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The Water-Drinking Test Revisited: An Analysis of Test Results in Subjects with Glaucoma

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Abstract

Purpose—The Water-Drinking Test (WDT) has been shown to predict the diurnal IOP change. This study evaluates the factors that may affect the WDT results.

Methods—This study was conducted on 203 glaucoma patients who had undergone trabeculectomy (53) or tube surgery (31), or had a medically controlled open-angle (82) or closed-angle (37) glaucoma. IOP was measured at baseline and then every 15 minutes over a one-hour period after drinking water. The main outcome measures were IOP change (increase in IOP from baseline) at all measurement time points, IOP peak (highest IOP after drinking water), IOP fluctuation (difference between IOP peak and baseline), and assessing the association of these IOPs with a patient's demographic and management modalities.

Results—The mean age of the participants was 54±18 years, and 113 (56%) were male. Female patients showed greater IOP fluctuation than males (7.28 vs. 5.92 mm Hg; $P=0.016$), and a greater IOP peak (22.7 vs. 20.1 mm Hg; $P=0.001$). The observed associations between gender and IOP changes were only significant in <50 years. IOP at 60 minutes was greater in tube than trabeculectomy (5.6 vs. 3.1 mm Hg; $P=0.007$). The number of topical medications showed a direct independent association with IOP changes ($P<0.001$). Compared to other classes of topical medications, latanoprost showed lower WDT-IOP profile ($P=0.0003$).

Conclusions—WDT-IOP change was diminished in subjects on latanoprost, and was greater in females <50 years, and those on greater number of medications.

Keywords

Glaucoma; trabeculectomy; tube surgery; water-drinking test

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DECLARATION OF INTEREST

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INTRODUCTION

The goal of glaucoma management is to lower intraocular pressure (IOP) below the level that is likely to cause further damage to the optic nerve, thus preventing progressive visual field loss. This safe range of eye pressure is called the target IOP, and is typically determined with data collected from isolated clinical measurements during usual office working hours. In a subset of patients, visual field loss continues in spite of normal in-office IOP readings.¹ This could be explained by undetected IOP fluctuation during the day or could be the result of pressure peaks outside of usual office hours.^{2,3} Studies that evaluate 24-hour IOP in glaucoma patients found that about 75% of them exhibit their highest IOP values outside of regular clinic hours.^{4,5}

It would be ideal to measure 24-hour IOP in all patients with glaucoma. A modified diurnal tension curve (IOP is tested every three hours over an 8–10 hour period) and home tonometry have also been explored as a way to identify IOP fluctuation.^{6,7} However, the cost and labor involved in 24-hour IOP monitoring make the process difficult. Additionally, these simplified evaluations can miss up to 70% of IOP spikes, because most of the highest IOP levels occur in the early morning hours with the individual in the supine position.⁸ Sleep laboratory serial IOP measurement has proven cumbersome and expensive.⁹ A contact lens sensor for continuous 24-hour monitoring of IOP had shown fair to good reproducibility without severe side-effects.¹⁰ However, this instrument is not always available commercially and has not yet gained wide popularity outside of highly specialized centers, and cost remains prohibitive.

In the 1960s, the water-drinking test (WDT) was described as a diagnostic test for glaucoma and to predict which ocular hypertensive patient is more prone to visual field loss, but now it is regarded as a stress test to assess the capacitance of aqueous outflow and to predict the IOP peak of the diurnal tension curve.^{11–13} Also, the WDT has been used to assess the effectiveness of treatments in controlling IOP, including medications¹⁴ and trabeculectomy patency.¹⁵ There are reports on the reproducibility of WDT for evaluating the IOP fluctuation; however, there are no reports on the variables that may affect the results. This study evaluates the effect of patients' demographic and management modalities on the WDT results.

MATERIAL AND METHODS

Study Population

This interventional case series was conducted after approval by the local ethics committee. Written informed consent was obtained from all study subjects. Study subjects at or below target IOP based on isolated office readings after prior surgery (trabeculectomy or tube shunt) and/or topical anti-glaucoma medications were prospectively and consecutively recruited. IOPs were measured in all visits with both a Goldmann applanation tonometer and a non-contact tonometer (CT80; Topcon Co., Tokyo, Japan), at a tertiary eye care hospital. All surgical procedures were performed by one surgeon (MRR). The trabeculectomy group (Trab) had undergone standard trabeculectomy with adjunctive Mitomycin-C (0.2 mg/ml for two minutes) and were followed for at least six months after surgery with IOPs at or below

target with or without IOP-lowering medications. The tube shunt group (Tube) had undergone Ahmed Glaucoma Valve (FP7, New World Medical, Rancho Cucamonga, LA, USA) implantation at least six months before study enrollment and their IOPs were at or below target with or without IOP lowering medications. The Medically Controlled Closed Angle Glaucoma Group (MCCAG) had laser iridotomy and an IOP at or below target with IOP-lowering medications. The Medically Controlled Open Angle Glaucoma Group (MCOAG) also had IOP at or below target with IOP-lowering medications but no prior surgical intervention.

All patients underwent a complete ophthalmic examination, which included Snellen visual acuity, IOP measurement, and a dilated stereoscopic fundus examination to assess the amount of optic nerve head damage using the Disc Damage Likelihood Scale.¹⁶ The average thickness of the peripapillary retinal nerve fiber layer on optical coherent tomography was also recorded. Subjects were excluded if they had a history of refractive surgery, current ocular infection, pregnancy, cardiac or renal diseases, history of urinary retention, any corneal abnormalities preventing reliable IOP measurements, previous argon laser or selective laser trabeculoplasty, more than one trabeculectomy or shunt surgery, follow-up of less than six months after trabeculectomy, shunt surgery, or laser iridotomy, and a target IOP greater than 22 mm Hg.

Water-Drinking Test

Subjects were instructed to refrain from food and fluid intake for three hours preceding the WDT. After checking the baseline IOP, patients were instructed to drink one liter of bottled water (15 mL/kg in those below 16 years) in five minutes. IOP was then measured every 15 minutes for one hour. Five IOP measurements were performed (baseline and then at 15 minutes, 30 minutes, 45 minutes, and 60 minutes after water consumption). One examiner measured the IOPs with a non-contact tonometer (CT80; Topcon Co., Tokyo, Japan). In a recent meta-analysis on all available tonometers compared with Goldmann applanation tonometer, the least amount of variability in IOP measurement (mean difference of 0.2 mm Hg) was seen with non-contact tonometers.¹⁷ The average of three measurements was recorded and the measurement was repeated if the difference between three measurements was greater than 3 mm Hg.

Outcome Measures

IOP change (increase in IOP from baseline) at all measurement time points, IOP peak (highest IOP after drinking water), IOP mean (the mean of the four IOPs after drinking water), IOP fluctuation (difference between IOP peak and baseline) were assessed and analyzed. Association between WDT results and the patient's demographic and management modalities were also evaluated.

Statistical Analysis

IOP was measured in both eyes, if both eyes met the eligibility criteria; one eye was randomly selected for inclusion in the study. All data were recorded and analyzed using IBM SPSS Statistics software version 21 (SPSS Inc., Chicago, IL) and MedCalc version 12.2.1 (MedCalc Software, Mariakerke, Belgium). Repeated-measures analysis of variance, linear

regression analysis, and linear mixed models (LMM) were used for statistical analysis. The tested variables included age, sex, surgery vs. medication, trabeculectomy vs. tube, OAG vs. CAG, number of topical medications, class of topical medications (Latanoprost vs. others, β -blockers vs. others, carbonic anhydrase inhibitors vs. others, and α_2 -agonists vs. others), weight, height, body mass index, spherical equivalent of refraction, astigmatism, lens status (phakic vs. pseudophakic, vs. aphakic), Disc Damage Likelihood Scale, visual field mean and pattern standard deviation, average retinal nerve fiber layer thickness, and IOP baseline. A *P* value of < 0.05 was considered statistically significant.

RESULTS

The data from 203 eyes of 203 patients were analyzed. Fifty-three eyes were in the Trab group, 31 in the Tube group, 82 with MCOAG, and 37 with MCCAG. Demographic and baseline characteristics of participants are presented in Table 1. Considering all 203 eyes, the mean IOP increased from 14.8 mm Hg at baseline to 17.8 mm Hg at 15 minutes after WDT ($P < 0.001$), then to 19.3 mm Hg at 30 minutes ($P < 0.001$) and remained stable afterwards. An IOP of 30–40 mm Hg was detected at 15, 30, 45, and 60 minutes in 2 (1.0%), 7 (3.4%), 12 (5.9%), and 11 (5.4%) patients, respectively. The results of the WDT in the four groups are given in Table 2 and Figure 1.

Table 3 lists different IOP parameters after WDT in all patients and within each group. The IOP peak occurred at 15 minutes in 34 patients (16.7%), at 30 minutes in 55 (27.1%), at 45 minutes in 56 (27.6%), and at 60 minutes in 43 (21.2%) cases. The highest frequency of IOP peak in the Trab group was observed at 45 minutes (30.2%), which did not differ from the Tube group (32.3% at 30 minutes), MCOAG (27% at 30 minutes), or MCCAG subjects (30.5% at 45 minutes). The frequency of different time-slots for the IOP peaks did not differ significantly in the four groups ($P = 0.53$).

Table 4 summarizes the possible association of several demographic and ocular variables to the IOP fluctuation. Female patients showed more prominent IOP change compared to males (Figure 2A). The averages of the IOP peak were 22.7 ± 5.8 mm Hg in females vs. 20.1 ± 5.4 mm Hg in males ($P = 0.001$). IOP fluctuation was significantly greater in females than males (7.2 ± 4.5 vs. 5.9 ± 3.6 , $P = 0.016$). Females under 50 years had greater IOP changes after WDT than those over 50 (Figure 2B), and the observed associations between gender and IOP fluctuation after WDT were only significant for patients < 50 years of age (Figure 2C). Comparing the Tube vs. Trab groups, greater IOP change was observed in the Tube group. IOP change at 60 minutes after WDT was significantly greater in the Tube group than the Trab group (5.6 ± 3.6 vs. 3.1 ± 4.3 ; $P = 0.007$; Figure 3).

The number of topical medications showed a direct independent association with IOP changes after WDT (Figure 4A and B). Compared to other classes of topical medications, Latanoprost showed lower IOP profile after WDT (Figure 4C).

DISCUSSION

In this study, many factors were found to have a statistically significant effect on the results of the WDT, but only the following factors were found to have significant associations in

multiple regression analysis with IOP change after WDT: female sex, type of surgery, number of medications, Latanoprost use, and IOP baseline.

The exact mechanism of IOP rise after WDT is yet to be determined. Bruculeri et al.¹⁸ found no variation in hematocrit, total plasma osmolality, or plasma colloid osmotic pressure and therefore concluded that neither vitreous hydration nor increased aqueous ultrafiltration could explain the IOP increase. The Diestelhorst and Krieglstein¹⁹ study showed an increase in episcleral venous pressure (from average of 8.2 mm Hg to 18.2 mm Hg) 60 minutes after drinking water. This increased episcleral venous pressure would reduce the conventional outflow via the trabecular meshwork. Although the physiology is not completely understood, recent studies have suggested an expansion of choroidal volume to contribute to the increase in IOP.²⁰ Whatever the mechanism, after WDT, there is an increase in the IOP. The ability of the eye to recover from this IOP elevation depends on its outflow facility.²¹ Brubaker,¹² in a computer simulation, proposed that the WDT could be used as an indirect tool to measure outflow facility. However, due to the limitations of currently available techniques to assess trabecular or uveoscleral outflow, it is difficult to directly and objectively determine whether the WDT is measuring specifically trabecular or uveoscleral outflow.

The number of topical medications demonstrated an independent association with IOP changes after WDT. The association can be explained as follows: a greater inherent resistance in the outflow pathway manifests as a higher unmedicated IOP, thus requiring more medications to maintain IOP at target level. In other words, the greater number of medications required to maintain target IOP may be an indirect measure for increased resistance in the outflow system. Although medications lower the IOP and reduce diurnal IOP changes, they are not able to compensate for decreased outflow facility in glaucoma patients after a challenge of 1000 ml of water ingestion, as in the WDT.

There was an independent association for IOP fluctuation and latanoprost. Currently, the five classes of drugs commonly used for treating glaucoma are β -blockers, prostaglandin analogues, α_2 -adrenergic agonists, carbonic anhydrase inhibitors, and cholinergic agents. The prostaglandin analogues reduce IOP primarily by increasing aqueous flow via the uveoscleral pathway.²² The major mechanism for other classes of medications except cholinergic agents, which are less commonly used these days, is decreasing aqueous production. Because latanoprost reduces overall aqueous outflow resistance, it follows that it would have the greatest effect on the WDT, as the only commonly used IOP-lowering medication that enhances overall aqueous outflow.^{23–25} When outflow facility is enhanced, the eye is capable of handling an increase in volume more efficiently and the IOP changes in response to the WDT would be blunted. This finding has been corroborated in other studies. In a study of a total of 280 primary OAG patients on IOP-lowering medications, 40 patients per group for each of the tested medications (timolol, dorzolamide, brinzolamide, travoprost, latanoprost, bimatoprost, and brimonidine) underwent the WDT. The prostaglandins gave the best results in controlling IOP during the WDT in terms of IOP mean rise, IOP mean peak, and IOP mean percentage increase.²⁶ It has been shown that the latanoprost effect on IOP resulted in less fluctuation throughout the circadian cycle compared with timolol and with dorzolamide.²⁷ In a study comparing IOP fluctuation in response to the WDT in

patients using latanoprost vs. unoprostone, the mean $\pm$ SD of IOP fluctuation of WDT was 5.2 ± 2.6 mm Hg in the unoprostone group and 3.7 ± 2.3 mm Hg in latanoprost group ($P = 0.006$).²⁸

There are mixed results about the effect of estrogen on IOP, but several studies have demonstrated that testosterone is associated with an increase in IOP.²⁹ The greater IOP change in women observed in this study may not be due entirely to a hormonal effect on the eye. Different male vs. female hormonal effects on body fat composition and water retention may play a role in the load of water influx into the eye and subsequently distinct responses to WDT. Aging, which is accompanied by diminished sex hormones in both sexes, may reduce the observed differences compared with younger individuals.

A study on WDT and choroidal thickness in 30 patients with primary OAG revealed that IOP peaks occurred 15 minutes after the increase in choroidal thickness was observed.²⁰ An increase in volume posteriorly in the choroid would be accommodated by fluid exit from the anterior chamber to compensate for the gradient pressures generated from volume dynamics within the globe. Therefore, the amount of change in choroidal volume and IOP could be dependent on the combination of choroidal thickness change and outflow facility. A study on 72 healthy reproductive-age and 72 post-menopausal women showed that the choroid was significantly thinner in the post-menopausal group (271.3 ± 65.6 μ m) compared to pre-menopausal group (325.4 ± 65.7 μ m; $P = 0.005$).³⁰ Li et al.³¹ investigated subfoveal choroidal thickness in 1323 children aged 11 to 12 years. They found that choroidal thickness in girls increased with body height and sexual maturation, whereas height or puberty had no effect on boy's measurements. The difference in choroidal thickness and the effect of female sex hormones on it may explain the differences in IOP profiles after WDT in women less than 50 years of age.

IOP baseline had an independent association with IOP peak ($r = 0.51$, $P < 0.001$), IOP range ($r = 0.06$, $P < 0.001$), and IOP mean ($r = 0.56$, $P < 0.001$). These results agree with previous reports showing that higher IOP baseline was associated with greater 24-hour IOP changes measured in the seated position.^{32,33} The Early Manifest Glaucoma Treatment Trial showed that lowering IOP halved the rate of optic nerve damage and visual field progression in patients with newly diagnosed open-angle glaucoma. For each 1-mm Hg reduction in IOP over the course of the study, the risk of glaucoma progression was reduced by 10%. One of the baseline risk factors for worsening visual field was higher IOP.³⁴ The response to WDT was also considered a risk factor for the development of visual field defect progression in OAG.³⁵ Yoshikawa et al.³⁶ evaluated the clinical tests that could predict the progression of visual field loss in normal tension glaucoma. The WDT was considered the main predictive test for glaucomatous progression in the study group. Therefore, when the IOP baseline is lower, the possibility of diurnal IOP changes might be reduced, which seems to be a contributing factor in progressive visual field loss.³⁷

Although the WDT is an inexpensive and feasible test, coexisting systemic diseases, including cardiac or renal disease, or history of urinary retention, are contraindications to this test. The majority of glaucoma patients are elderly, thus increasing the likelihood of a coexisting comorbidity that may preclude performing WDT. After drinking the water, the

kidney is the primary organ to handle the ingested water load via diuresis.³⁸ For these reasons, patients with cardiovascular or renal disease and males with urinary retention should not undergo this test.

One of the potential limitations of this study includes the use of non-contact tonometry for IOP measurement. Non-contact tonometry was used in this large sample size study as an alternative to Goldmann applanation tonometer because it has been shown to closely correspond with Goldmann IOP readings, with a mean difference of 0.2 mm Hg.¹⁷ To control for potential differences, all IOP measurements were performed by one examiner and the average of three measurements was recorded. Measurements were repeated if the difference between three measurements was greater than 3 mm Hg in effort to increase the accuracy of IOP measurement.

In conclusion, this study showed that females under 50 years of age, subjects with higher IOP baseline and greater number of medications experienced higher IOP changes during the WDT. In contrast, those on latanoprost had fewer IOP changes.

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FIGURE 1.

Mean difference of IOP in four groups at each timeslot: MCCAG, medically controlled closed angle glaucoma; MCOAG, medically controlled open angle glaucoma; Trab, trabeculectomy; Tube, tube-shunt surgery.

FIGURE 2.

(A) Higher IOP profile in females ($P=0.047$, LMM controlling for IOP baseline and number of medications); (B) IOP change in females over and under 50 years; (C) comparison of IOP fluctuation in males vs. females categorized by age groups.

FIGURE 3.

Greater IOP change in the Tube compared to the Trabeculectomy group ($P=0.03$ for surgery $\times$ time interaction on LMM).

FIGURE 4.

(A) Greater IOP change with greater number of medications ($P<0.0001$, LMM after controlling for baseline IOP); (B) higher IOP fluctuation with higher number of topical medications ($P<0.0001$ in univariate analysis); (C) lower IOP profile in those on latanoprost ($P=0.0003$, LMM after controlling for baseline and number of meds).

TABLE 1

Demographic and baseline characteristics of participants.

Number	203
Age, years	Mean (SD): 54 (18) Range: 7 to 88
Gender (Male/Female)	113/90
Eye (Right/Left)	97/106
Weight, kg	Mean (SD): 67 (15) Range: 21 to 106
Height, cm	Mean (SD): 161 (11) Range: 122 to 194
Body Mass Index, kg/m ²	Mean (SD): 25.7 (5.0) Range: 14.1 to 40.6
Spherical Equivalent, Diopters	Mean (SD): -0.8 (2.8) Range: -12.5 to 12.0
Astigmatism, Diopters	Mean (SD): -1.2 (1.1) Range: -5.0 to 0
Optic Nerve Head Damage (DDLS)	Mean (SD): 6.8 (1.8) Range: 1 to 9
Mean Deviation of Humphery Visual Field	Mean (SD): -9.8 (9.0) Range: -30.1 to 0.8
Pattern Standard Deviation	Mean (SD): 6.2 (4.2) Range: 1.1 to 17.4
Average Retinal Nerve Fiber Layer Thickness in Optical Coherent Tomography, μm	Mean (SD): 68 (20) Range: 34 to 122
Intraocular Pressure Baseline, mm Hg	Mean (SD): 14.8 (3.4) Range: 6.5 to 22
Primary glaucoma diagnosis, n (%)	Primary open angle: 103 (50.7) Primary closed angle: 40 (19.7) Pseudoexfoliative: 24 (11.8) Congenital: 8 (3.9) Others: 28 (13.8)
Lens status, n (%)	Phakic: 141 (69.5) Pseudophakic: 57 (28.1) Aphakic: 5 (2.5)
Glaucoma medications, n (%)	None: 24 (11.8) 1: 26 (12.8) 2: 50 (24.6) 3: 103 (50.7)
Group, n (%)	Trab Group: 53 (26.1) Tube Group: 31 (15.3) MCOAG Group: 82 (40.4)

Number	203
	MCCAG Group: 37 (18.2)

MCOAG: Medically Controlled Open Angle Glaucoma; MCCAG: Medically Controlled Closed Angle Glaucoma; SD: Standard Deviation; DDLS: Disc Damage Likelihood Scale.

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TABLE 2

Intraocular pressure measurements at baseline and after water-drinking test in four groups.

	Intraocular Pressure, mm Hg ^a					<i>P</i> value ^b
	Baseline	15 minutes	30 minutes	45 minutes	60 minutes	
Trab Group	14.1±3.2	16.9±5.4 ^c	17.9±5.3 ^c	17.6±5.2 ^c	17.3±5.6 ^c	<0.001
Tube Group	14.3±3.9	17.3±5.6 ^c	19.0±5.6 ^{c, d}	19.4±5.8 ^c	19.9±6.0 ^c	<0.001
MCOAG Group	14.9±3.1	18.2±4.2 ^c	20.1±5.1 ^{c, d}	20.0±5.8 ^c	19.8±5.6 ^c	<0.001
MCCAG Group	15.8±3.6	18.7±4.2 ^c	19.9±5.0 ^c	20.4±5.8 ^c	19.9±6.1 ^c	<0.001

^a Presented as Mean ± SD.

^b Calculated using repeated-measures ANOVA with pairwise comparison using Bonferroni correction.

^c Indicates that the measurement is statistically different from the baseline measurement of the same group.

^d Indicates that the measurement is statistically different from the previous measurement of the same group.

MCCAG: Medically Controlled Closed Angle Glaucoma; MCOAG: Medically Controlled Open Angle Glaucoma; Trab: Trabeculectomy; Tube: Tube-Shunt Surgery.

TABLE 3

Comparison of IOP parameters in four groups.

IOP parameters ^a	All Cases	Trab Group	Tube Group	MCOAG Group	MCCAG Group
IOP peak, mm Hg	21.2±5.7	19.6±6.0	21.1±5.8	21.8±5.3	22.3±5.8
IOP mean, mm Hg	18.9±5.0	17.4±4.9	18.9±5.4	19.5±4.7	19.7±4.8
IOP fluctuation, mm Hg	6.5±4.1	5.5±4.4	6.8±3.4	6.9±4.0	6.5±4.3
IOP change at 60 minutes, mm Hg	4.4±4.4	3.1±4.3	5.6±3.6	4.9±4.6	4.1±4.5

^aPresented as Mean ± SD.

MCCAG: Medically Controlled Closed Angle Glaucoma; IOP: intraocular pressure; MCOAG: Medically Controlled Open Angle Glaucoma.

TABLE 4

Effect of selected covariates on the IOP fluctuation after water-drinking test.

Variable		Number	IOP Fluctuation (Mean± Standard Deviation)	P value
Gender	Female	113	7.28 ± 4.44	0.02
	Male	90	5.92 ± 3.65	
Group	Trab	53	5.48 ± 4.38	0.16
	Tube	31	6.84 ± 3.36	
	MCOAG	37	6.62 ± 4.13	
	MCCAG	82	7.02 ± 4.01	
Trab vs. Tube	Trab	53	5.48 ± 4.38	0.13
	Tube	31	6.84 ± 3.36	
Latanoprost	Yes	79	6.12 ± 4.17	0.26
	No	124	6.78 ± 3.99	
Number of medications	0	24	4.21 ± 3.41	<0.0001
	1	26	5.50 ± 4.80	
	2	50	6.43 ± 3.26	
	3	75	6.86 ± 4.05	
	4	25	8.26 ± 4.09	
	5	3	12.67 ± 1.53	
Females	Under 50	31	8.37 ± 4.70	0.096
	Over 50	59	6.71 ± 4.22	
Surgery (Trab or Tube)	yes	84	5.98 ± 4.07	0.11
	no	119	6.91 ± 4.04	