Original Article

Comparison of intraocular pressure variability detected by day diurnal variation to that evoked by water drinking

Sujatha V Kadambi, Shantha Balekudaru, Vijaya Lingam, Ronnie George

Purpose: To determine correlation and agreement between intraocular pressure (IOP) peak and fluctuations detected by day diurnal variation (day DVT) to that after the water-drinking test (WDT). **Methods:** Patients (18–80 years) with glaucoma, suspects, and ocular hypertension (OHT) were enrolled. IOP readings were taken on applanation tonometer, at 2-h intervals, from 8 AM to 3 PM (DVT). 3 PM IOP served as WDT baseline. Patients consumed water (10 mL/kg) in 5–15 min, at 3 PM, after they fluid fasted for 2 h. IOP was recorded every 15 min, from 3.30 to 4.30 PM. **Results:** A total of 200 eyes (100 patients) were included. 58.5% were established glaucoma, 32% suspects, 9.5% OHT. Correlation between mean and peak IOP by WDT and day DVT was strong and significant ($r = 0.89$, $P < 0.00$; $r = 0.73$, $P < 0.00$) while it was weak for fluctuation ($r = 0.12$, $P < 0.07$). Agreement on Bland and Altman plots was limited for mean IOP and poor for peak and fluctuations. **Conclusion:** An exaggerated WDT response may indicate a compromised outflow facility and warrant close patient monitoring but the WDT cannot substitute day DVT in our clinical practice.

Key words: Day diurnal variation, DVT, intraocular pressure, water drinking

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Intraocular pressure (IOP) is the only known modifiable risk factor in glaucoma management and reduction of IOP to an individualized target is the key treatment strategy in contemporary glaucoma practice.[1,2] In apparently well-controlled glaucoma patients, IOP peaks and large diurnal IOP fluctuations may be responsible for glaucoma progression.[2-4]

A 24-h IOP phasing provides us a comprehensive understanding of the patient's circadian IOP variability but is inconvenient and, not cost and labor effective. Day diurnal variation test (day DVT), a more practical substitute for 24-h IOP phasing, can detect peaks in about 24% of people, which is missed during single IOP measurements.[5] This itself is time and resource consuming. The water-drinking stress test (WDT) seems to address this limitation.

The water-drinking provocative test was abandoned as a test for glaucoma diagnosis due to its low sensitivity and specificity.[6] It has regained interest amongst researchers and clinicians in recent days and has been proposed as a surrogate for determining outflow facility and also the likelihood of progression in patients with apparently well-controlled IOP.[7-9]

The IOP peak obtained by this test has been reported to strongly correlate with the IOP peaks that occur during the day.[10,11] The aim of this study is to assess, if WDT can be used as a substitute to day diurnal variation test in our routine clinical practice, saving time and resources of both the patient and the clinician.

Methods

This was a prospective study. Patients attending the glaucoma clinic at a tertiary eye hospital in Chennai, between October 2017 and March 2018 were recruited. The study was conducted in accordance with the tenets of the Declaration of Helsinki and approved by our institution's ethics committee. Written informed consent was obtained from all the patients prior to inclusion.

Hundred patients, aged 18–80 years, with primary open, angle closure, pseudoexfoliation, pigmentary glaucoma, ocular hypertension, and glaucoma suspects who were undergoing day diurnal variation test as deemed necessary by their treating physician were subjected to the WDT. Patients unwilling or unable to give consent, patients unable to tolerate intake of 10 mL/kg of water in 15 min, patients with a history of renal impairment, cardiac disease, prostatic hypertrophy and pregnant women, patients with retinal disease and nonglaucomatous optic neuropathy that could produce abnormal visual field results, patients with severe end-stage glaucoma with macular split fixation and patients with visual acuity <20/200 or visual field less than 10 degrees in the better eye were excluded from the study.

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A patient with glaucoma was included if he/she had glaucomatous optic disc changes with corresponding typical visual field defects that were repeatable and reliable. Ocular hypertensives had IOP >21 mm Hg, open angles, and no disc or visual field changes. Patients with cup disc ratio >0.7, rim width <0.1 disc diameter, presence of any retinal nerve fiber layer defect, disc hemorrhage with normal visual field were classified as a glaucoma suspect.

IOP measurements were made by a trained optometrist on a Goldmann applanation tonometer, at 2-h intervals, from 8 AM to 3 PM (constituting day DVT). The 3 PM IOP reading served as the baseline for WDT. Patients were asked to consume water (10 mL/kg body weight) in 5–15 min, at 3 PM, after they fluid fasted for 2 h. The same observer then took IOP measurements, at 15-min intervals from 3.30 PM, till IOP readings returned to baseline.

Data from 200 eyes of 100 patients were used for analysis. Day DVT peak was the highest IOP recorded between 8 AM and 3 PM and WDT peak was the highest IOP recorded, post the water-drinking challenge, when IOP measurements were made between 3.30 and 4.30 pm. Mean day DVT IOP was the average of IOP readings taken from 8 AM to 3 PM and WDT mean was the average of IOP readings taken post water intake. T test was used to compare the mean IOP, IOP peak, and IOP fluctuations by day DVT and WDT. The correlation between these parameters measured by the two methods was studied by Pearson correlation coefficient and agreement between them by Bland Altman plots.

Results

200 eyes of 100 patients were included in the study. The average age was 55.66 ± 14.58 years. 78 patients amongst them were males. The pattern of glaucoma subtype distribution in the sample population is shown in Fig. 1. Of 200 eyes, 110 eyes showed a WDT response >2 mm Hg. We had attributed <= 2 mm Hg as intraobserver variability of IOP measurements on Goldmann applanation tonometer.

The frequency distribution of the difference between WDT and day DVT peak is shown in Fig. 2. T test performed to note the difference between the two measures was significant ($P = 0.001$). The correlation between mean and peak IOP by day DVT and WDT was strong and significant ($r = 0.89$, $P < 0.00$; $r = 0.73$, $P < 0.00$), while it was weak for IOP fluctuation ($r = 0.12$, $P < 0.07$).

Bland Altman plots were drawn to study the agreement between the 2 methods. It showed limited agreement for mean IOP and poor agreement for peak IOP and IOP fluctuations. [Fig. 3]. When subgroup analysis was done as established glaucoma and OHT-suspect group it yielded similar results**.** The established glaucoma group was further analyzed based on the severity of glaucoma [Table 1].

We also analyzed if prostaglandin analogs that decrease uveoscleral outflow, produce a greater attenuation of water-drinking response, which would be secondary to the diminished outflow facility. We observed that 67.2% (45/200 eyes) which were treated with prostaglandin analog showed a WDT response less than 3 but the value was not statistically significant. (*P*-0.335).

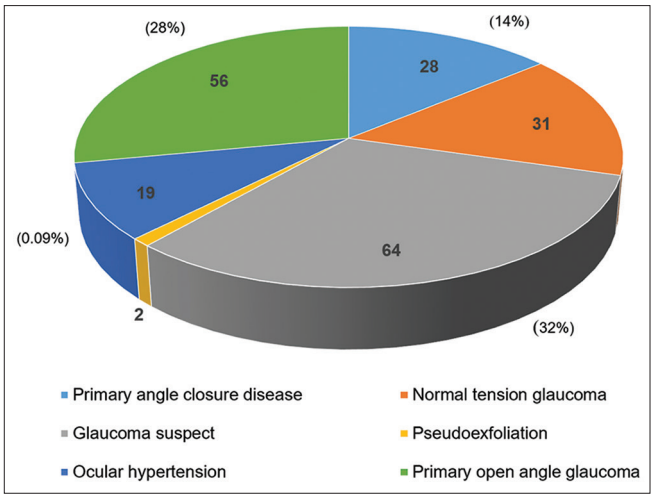

Figure 1: Pattern of glaucoma distribution in sample population

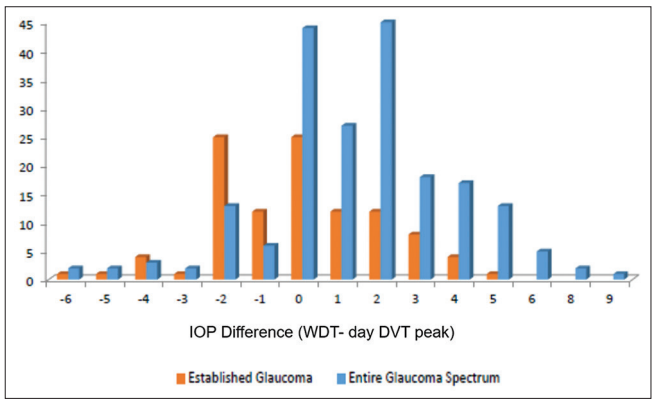

Figure 2: Frequency distribution of difference between WDT and day DVT peak in entire glaucoma spectrum as well as in established glaucoma subset

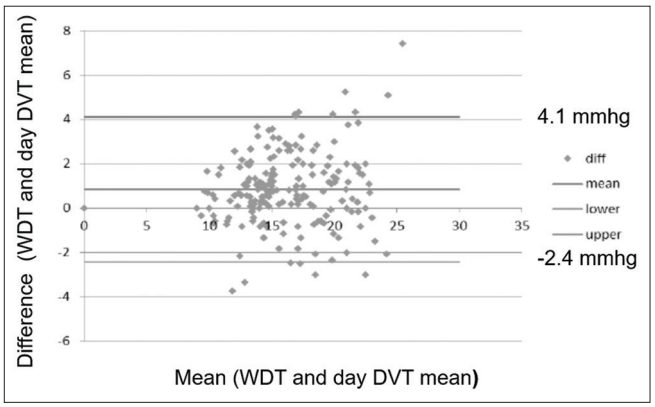

Figure 3: Bland Altman plot showing limited agreement between WDT and day DVT mean

Since we have used both eyes of all patients in our analysis, we calculated the intraclass correlation coefficient (ICC) to see if the inter-eye correlation is likely to be a problem in our statistical analysis, for tests that assume independence.[12,13] We got a significant ICC of 0.8. So generalized estimating equation (a model that copes with the problem of inter-eye

Table 1: Summary of results of Bland Altman agreement plots between WDT and day DVT

	WDT and day DVT Mean	WDT and day DVT Peak	WDT and day DVT Fluctuations
Entire spectrum	Limited	Poor	Poor
LOA (in mm Hg)	-2.4 to 4.1	-4.5 to 7.3	-3.9 to 5.6
OHT-Glaucoma Suspects	Limited	Poor	Poor
LOA	-2.8 to 3.6	-6.8 to 8.18	-4 to 5.37
Established glaucoma	Limited	Limited	Poor
LOA	-2.1 to 4.4	-2.4 to 6	-3.9 to 5.85
Mild glaucoma	Limited	Poor	Poor
LOA	-2.4 to 5.5	-2.5 to 6.5	-3.4 to 5.17
Moderate	Poor	Poor	Poor
LOA	-1 to 4.5	-1.9 to 6.4	-3 to 4.93
Severe glaucoma	Limited	Poor	Poor
LOA	-1.8 to 3.34	-2.7 to 5.34	-5 to 7.2

*LOA -limits of agreement

correlation),[13] was used to identify risk factors that were associated with a water-drinking response greater than 3. We found central corneal thickness (OR 1.009, P = 0.041), worse mean deviation on visual field (OR = 0.96, P = 0.027) as significant risk factors, while glaucoma suspect diagnosis was protective (OR = 0.39, P = 036) on univariate analysis. None of them were significant on multivariate analysis [Table 2].

Table 2: Generalised estimating equation analysis of risk factors associated with water-drinking response greater than 3

Generalized Estimating Equation				
Univariate Analysis	Odds Ratio	95% confidence Interval		*P*
Variables		Lower Limit	Upper Limit	
Age	1.036	0.994	1.039	0.165
PGA	1.368	0.171	2.597	0.471
Quantity of water	1	0.997	1.002	0.965
CCT	1.009	1	1.019	0.041
PACD	1	0.379	2.642	0.999
NTG	1.333	0.534	3.328	0.538
Glaucoma Suspect	0.391	0.163	0.94	0.036
PXFG	2.111	0.125	35.701	0.605
OHT	1.231	0.415	3.655	0.708
VF.MD	0.961	0.928	0.996	0.027
Mean.DVT	1.028	0.947	1.116	0.508
DVT Peak	1.01	0.94	1.086	0.781
DVT Fluctuations	0.998	0.821	1.213	0.981
Water <=500 ml	1.284	0.458	3.605	0.635
IOP lowering agents	1.195	0.914	1.562	0.193
VF MD (Less than-6)	0.733	0.27	1.995	0.543
VF MD (-6 to-12)	1.44	0.56	3.701	0.449
Multivariate				
CCT	1.006	0.995	1.018	0.261
Glaucoma Suspect	0.582	0.165	2.054	0.4
VF.MD	0.953	0.891	1.019	0.157

*PGA - prostaglandin analog

Discussion

In current times, long hospital waiting hours for the patient and attendant is a deterrent factor in the health-seeking behavior and follow-up in a patient with a chronic disease like glaucoma. An office day diurnal variation test, a more practical substitute for 24 h phasing is in itself time and resource consuming. In such a scenario, it would be useful to know, if the circadian peak would be simulated after water-drinking and if the WDT can be used as a substitute for day DVT.

Previous studies suggest that although IOP fluctuation is a risk factor for glaucoma progression, it is peak IOP which is a better predictor and a more practical guide to target and tailor management.[14,15] WDT has also been found to have excellent reproducibility for IOP peak measurements and a fair reproducibility for IOP fluctuations.[16,17]

In our study we found the correlation between WDT and day DVT peak IOP in healthy eyes, suspects as well as patients with established glaucoma, to be strong and significant while it was weak for IOP fluctuations in all the subgroups. This would imply that if an eye presented with high peak during this stress test, it is likely to show a high peak when a complete day DVT is performed. This was in sync with the findings by Kumar *et al*.[10] and Moraes *et al*.[11] who had studied the correlation in a group of untreated open-angle glaucoma patients.

Susanna *et al*. investigated the relationship between visual field damage and WDT response in patients with bilateral asymmetric glaucoma and found that despite similar baseline IOP, the eye with worse visual field MD had an exaggerated WDT response, a reflection of compromised outflow facility.[18] In another prospective longitudinal study, Moraes *et al*., found that higher WDT response was predictive of glaucomatous visual field progression whereas mean and peak office IOP were not significantly associated with progression.[19] In our study we found a similar pattern, but since we had only 20 eyes amongst 130 (established glaucoma and OHTs) which progressed, when split into subsets with similar baseline IOP, the numbers in each subgroup were small to get a statistically significant result.

For the WDT to have clinical significance and for us to consider it as a substitute, the two should have good agreement. Moraes *et al*.[11] found limited agreement between WDT and modified diurnal tension curves (mDTC) IOP peaks, with 95% limits of agreement ranging from –3.9 mm Hg to 8.2 mm Hg. Here, the mDTC had IOP measurements from 8 AM to 4 PM following which the WDT was performed. The same author, in another study found significant agreement between WDT peak (performed at the initial visit) and highest office IOP during subsequent visits in a 6–12 month follow-up period.[20]

In our study we found, Bland and Altman plots showed limited agreement for mean IOP by the two methods (limits ranging from –2.4 to 4.1 mm Hg). However, the agreement was poor for peak IOP and IOP fluctuations by day DVT and WDT. This could be because the DVT was only from 8 AM-3 PM, probably missing the circadian peak between 5 and 7 AM. The decreased duration of DVT, flatter DVT curves as patients were on multiple IOP lowering agents, in a relaxed state, not performing their routine physiological activities- are possible reasons to explain this difference.

Conclusion

In conclusion, an exaggerated response on water drinking may indicate a compromised outflow facility and warrant close patient monitoring but the WDT cannot substitute day DVT in our clinical practice.

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Conflicts of interest

There are no conflicts of interest.

References

1. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M; Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression: Results from the early manifest glaucoma trial. Arch Ophthalmol 2002;120:1268-79.
2. Musch DC, Gillespie BW, Niziol LM, Lichter PR, Varma R; CIGTS study Group. Intraocular pressure control and long-term visual field loss in the Collaborative initial glaucoma treatment study. Ophthalmology 2011;118:1766-73.
3. Leske MC, Heijl A, Hyman L, Bengtsson B, Dong L, Yang Z; EMGT Group. Predictors of long-term progression in the early manifest glaucoma trial. Ophthalmology 2007;114:1965-72.
4. Asrani S, Zeimer R, Wilensky J, Gieser D, Vitale S, Lindenmuth K. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. J Glaucoma 2000;9:134-42.
5. Barkana Y, Anis S, Liebmann J, Tello C, Ritch R. Clinical utility of intraocular pressure monitoring outside of normal office hours in patients with glaucoma. Arch Ophthalmol 2006;124:793-7.
6. Roth JA. Inadequate diagnostic value of the water-drinking test. Br J Ophthalmol 1974;58:55-61.
7. Clement C, Goldberg I. Water drinking test: New applications. Clin Exp Ophthalmol 2016;44:87-8.
8. Landers J. Challenging glaucoma with a water-drinking test. Clin Exp Ophthalmol 2015;43:200-1.
9. Susanna R Jr, Clement C, Goldberg I, Hatanaka M. Applications of the water drinking test in glaucoma management. Clin Exp Ophthalmol 2017;45:625-31.
10. Kumar RS, de Guzman MH, Ong PY, Goldberg I. Does peak intraocular pressure measured by water drinking test reflect peak circadian levels? A pilot study. Clin Exp Ophthalmol 2008;36:312-5.
11. Vasconcelos-Moraes CG, Susanna R Jr. Correlation between the water drinking test and modified diurnal tension curve in untreated glaucomatous eyes. Clinics (Sao Paulo) 2008;63:433-6.
12. Karakosta A, Vassilaki M, Plainis S, Elfadl NH, Tsilimbaris M, Moschandreas J. Choice of analytic approach for eye-specific outcomes: One eye or two? Am J Ophthalmol 2012;153:571-9.
13. Murdoch IE, Morris SS, Cousens SN. People and eyes: Statistical approaches in ophthalmology. Br J Ophthalmol 1998;82:971-3.
14. De Moraes CG, Juthani VJ, Liebmann JM, Teng CC, Tello C, Susanna R Jr, *et al*. Risk factors for visual field progression in treated glaucoma. Arch Ophthalmol 2011;129:562-8.
15. Gardiner SK, Johnson CA, Demirel S. Factors predicting the rate of functional progression in early and suspected glaucoma. Invest Ophthalmol Vis Sci 2012;53:3598-604.
16. Hatanaka M, Alencar LM, De Moraes CG, Susanna R Jr. Reproducibility of intraocular pressure peak and fluctuation of the water-drinking test. Clin Exp Ophthalmol 2013;41:355-9.
17. Babic M, De Moraes CG, Hatanaka M, Ju G, Susanna R Jr. Reproducibility of the water drinking test in treated glaucomatous patients. Clin Exp Ophthalmol 2015;43:228-33.
18. Susanna R Jr, Vessani RM, Sakata L, Zacarias LC, Hatanaka M. The relation between intraocular pressure peak in the water drinking test and visual field progression in glaucoma. Br J Ophthalmol 2005;89:1298-301.
19. De Moraes CG, Susanna R Jr, Sakata LM, Hatanaka M. Predictive value of the water drinking test and the risk of glaucomatous visual field progression. J Glaucoma. 2017;26:767-73.
20. De Moraes CG, Furlanetto RL, Reis AS, Vegini F, Cavalcanti NF, Susanna R Jr. Agreement between stress intraocular pressure and long-term intraocular pressure measurements in primary open angle glaucoma. Clin Exp Ophthalmol 2009;37:270-4.