

Clinical study of 24-hour intraocular pressure curve measurement strategy

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Abstract

Background To investigate the measurement time of 24-hour intraocular pressure(IOP) curve: the representativeness of 4 and 6 times IOP to the fluctuation of IOP at night and day.

Methods From September 2018 to January 2019, 41 patients with suspected primary open angle glaucoma(POAG), who were admitted to the Department of Ophthalmology, Peking University International Hospital, underwent 24-hour IOP monitoring. The measuring time points were set as: 0:00, 2:00, 5:00, 7:00, 8:00, 10:00, 11:00, 14:00, 16:00, 18:00, 20:00 and 22:00, of which 8:00, 11:00, 14:00, 16:00 were the customary measuring time of IOP daily curve for 4 times; 5:00, 7:00, 10:00, 14:00, 18:00, 22:00 were the conventional measuring time points for IOP curve for 6 times. The time points of the two groups was increased by 0:00, 2:00 and 20:00 to 12 times IOP measurements. Goldmann tonometer was used to measure IOP . Oxybuprocainehydrochloride eye drops were anesthetized by the same ophthalmologist. The sensitivity of the two methods to detect 24-hour intraocular pressure fluctuations was calculated according to whether the peak values of 12 times IOP measurements could be included by 4 or 6 times IOP measurements.

Results A total of 41 patients (82 eyes) were enrolled, including 21 males (42 eyes) and 20 females (40 eyes). The age ranged from 23 to 77 $\bar{44.60\pm 14.67}$. The peak IOP measured by 4 times, 6 times and 12 times IOP measurements were $19.91\pm 4.38\text{mmHg}$ $20.54\pm 4.10\text{ mmHg}$ and $21.09\pm 4.15\text{ mmHg}$ respectively, and there were significant differences between the two methods ($P < 0.05$); the trough values of IOP were $15.46\pm 3.63\text{ mmHg}$ $14.63\pm 3.49\text{ mmHg}$ and $13.93\pm 3.38\text{ mmHg}$ respectively, with statistical significance ($P < 0.05$). The peak IOP co-occurrence is 74.39% between 6 times and 12 times IOP measurements. The peak IOP co-occurrence is 43.90% between 4 times and 12 times IOP measurements. The sensitivity of 4 and 6 times IOP measurements to detect 24-hour IOP fluctuations were 36.11% and 55.56%, respectively.

Conclusion For suspected glaucoma patients, neither 4 times IOP measurements nor 6 times IOP measurements during a day can accurately reflect the range of IOP fluctuations, which may easily lead to missed diagnosis.

Background

As is known to all, Glaucoma is the most important cause of irreversible blindness worldwide. [1][2] Intraocular pressure (IOP) is not only one of the most significant risk factors in development of the disease, but also the only modifiable one. Accuracy of IOP measurement therefore is critical to predicting and monitoring the course of the disease. The IOP has fluctuation and rhythmicity during all the day. In primary open-angle glaucoma(POAG), the change of IOP is not stable in the early stage. It is usually manifested as elevated IOP at some time during the day and night. With the progress of the disease, it gradually develops into persistent high IOP. Hence it is very important to make 24-hour IOP monitoring,

especially to catch the peak and the valley values. The fluctuation of IOP is negative when $>10\text{mmHg}$, suspect when $>6\text{mmHg}$.

Though contact lens sensor has been used to measure 24-hour IOP in some laboratory, we don't have any employment to measure real-time IOP accurately in clinic. Twelve times IOP measurement is universally accepted to be a good method include both diurnal and nocturnal IOP. Most hospitals can't be able to measure as this because its complexity. Specialist consensus 2008 of china point out that the IOP are measured at least 6 times one day: 5:00-7:00-10:00-14:00-18:00-22:00. In order to measure the IOP of outpatients, we measured IOP four times a day: 8:00-11:00-14:00-16:00. This study is aimed at indicating if 4 times IOP measurement or 6 times IOP measurement can represent the fluctuation of IOP all the day and night.

Methods

The 24-hour IOP data in our study was gathered from suspicious POAG patients at Ophthalmic Center of Peking University International Hospital, over half a year period (September, 2018 to January, 2019). This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of Peking University International Hospital. Written informed consent was obtained from each subject after an explanation of the risks, benefits, and alternatives of the study.

Eyes with suspicious appearance of glaucoma were included: 1- elevated office hour IOP above 21mmHg ; 2- retinal nerve fiber layer (RNFL) structural abnormalities; 3- cup disc ratio greater than 0.4; 4- visual field abnormality. The procedures to measure 24-hour IOP required the patients to be hospitalized from 10 AM and to stay for the subsequent 24 hours. Exclusion criteria included a baseline untreated IOP of $>30\text{mmHg}$; any abnormalities restricting adequate examination of the ocular fundus or anterior chamber; any concurrent infectious or noninfectious inflammation within the prior month; any systemic conditions that would make the patients ineligible to participate in the examination; and any regular use of medications that significantly disturb the sleep-wake cycle and IOP rhythms.

We measured the IOP of each patient at 0:00-2:00-5:00-7:00-8:00-10:00-11:00-14:00-16:00-18:00-20:00-22:00, defined which as strategy 1. Defined 5:00-7:00-10:00-14:00-18:00-22:00 IOP as strategy 2. Defined 8:00-11:00-14:00-16:00 IOP as strategy 3. Both strategy 2 and strategy 3 are selected from strategy 1. Oxybuprocaine Hydrochloride eye drops (Benoxil 0.4% solution, Santen) instilled on a fluorescein paper strip were used as topical anesthetic for IOP assessment. The IOP measurements were taken with Goldmann applanation tonometer at the slit lamp. During the night, the patients were awakened approximately 10 min before each measurement to prevent a sudden increase in IOP. All measurements were taken three times at each time point by a well-trained glaucoma specialist. The mean of three recordings was used for the analysis.

Strategy 1: measure IOP at 0:00-2:00-5:00-7:00-8:00-10:00-11:00-14:00-16:00-18:00-20:00-22:00.

Strategy 2: measure IOP at 5:00-7:00-10:00-14:00-18:00-22:00 (selected from strategy 1).

Strategy 3: measure IOP at 8:00-11:00-14:00-16:00 (selected from strategy 1).

Results

In the end, we include 82 eyes of 41 patients, in which 21 males and 20 females, with the age of 23 to 77 years old (44.60 ± 14.67). The demographics of patients are lined in table 1.

Table 1 demographics of patients

demographics	
total	41 patients 82 eyes
male	21 patients 42 eyes
female	20 patients 40 eyes
age	23-77-44.60-14.67

The peak IOP of the three strategies are 21.09 ± 4.15 mmHg, 20.54 ± 4.10 mmHg and 19.91 ± 4.38 mmHg respectively. There was statistical significance between any two groups (pair T test. $P < 0.05$). The valley value of them are 13.93 ± 3.38 mmHg, 14.63 ± 3.49 mmHg and 15.46 ± 3.63 mmHg respectively. There was statistical significance between any two groups (pair T test. $P < 0.05$).

We wanted to check whether or not strategy 2 and strategy 3 can efficiently indicate the peak IOP in strategy 1. In strategy 2, 61 cases were able to measure the peak intraocular pressure in strategy 1. The peak IOP co-occurrence is 74.39% between strategy 2 and strategy 1. Meanwhile, in Strategy 3, 36 cases were able to measure the peak intraocular pressure in Strategy 1. The peak IOP co-occurrence is 43.90% between strategy 3 and strategy 1.

We checked the sensitivity and specificity of the two methods when strategy 1 was regarded as the gold standard. Our positive diagnostic criteria of glaucoma is that the fluctuation of IOP be large than 10mmHg. On account of which, we calculate the positive diagnosis rate of glaucoma. There are 36 positive and 46 negative in strategy 1 group, 20 positive and 62 negative in strategy 2 group, 13 positive and 69 negative in strategy 3 group. We compare the positive rate of the two methods respectively to the golden standard. We evaluated the diagnostic tests of these three methods compared strategy 3 and strategy 1: $X^2 = 15.306$, $P = 0.000$; compared strategy 2 and strategy 1: $X^2 = 6.942$, $P = 0.008$. The results are lined in table 2 and table 3.

Table 2: Strategy 2 fourfold table

Strategy2	Strategy1		total
	positive	negative	
Positive	20	0	20
Negative	16	46	62
Total	36	46	82

sensitivity=55.56%

specificity=100%

misdiagnosis rate=0

missed diagnosis rate=44.44%

Table 3: strategy 3 fourfold table

Strategy3	Strategy1		tote
	positive	negative	
positive	13	0	13
negative	23	46	69
tote	36	46	82

sensitivity=36.11%

specificity=100%

misdiagnosis rate=0

missed diagnosis rate=63.89%

Discussion

In the formation and development of glaucoma, IOP is the most important and controllable risk factor. A number of population-based studies have demonstrated that the prevalence of POAG increases as the level of IOP increases. Meanwhile, a lot of studies provide strong evidence that IOP plays an important role in the optic neuropathy of POAG. [3][4] As a biology phenomenon, IOP isn't stable but fluctuate All the day. [5] meanwhile, treated eyes that have a greater IOP fluctuation may be at increased risk of progression. [6] In the Early Manifest Glaucoma Trial, each 1 mmHg increase in mean IOP over all follow-up visits was associated with a 12% higher risk of progress.[7]

Simply measuring IOP once can not reflect the characteristics of IOP fluctuation of a patient as a whole. [8]It is not enough to detect abnormal IOP in glaucoma patients. The monitoring and management of IOP plays an important role in the treatment and future development prediction of glaucoma. By measuring

the characteristics of IOP (mean, peak and fluctuation), the diagnosis and follow-up treatment of glaucoma can be truly evaluated. Every glaucoma patient should receive 24-hour IOP measurements before receiving treatment. However, this scheme is not easy to achieve, because 24-hour IOP measurement requires hospitalization of patients and consumes a lot of human and material resources. One of the major limitations of glaucoma treatment is the inability to obtain real IOP data.

This study found that strategy 1 had higher peak and lower trough values than strategy 2 or strategy 3. Therefore, it can be inferred that the more IOP be measured, the real peak and trough values are captured. At the same time, it can be concluded that the more frequently we performed the measurement, the higher sensitivity of diagnose glaucoma and the lower missed diagnosis rate we will get. In order to quantitatively compare the missed diagnosis rates of several IOP measurements, we calculated them separately. We found that office-hour IOP measurement (strategy 3) can capture 43.90% of the patients' intraocular pressure peaks, which means that more than half of the patients' peak values are missed and may cause missed diagnosis. If night intraocular pressure monitoring is omitted, 74.39% of patients' intraocular pressure peaks can be captured. Almost 1/4 of the patients had missed the peak value, which might lead to missed diagnosis. This is similar to the current literature reports. There is a survey that the peak IOP could be captured outside office hours in 56.2% of the subjects in the young control group compared with 65.0% in the elderly control group and 61.5% of glaucoma patients. [9] A similar study found that Maximum 24-hour IOP was observed during office hours in 33.8% of eyes. [10] Another survey found that IOP peaked outside office hours in 65 % of all patients (timolol, 58 %; latanoprost, 76 %; brimonidine, 60 %; FCDT, 58 %). [11]

Studies have shown that IOP is highest in the first hour of the morning. Others have found that 45% of untreated exfoliation syndrome patients and 22.5% of POAG peak IOP occurs during off-hours. [12] A study from a sleep center in the United States found that peak IOP occurred in the first few hours of the night.[13][14]

The evaluation of diagnostic tests carried out in this study also confirmed that the missed diagnosis rate of strategy3 was 63.89%, and that of strategy 2 was 44.44%. Therefore, if any of the two strategy is used as the diagnostic criteria for glaucoma, it will cause more than half of the patients to miss the diagnosis. Despite the amplitude of IOP fluctuation and the peak value are negative, the possibility of glaucoma should still be highly suspected if the visual field or retinal nerve fiber layer thickness are suspicious. If it is really difficult to diagnose, the possibility of glaucoma should be highly suspected. Patients should be ordered to strengthen follow-up in order to avoid missed diagnosis. On the other hand, the specificities of the two methods are high.

In this study, 12 times measurements were used as the gold standard, but theoretically, the peak IOP may occur at a time point other than the 12 timings, so the actual probability of missed diagnosis may be higher. This is one of the shortcomings of this study. In addition, for the measurement of IOP at night, the method of customary body position measurement is not used. Meanwhile, several papers reported the

importance of supine IOP. The change of body position will also cause the error of IOP measurement in our study. [15]

Conclusion

For suspected glaucoma patients, neither four times IOP measurements nor six times IOP measurements during a day can accurately reflect the range of IOP fluctuations, which may easily lead to missed diagnosis. In the future, we should devote ourselves to non-invasive methods for obtaining continuous, Goldmann IOP measurement on all patients prior to treatment decision. We should also try to study the exact relationship between 24-hour IOP fluctuations and glaucoma progression.

Abbreviations

POAG: Primary open angle glaucoma

IOP: Intraocular pressure

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of Peking University International Hospital. Written informed consent was obtained from each subject after an explanation of the risks, benefits, and alternatives of the study.

Consent for publication

Written informed consent was obtained from all patients for the publication of personal or clinical details along with any identifying images to be published in this study.

Availability of data and material

The data used to support the findings of this study are available from the corresponding author upon request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Zeqin Ren: the corresponding author, collected cases and formulated criteria for enrollment or exclusion, guided the application of statistical methods.

Jiayin Qin: measured and analyzed the IOP of the participates, wrote the major part of the manuscript.

Xijuan Wang: collected the data pool and shared writing the manuscript.

Mingwu Li: contributed in collection of the data and followed up the cases.

All authors read and approved the final manuscript.

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