five times per day for 3 days. These studies indirectly demonstrated repeatability of the diurnal curve pattern without direct comparison of IOP at each time point. Although curve patterns were occasionally repeated for several consecutive days in some subjects, this was not always the case. Realini et al. [29] reported fair to good agreement (ICCs ranging from 0.35 to 0.71) of diurnal IOP in 40 healthy subjects measured in the seated position, evaluated during a 1-week interval using Goldmann tonometry. On the other hand, Mottet et al. [26] reported excellent agreement (ICCs, 0.81) of a midline estimating statistic of rhythm and also noted variable agreement at each time point (ICCs ranging from –0.27 to 0.90) using a Modular one pneumatonometer in six normal Caucasian subjects in the supine position every week over 6 weeks. The studies listed above primarily used data from a white population [26,27,29,36]. The current study demonstrated excellent repeatability (ICCs ranging from 0.812 to 0.946) of diurnal IOP, evaluated during an 8-week interval using Goldmann applanation tonometry in 23 normal Asian subjects in the sitting position. The differences in study findings could be due to differing study designs, differences between the racial groups studied, and different measurement methods, including IOP evaluation time, repeat interval, evaluation instrument, and subject position. Similar conditions are observed in the agreement of diurnal IOP in ocular hypertension or primary open angle glaucoma subjects. Some studies have shown poor to good agreement [28,30], while other studies showed excellent agreement [24,25].

Our results were consistent with that of a report by Song et al. [37]. They demonstrated the excellent reliability of the maximum/minimum values of IOP and blood pressure phasing over a 24-hour rhythm, once a week for 5 consecutive weeks, while patients were in both sitting and supine positions. Also, they emphasized the poor reliability of 24-hour IOP fluctuation. Similarly, we determined excellent repeatability for point IOP, peak IOP, and minimum IOP and poor repeatability for IOP fluctuations even though our study measured IOP using only Goldmann applanation tonometry in a sitting position between 9 AM and 11 PM over an 8-week interval. Although IOP fluctuation may not be a sufficient way to characterize circadian IOP rhythm, IOP measurements at standardized times of day may be useful for assessing the effectiveness of glaucoma therapy.

Realini et al. [28,29] and de Venecia and Davis [36] mentioned the "white-coat" phenomenon, wherein IOP was lower at the second visit compared to the first visit due to subject relaxation and experience with ocular examinations. Realini et al. [28,29] reported that the mean difference between visits was consistently 1 mmHg at all time points. However, we did not find a similar tendency in IOP difference (lower at visit 2 than visit 1) between visits, and the mean difference in IOP between the two visits was only 0.25 mmHg in this study. These discrepant results may be due to the difference in time between measurements; the previous studies evaluated the second diurnal IOP 1 day or 1 week after the first. Therefore, subjects could easily adapt to the previously unfamiliar environment and could remember the process of the study at the second visit. On the other hand, our study evaluated the second measurement 8 weeks after the first, which may have limited the bias of subject adaptation to the uncomfortable Goldmann applanation tonometry, as participants were more likely to have similar feelings about IOP measurements 8 weeks later. In addition, IOP measurements were performed by only one ophthalmologist using the same Goldmann applanation tonometry instrument with the same slit-lamp microscope. Thus, the long-term repeat-

ability of diurnal IOP was excellent, with ICCs greater than 0.8.

Our study has some limitations. First, we studied a relatively small number of participants and did not evaluate the IOP over a 24-hour period. However, in an outpatient setting, patients typically visit the clinic during wakeful periods when the seated position is normal. Therefore, the long-term repeatability of diurnal IOP during this time is likely valuable data for glaucoma management. Second, physical activity and body position variations such as the supine, prone, or lateral decubitus positions [4,6,10-14], which may have influenced the IOP variation, were not restricted between diurnal IOP measurements even though the IOP was measured after a sitting position was maintained for 10 minutes. Also, diet, including intake of water or caffeinated beverages, before the visit and/or between diurnal IOP measurements was not restricted. Third, IOP in glaucoma patients is known to fluctuate more than that in normal controls [38,39]. Therefore, there may be more variability in diurnal IOP measurements in glaucoma patients compared to normal controls. Additionally, the mean IOPs in Koreans in the Namil study or other Korean epidemiologic studies were lower than the IOPs of people of European or American descent [40]. Therefore, it is possible that IOP variability in Koreans is lower than that of other races and ethnicities. In particular, the mean IOP in our study was around 12.2 mmHg, lower than that in the Namil study [40]. Therefore, we cannot eliminate the influence of selection bias, and care must be exerted in the generalization of these results to glaucoma patients.

In conclusion, this study demonstrated excellent repeatability of diurnal IOP measurements 8 weeks apart in healthy Asian subjects. There was also excellent reliability in mean IOP, peak IOP, and minimum IOP, though IOP fluctuation showed poor reliability. We suggest that a single IOP measurement to assess the effectiveness of IOP-lowering therapy may not be worse than multiple measurements of IOP both at baseline and posttreatment follow-up.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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