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A COMPARISON OF DIURNAL VARIATION AND SPLIT DIURNAL VARIATION IN INTRAOCULAR PRESSURE: A PROSPECTIVE STUDY

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ABSTRACT

Glaucoma is an important cause of blindness. Intraocular pressure (IOP) is easily measurable and identified modifiable risk factor for the prevention of progressive glaucomatous field defects. IOP measurements during different hours of the day have a well recognized clinical importance which can directly affect the diagnosis. This study was to compare the two methods of measuring the diurnal fluctuations in IOP. A total of 50 eyes of Primary open angle glaucoma (POAG) patients and 50 eyes of normal subjects had included in this study. The prevalence rate was higher in male patients compared with female. There was a strong correlation for the maximum and the minimum IOP as well as for all the individual measurements. The minimum and maximum IOP as well as fluctuation in IOP were recorded by either of the methods i.e. diurnal variation (DV) and split diurnal variation (SDV). It was observed that POAG subjects had higher peak IOP and larger diurnal fluctuations as compared to normal subjects and also POAG patients patients who were under treatment had low peak IOP and significantly less range of diurnal fluctuation in IOP. There is a strong correlation between the diurnal variation and split diurnal variation. Therefore diurnal IOP variation in POAG patients can be assessed by IOP measurements at different time points on different days. Measuring the split diurnal variation in IOP could be a valid choice and can be used as a surrogate measure to diurnal variation in IOP in a single day.

KEYWORDS: Glaucoma, Intraocular pressure, Primary open angle glaucoma, diurnal variation, split diurnal variation

INTRODUCTION

Glaucoma, a chronic progressive optic neuropathy, is an important cause of blindness.[1] It is estimated that 5.8% of blindness in India is caused by glaucoma and that there will be 79.6 million cases of glaucoma worldwide by 2020.[2] Of these, 74% will have open angle glaucoma. Early diagnosis and treatment can slow down the progression of the disease. Intraocular pressure (IOP) is easily measurable and has been identified as the most important and only modifiable risk factor for the prevention of progressive glaucomatous field defects. So, consecutively most therapeutic interventions are directed at its modification. Normal IOP varies with age, sex, race, time of day, season and posture of the patient, cardiac and respiratory cycles, systemic blood pressure and method of measurement. IOP is subjected to chronobiological rhythms similar to other physiological values in the human body. IOP measurements during different hours of the day have a well recognized clinical importance which can directly affect the diagnosis and management of the patients with IOP related conditions. IOP varies throughout the night and day.[3] There is general agreement with respect to the range of IOP fluctuation. It has been shown that this does not usually exceed 3-6 mm/ Hg in normal eyes. Patients with glaucoma may have larger diurnal IOP fluctuations than the normal subjects and can reach 10 mm Hg and more before initiating treatment. An isolated IOP measurement during office hours may not detect the IOP spikes and larger diurnal fluctuations as observed in glaucomatous subjects. These IOP peaks or large diurnal fluctuations may increase the rate of glaucoma progression.

Further, a single office IOP measure may not be adequate in determining the target pressure in glaucoma patients. Rather, it is important to have serial IOP measurements during the day in order to detect peaks and fluctuation that otherwise would not be detected by single office hour measurements. Assessing the diurnal variation of IOP is necessary for the better understanding and management of the individual's disease process but the method that evaluates the diurnal fluctuation over a single day may be inconvenient to the patient and the physician in terms of time and cost. This evaluation of

DV may be avoided by physicians and rejected by patients due to the cost and inconvenience of spending an entire day at the clinic to perform a diurnal curve, which turns it into a restricted tool in routine clinical practice. Attempts have been made to find out an alternative to the conventional method of recording IOP fluctuations over a single day in the form of assessing IOP at different time points but on different days i.e. split diurnal variation. The split diurnal variation may have the advantages over diurnal variation of recording IOP without altering daily routine of the patient.

So, the objective of our study was to compare the two methods of measuring the diurnal fluctuations in IOP on the same day (diurnal variation) versus assessing the IOP at different time points on different days (split diurnal variation) and the pattern of diurnal variation in IOP in newly diagnosed primary open angle glaucoma (POAG) patients and those who were under treatment.

MATERIAL AND METHODS

The present prospective study was conducted in Department of Ophthalmology, Gajra Raja Medical College, Gwalior from August 2013 to October 2014. The study was conducted on 50 eyes of POAG patients (group A) and 50 eyes of normal subjects (group B). A total of the 50 POAG eyes in group A, 29 eyes were of newly diagnosed patients not under any treatment (group A1) and 21 were under topical antiglaucoma medications (group A2).

Exclusion criteria

- Refusal to participate in the study,
- Inability to follow the protocol.
- IOP greater than 35 mm/Hg.
- Any pathology that could interfere with the applanation tonometry (e.g. corneal scarring or keratoconus, ocular herpes or trauma).
- All patients with secondary glaucoma such as inflammatory or post inflammatory, traumatic glaucoma, lens induced glaucoma, neoplastic glaucomas etc.
- Any history of prior laser therapy or glaucoma surgery.
- Change in the IOP-lowering treatment during last 3 months, and
- Poor compliance.

All the patients were recorded in a pre designed proforma; that included - demographic data and the associated relevant examinations including visual acuity, pupillary reaction, flashlight test, Van Herick test, slit lamp bio-microscopy for fundus examination, gonioscopy, IOP measurement and diurnal variation in IOP. IOP was recorded using Goldman applanation tonometry (GAT).[4]

RESULTS

A total of 50 eyes of POAG patients (group A) and 50 eyes of normal subjects (group B) were included in this study. The study in relation to age group was noted in mean age i.e. group A subjects was 58 ± 7.8 years and group B was 55.6 ± 6.32 years [Table 1]. We also compared with sex. The prevalence rate was higher in male (58%) patients compared with female (42%). The male to female ratio in group A subjects was 30:20 and in group B patients was 26:24. There was a strong correlation for the maximum and the minimum IOP as well as for all the individual measurements by either method i.e. diurnal variation or split diurnal variation [Table 2]. There was a strong correlation for the maximum and the minimum IOP as well as for all the individual measurements by either of the methods i.e. diurnal variation and split diurnal variation [Table 3]. The minimum and maximum IOP as well as fluctuation in IOP recorded by either of the methods i.e. DV and SDV was found to be similar and the difference between the two was not found to be statistically significant [Table 4]. The minimum and maximum IOP as well as fluctuation in IOP recorded by either of the methods i.e. DV and SDV was found to be similar and the difference between the two was not found to be statistically significant [Table 5]. It was observed that POAG subjects had higher peak IOP and larger diurnal fluctuations as compared to normal subjects [Table 6]. It was observed that those POAG patients who were under treatment had low peak IOP and significantly less range of diurnal fluctuation in IOP [Table 7].

Table No. 1: Age Distribution

Age Group (years)	Group A		Group B
	A1	A2	
40-50	9	3	14
51-60	8	12	24
61-70	12	4	12
71-80	0	2	0
Total	29	21	50
	50		

Table No. 2: Diurnal Variation and Split Diurnal Variation in POAG subjects

Time Point	DV	SDV	r	p
8.00	22.4 ± 5.6	23 ± 6.17	0.9423	<0.0001
10.30	22.4± 5.25	21.88± 4.78	0.901	<0.0001
1.00	22.36± 5.34	21.92± 5.07	0.9191	<0.0001
3.30	21.64± 4.99	21.72± 5.79	0.9352	<0.0001
6.00	21.8± 5.8	21.96± 5.9	0.9219	<0.0001
Min	19.8±4.9	19.88±4.8	0.9598	<0.0001
Max	24.6± 5.57	24.8 ±5.52	0.9596	<0.0001

Table No. 3: Diurnal Variation and Split Diurnal Variation In Normal subjects

Time Point	DV	SDV	r	p
8.00	17.28±1.96	16.76±2.28	0.8144	<0.0001
10.30	16.32±2.15	15.92±2.13	0.6271	<0.0001
1.00	15.76±2.08	15.32±2.16	0.6874	<0.0001
3.30	15.08±1.77	15.08±1.98	0.6357	<0.0001
6.00	14.28±1.76	14.28±2.17	0.7669	<0.0001
Min	13.92±1.61	13.68±1.53	0.7490	<0.0001
Max	17.48± 1.97	17.36±2.19	0.8656	<0.0001

Table No. 4: Peak, Trough and Fluctuations In IOP In POAG Subjects

IOP	DV	SDV	p	95% Confidence Interval
Min	19.8±4.9	19.88±4.8	0.9	(-1.85, 2.01)
Max	24.6±5.57	24.8±5.52	0.8	(-2.00, 2.40)
Fluctuation	4.8±1.8	4.9±2.2	0.7	(-0.68, 0.92)

Table No. 5: Peak, Trough and Fluctuations In IOP In Normal Subjects

IOP	DV	SDV	p	95% Confidence Interval
Min	13.92±1.61	13.68±1.53	0.4	(-0.38, 0.86)
Max	17.48±1.97	17.36±2.19	0.7	(-0.71, 0.95)
Fluctuation	3.6±1.21	3.64±1.32	0.8	(-0.46, 0.54)

Table No. 6: Comparison of Peak, Trough and Fluctuations in IOP In POAG Patients and normal subjects

IOP	POAG	Normal	p
Min	19.8±4.9	13.92±1.61	<0.05
Max	24.6±5.57	17.48±1.97	<0.05
Fluctuation	4.8±1.8	3.6±1.2	<0.05

Table No. 7: Effect of treatment on Peak, Trough and Fluctuations In IOP

IOP	Newly Diagnosed	Under t/t	P
Min	22.2±4.9	16.47±5.2	<0.05
Max	27.58±5.1	20.47±2.96	<0.05
Fluctuation	5.37±1.85	4.0±1.41	<0.05

DISCUSSION

The advantages offered by diurnal variation curve are manifold. Glaucoma treatment is based mainly on IOP reduction to a level at which no additional damage is expected to occur. This level, the so called target IOP, is established on an individual basis and is usually assessed by single office measurements during working hours.[5] A single office IOP measure may miss the spikes and fluctuations in IOP and is not adequate in determining the target pressure in glaucoma patients.[6,7] This may be the reason why a significant number of patients still develop glaucomatous progression despite IOP values considered within adequate limits.[8,9] Additionally, the IOP peaks and larger diurnal fluctuations have been proved to be responsible for disease progression in glaucoma patients. A study by Zeimer et al showed that 29% of patients with progressive visual field damage presented IOP peaks in comparison to 5% of patients with stable visual fields. [7] Another studies Martinez-Bello et al also indicate that the occurrence of visual field loss was related to IOP peaks.[10] These studies highlight the importance of detecting IOP peaks in glaucoma treatment.

Furthermore, a large diurnal fluctuation in IOP has been suggested as an independent risk factor for glaucoma progression. A strong correlation between diurnal fluctuation in intraocular pressure and visual field progression has been reported by Asrani et al.[11] Various other studies also state that larger diurnal fluctuations in IOP cause the progression of the disease even when the patient's intraocular pressure seems to be apparently controlled.[12,13] Thus, monitoring the diurnal curve for IOP could be considered the best way to assess the IOP profile of glaucomatous patients.[5] This ensures better understanding and management of the individual's disease process and for these reasons; performing the diurnal IOP examinations over a single day has been widely practiced in glaucoma clinics for many years.

Split Diurnal Variation

Diurnal variation may be a time consuming test associated with lot of inconvenience to the patient and hospitalization which may increase the cost of this investigation. As an alternate to diurnal variation, a more convenient and practical method has been used which we call as split diurnal variation i.e. recording IOP at different time points on different days. Katavisto et al found that 80% of glaucomatous eyes exhibited a reproducible curve shape upon retesting using Schiotz tonometry.[6] In contrast, Wilensky et al found that only 28% of eyes with ocular hypertension and 34% of eyes with primary open-angle glaucoma (POAG) had reproducible curve shapes upon retesting using a home applanation tonometer operated by the patient.[24] This study suffers from device-related limitations of self-

tonometry and subjective curve assessment that can be affected by interpreter bias.

A study evaluated the short-term repeatability of diurnal IOP patterns in healthy subjects and those with POAG.[14,15] There was fair to good agreement for IOP at any given time on different days (ICCs ranging from 0.35 to 0.71), but essentially no agreement for IOP change over time periods between time points on different days (ICCs −0.40 to 0.22.) The authors concluded that diurnal IOP patterns are not repeatable in short term and healthy subjects and treated POAG patients and they do not follow a conserved IOP pattern from day to day. Although there was no general agreement regarding the reproducibility of diurnal curve, a sizable number of subjects still showed a reproducible curve and also there was fair to good agreement for IOP at any given time point on different days, but essentially no agreement for IOP change over time periods between time points on different days. Hatanaka et al evaluated the reproducibility of diurnal IOP patterns in patients with untreated POAG or ocular hypertension on two consecutive days (24-hour repeatability).[14] There was excellent agreement among the intervisit IOP values measured at any given time of day. They concluded that IOP follows a repeatable diurnal pattern in patients with untreated glaucoma and ocular hypertension and diurnal intraocular pressure data collected on a single day characterize the diurnal intraocular pressure variability over 24 hours in primary open-angle glaucoma and ocular hypertensive patients. This observation validates the clinical value of one day diurnal IOP testing in clinical practice, when the consecutive day is used to determine the IOP-lowering efficacy of glaucoma therapies. IOP varies spontaneously over time, and it is generally accepted that this spontaneous variation follows a conserved circadian pattern in both glaucomatous and non-glaucomatous eyes. The presumed repeatability of this IOP pattern from day to day underlies several clinical and research practices. As an example, IOP is typically measured at the same time of day both before and after initiating therapy to minimize inter-day variation. This practice assumes that IOP is constant at any given time of day, regardless of the day on which it is measured. Thus, any changes observed after initiating therapy should be directly attributable to treatment efficacy.[14]

IOP varies spontaneously over time, and it is generally accepted that this spontaneous variation follows a conserved circadian pattern in both glaucomatous and non-glaucomatous eyes. It has been hypothesized that "each individual has a characteristic rhythm which is obstinately maintained".[16] The existence of circadian control suggests that IOP rhythm could be constant and repeatable unless it is influenced by some external factors e.g. environmental, physical exercise or the effect of treatment.

Correlation between Diurnal Variation and Split Diurnal Variation

Magacho et al compared the diurnal fluctuations in IOP in the same day versus over different days in 25 POAG patients and found a high correlation for all measurements as well as for minimum and maximum IOP by either method of measuring during the same day or different days.[17] Hatanaka et al although did not perform comparison between diurnal variation and split diurnal variation; but they observed that there is a good correlation if the diurnal curve is spaced by a day.[14] In the present study, a strong correlation was found for all the 5 individual measurements as well as for peak and trough IOP by either method of recording diurnal variation in IOP. Normal subjects in the present study also showed a strong correlation for all the 5 individual measurements and for the minimum and maximum IOP by either method. Magacho et al found no difference regarding the minimum or maximum IOP assessed in the diurnal curve.[18] The IOP fluctuation (maximum – minimum) was also found to be similar when IOP was measured on different days vs. in the same day. In the present study, the minimum and maximum IOP as well as fluctuation in IOP recorded by either of the methods i.e. DV and SDV were found to be similar and the difference between the two was not statistically significant ($p>0.05$). Most of the previous studies suffer from several methodological flaws like use of self tonometry, small sample size and incomplete statistical analysis. However using correct methodology, use of applanation tonometry and application of appropriate statistical tools, we found a strong correlation between diurnal variations and split diurnal variation. Clearly, studies indicate that diurnal IOP variation in POAG patients can be assessed by IOP measurements at different time points on different days (Split Diurnal Variation) and it strongly correlates with the Diurnal Variation curve.

This method not only helps us to detect pressure peaks and fluctuation; it has several added advantages over diurnal variation as stated below.[17]

1. This IOP measurement over several days may be a more realistic sampling of the patient's IOP as the patients experience less modification in their normal routine.
2. It may also be a better evaluation of the patient's compliance with medications and physiologic changes (e.g., hormonal or metabolic) that may take place over days and weeks rather than hours and thus better detected by multiple day measurements.
3. Considering the type of glaucoma is also important while assessing diurnal fluctuations in IOP.[17]

– Pigmentary glaucoma may show more variability over several days than on a single day especially if the patient is more active or exercising and in the dispersion phase and better assessed by split diurnal variation.

- Pseudoexfoliation syndrome has a tendency for IOP spikes[19] that can be missed by single day measurement and are more likely to be caught by multiple measurements over multiple days.

Thus, measuring the split diurnal variation in IOP could be a valid choice and can be used as a surrogate measure to diurnal variation in IOP.

Normal versus Glaucomatous

In the present study, it was observed that POAG subjects had higher Peak IOP and larger diurnal fluctuations as compared to normal subjects. In normal individuals, IOP fluctuates by 2 to 6 mmHg over a 24 hour period. IOP fluctuations of as much as 4-5 mmHg in healthy individuals and, substantially higher, in some glaucoma patients have been reported.[20,21] There is general agreement that the diurnal IOP range is greater in glaucomatous subjects than in normal ones.[22,23]

CONCLUSION

There is a strong correlation between the diurnal variation and split diurnal variation. Thus, diurnal IOP variation in POAG patients can be assessed by IOP measurements at different time points on different days (Split Diurnal Variation). Measuring the split diurnal variation in IOP could be a valid choice and can be used as a surrogate measure to diurnal variation in IOP in a single day with many added advantages such as more realistic sampling of the patient's IOP with less modification in their normal routine, better evaluation of the patient's compliance with medications and physiologic changes (e.g., hormonal or metabolic) that may take place over days and weeks rather than hours and better in picking up the spikes and fluctuations in IOP observed in pigmentary glaucoma and pseudoexfoliatory glaucoma patients.

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