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Reproducibility of the water-drinking test in patients with exfoliation syndrome and exfoliative glaucoma

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ABSTRACT.

Purpose: **To evaluate the reproducibility of intraocular pressure (IOP) peaks and fluctuations detected during the water-drinking test (WDT) in patients with exfoliation syndrome (XFS) and exfoliative glaucoma (XFG).**

Methods: **This prospective study included 34 XFS and 30 XFG patients. Each patient was evaluated twice, with the two WDTs performed on a 30-day interval. We recorded IOP peak (highest IOP during the WDT) and IOP fluctuation (IOP peak minus IOP before the test). Bland–Altman analysis was applied to assess the agreement of IOP peaks and fluctuations between the two consecutive visits. We defined reproducible as within 4 mmHg for IOP peak and within 2 mmHg for IOP fluctuation.**

Results: **There were no significant differences in IOP values, IOP peaks and IOP fluctuations between the two visits for both XFS and XFG patients ($p > 0.05$, for all). The coefficient of repeatability for IOP peak was 2.5 mmHg and 3.5 mmHg in XFS and XFG patients respectively and for IOP fluctuation, it was 2.1 mmHg and 2.2 mmHg. None of the XFS or XFG patients had an IOP peak difference higher than 4 mmHg. Intraocular pressure (IOP) fluctuation differences above 2.0 mmHg were found in 8.8% of XFS patients and 16.6% of XFG patients.**

Conclusions: **Intraocular pressure (IOP) peak and IOP fluctuation have a reproducibility, both in XFS and in XFG.**

Key words: exfoliation syndrome – exfoliative glaucoma – intraocular pressure – intraocular pressure fluctuation – water-drinking test

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Introduction

The water-drinking test (WDT) was initially used to diagnose glaucoma patients (Leydhecker 1950). Because several studies revealed low sensitivities and specificities of the WDT for the diagnosis of glaucoma (Roth 1974; Rasmussen & Jorgensen 1976), it has been abandoned. Recently, the WDT has been used as a stress test to evaluate trabecular outflow facility (Brubaker 2001). It has also been used to assess the effect of treatment on the reduction in intraocular pressure (IOP) peak and fluctuation with both ocular hypotensive medication and filtering surgery (Chen et al. 2000; Susanna & Sheu 2004; Vetrugno et al. 2005; Hatanaka et al. 2008; Kerr & Danesh-Meyer 2010).

Studies have shown that the IOP peak levels of the WDT strongly correlate with the peak of shortened diurnal tension curves and long-term IOP measurements (Kumar et al. 2008; De Moraes et al. 2009). The WDT may be used as a determinative test for detecting patients whose IOP spikes are not observed during office hours. However, to be clinically applicable, a test must provide reproducible results with consistent measurements.

The reproducibility of IOP peaks and fluctuations with the WDT in untreated open-angle glaucoma and ocular hypertension patients and treated open-angle glaucoma patients had been reported (Hatanaka et al. 2013; Babic et al. 2015). Recently, it has also been reported that the WDT reveals significant IOP elevations in eyes with medically treated exfoliative glaucoma (XFG) and similar IOP characteristics in patients with exfoliation syndrome (XFS) when compared with healthy controls (Mocan et al. 2016). However, the reproducibility of IOP peaks and fluctuations with the WDT in XFG and XFS is not known.

The aim of this study was to determine the reproducibility of the WDT in patients with XFS and XFG. We hypothesized that if the difference between the WDT results in two consecutive visits is within 4 mmHg for the IOP peaks and 2 mmHg for the IOP fluctuations, the WDT can be accepted as a reproducible test given the normal range of diurnal changes (Wilensky 1991).

Patients and Methods

Consecutive patients with normotensive XFS and medically treated XFG were included. This prospective, observational study was performed according to the tenets of the Declaration of Helsinki. All patients signed a written informed consent agreement approved by an institutional review board before any procedure was performed.

Exfoliation syndrome was defined as the presence of exfoliative material on the lens anterior capsule or the edge of the pupil before or after dilatation during biomicroscopical examination without any sign of glaucomatous optic nerve damage and an IOP elevation above 21 mmHg on two consecutive visits before being enrolled to the study. The patients with exfoliative material with an IOP of 21 mmHg or less under antiglaucomatous therapy (up to three medications) on two consecutive visits prior to the WDT, glaucomatous damage in the optic disc [vertical cup-to-disc (C/D) ratio of >0.5, C/D asymmetry of >0.2 between the eyes, focal notching and localized nerve fibre layer defects] and glaucomatous damage during a visual field examination were diagnosed as having XFG. Visual fields were performed with the Humphrey perimeter (Carl Zeiss Meditec Inc., Dublin, California, USA) using the Swedish Interactive Threshold Algorithm (SITA; Carl Zeiss Meditec, Inc.) strategy and 24–2 program. The glaucomatous visual field was considered when one of the following criteria was fulfilled on two consecutive examinations: a glaucoma hemifield test outside the normal limits; a band of three or more non-edge points approved with a $p < 0.05$ probability of normality, one of which should have $p < 0.01$ and none of which should be contiguous with the blind spot; or a pattern standard deviation value with $p < 0.05$. Visual field results had to be reliable based on false-positive rates ≤25% and false-negative rates and fixation losses ≤33%. One eye of each eligible subject was considered for the study. If both eyes were eligible, the right eye was included for the analysis.

Exclusion criteria were previous incisional ocular surgery, laser trabeculoplasty, any other ocular disease that could affect the visual fields or lead to increased IOP, history of cardiac or renal disease, and any change in the therapeutic regimen between the two WDT periods for XFG patients.

Each patient was evaluated twice, with the two WDTs performed on 30-day intervals at the same time of day by the same investigator and using the same calibrated Goldmann applanation tonometer (CLSI 2004). For the second WDT, the investigator was masked to the results of the first test.

The WDT was performed as follows: patients were asked not to ingest fluids 2 hr prior to the WDT. The IOP was measured before the ingestion of water (baseline IOP) and after drinking 1L of water in less than 5 min. Intraocular pressure (IOP) was measured 15, 30, 45 and 60 min after water ingestion. The average of three measurements with Goldmann applanation tonometry was recorded at each time-point. All measurements were performed between 2 p.m. and 4 p.m.

The IOP peak was defined as the maximum IOP measured during the WDT. Intraocular pressure (IOP) fluctuation was defined as the difference between the IOP peak and baseline IOP.

Statistical analysis

The paired samples *t*-test was used to compare means within each group, while the unpaired samples *t*-test was used to compare differences between groups. Bland–Altman analysis was applied to assess the agreement of the IOP peaks and fluctuations measured between two consecutive visits. Through this analysis method, the coefficient of repeatability, which is two standard deviations (SD) of the differences, was obtained. The level of significance was set at $p < 0.05$.

Results

Sixty-four patients were enrolled in this study. The mean age of all patients was 65.6 ± 10.7 (range 51–86), and 60% were female. Thirty-four eyes of 34 patients had XFS, and 30 eyes of 30 patients had XFG. Central corneal thickness was 542.3 ± 24.6 μm in eyes with XFS and 559.7 ± 32.2 μm in eyes with XFG. In the XFG group, 16 eyes (53.3%) were on monotherapy with prostaglandin analogue [travoprost ($n = 8$); bimatoprost ($n = 4$); latanoprost ($n = 4$)]; nine eyes (30%) were on fixed combination therapy with prostaglandin analogue and beta blocker [travoprost/timolol ($n = 4$); bimatoprost/timolol ($n = 2$)] or carbonic anhydrase inhibitor and beta blocker [dorzolamide/timolol ($n = 3$)]; and five eyes (16.7%) were on combination therapy with prostaglandin analogue–beta blocker and alfa agonist [travoprost/timolol + brimonidine ($n = 2$); bimatoprost/timolol + brimonidine ($n = 1$)] or carbonic anhydrase inhibitor–beta blocker and alfa agonist [dorzolamide/timolol + brimonidine ($n = 2$)].

There were no significant differences in mean IOP values at each time-point between two WDTs for both XFS and XFG (Table 1). Exfoliative glaucoma (XFG) patients had statistically higher IOP peak and fluctuation values than XFS patients in both the first and second visits ($p < 0.001$, for both).

For XFS, the IOP peak did not differ between the two measurements (18.1 ± 2.9 versus 18.0 ± 3.4 mmHg, $p = 0.82$). The coefficient of repeatability was 2.5 mmHg; Figure 1A shows the corresponding Bland–Altman plot. Intraocular pressure (IOP) fluctuation for XFS also did not differ between the first and second test days (3.4 ± 1.2 versus 3.3 ± 1.4 mmHg, $p = 0.50$).

Table 1. Mean intraocular pressure (IOP) measurements at baseline and each time-point following the water-drinking test at each visit for XFS and XFG patients.

		Baseline	15 min	30 min	45 min	60 min
XFS	First visit	16.3 ± 1.9	18.8 ± 2.2	19.7 ± 1.4	18.0 ± 1.9	16.9 ± 1.7
	Second visit	16.5 ± 1.8	19.1 ± 2.0	19.9 ± 2.2	18.8 ± 2.1	17.0 ± 1.9
	p*	0.29	0.32	0.18	0.3	0.28
XFG	First visit	19.7 ± 1.2	24.5 ± 1.9	27.1 ± 1.9	25.6 ± 1.6	23.9 ± 1.4
	Second visit	19.8 ± 1.1	24.7 ± 2.1	27.2 ± 1.7	26.8 ± 1.9	24.3 ± 1.2
	p*	0.60	0.49	0.52	0.28	0.4

XFS = exfoliation syndrome, XFG = exfoliative glaucoma.
* Paired samples *t*-test.

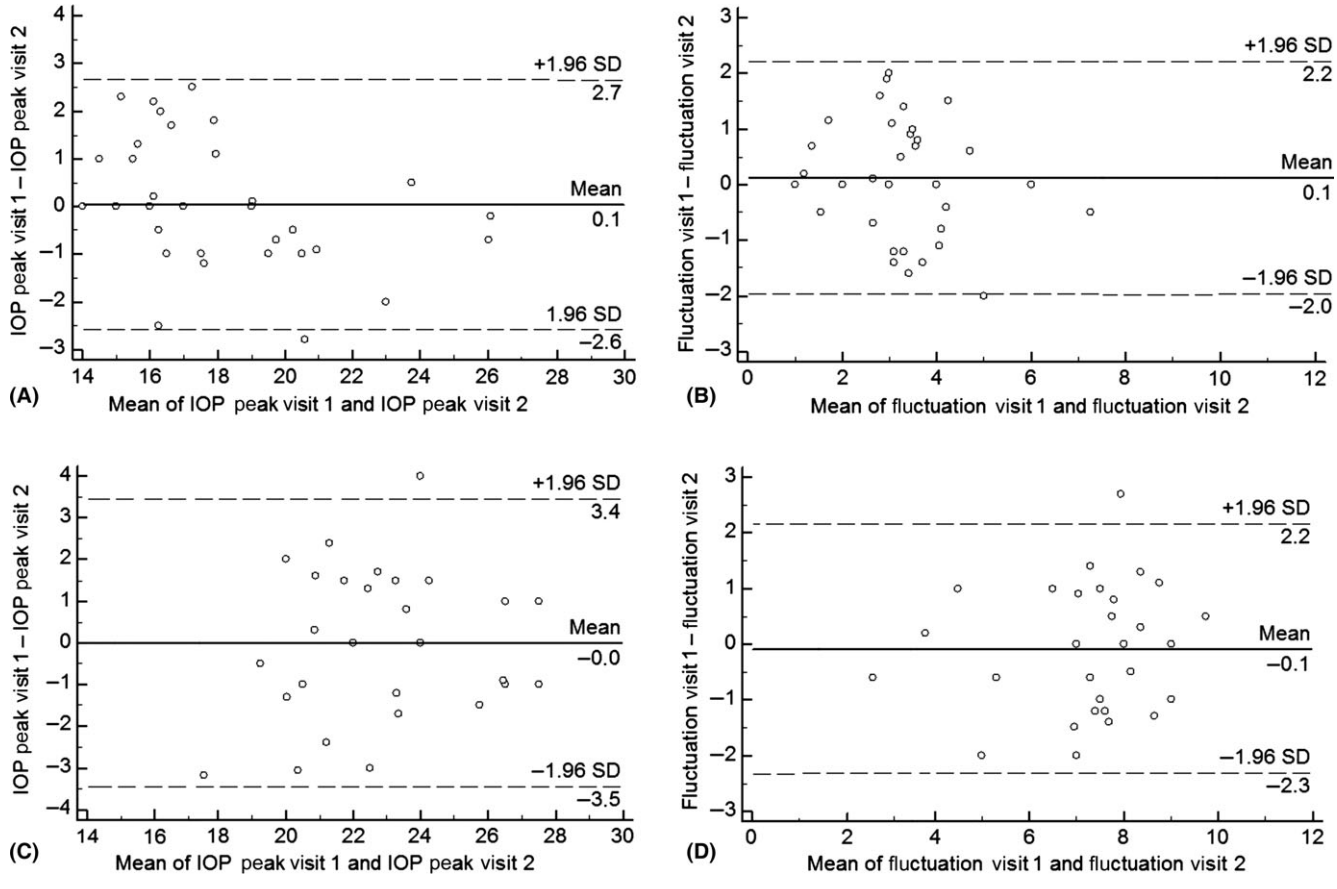

Fig. 1. Bland–Altman plot of intraocular pressure (IOP) peaks (A) and fluctuations (B) in patients with exfoliation syndrome; Bland–Altman plot of IOP peaks (C) and fluctuations (D) in patients with exfoliative glaucoma during the water-drinking test. SD, standard deviation.

The coefficient of repeatability was 2.1 mmHg; Figure 1B shows the corresponding Bland–Altman plot.

For XFG, the IOP peak did not differ between the two measurements (26.9 ± 2.8 versus 27.0 ± 2.5 mmHg, p = 0.54). The coefficient of repeatability was 3.4 mmHg; Figure 1C shows the corresponding Bland–Altman plot. Intraocular pressure (IOP) fluctuation for XFG also did not differ between the two visits (7.2 ± 1.7 versus 7.1 ± 4.0 mmHg, p = 0.42). The coefficient of repeatability was 2.2 mmHg; Figure 1D shows the corresponding Bland–Altman plot.

None of the XFS or XFG patients had an IOP peak difference higher than 4 mmHg. A difference of ≥2.0 mmHg among IOP fluctuation was found in 8.8% of XFS patients and 16.6% of XFG patients.

Discussion

We have tested the hypothesis that the WDT is a reproducible test when IOP peak differences are within 4 mmHg and IOP fluctuation differences are within 2 mmHg between the two WDTs. For both XFS and XFG, the coefficient of repeatability values indicates that IOP peak differences were within the hypothesized limits; however, IOP fluctuation differences were not.

The WDT is utilized as a provocative test to evaluate trabecular outflow capacitance. The mechanism of IOP increase after water ingestion remains unclear. Many mechanisms, such as plasma hypoosmolarity-induced aqueous ultrafiltration, autonomic nervous system stimulation, increased episcleral venous pressure and choroidal expansion have been proposed (Chen et al. 2000; Danesh-Meyer 2008; De Moraes et al. 2009; Goldberg & Clement 2010).

In our study, patients with XFG showed higher IOP peak and IOP fluctuation values compared to XFS patients. The difference in response to the WDT between XFG and XFS patients could be based on impaired outflow in eyes with glaucoma, as the WDT is a surrogate marker for outflow facility. Similarly, higher IOP peak, mean IOP and percentage of IOP fluctuation values were reported in XFG patients compared to XFS patients and controls during the WDT (Mocan et al. 2016). As a result, the WDT results on treated XFG patients may imply the need for more aggressive treatment management when controlling IOP peaks and fluctuations at lower values.

In this study, we included XFG patients under antiglaucomatous medication. Untreated XFG patients could show higher IOP peak and IOP fluctuation levels than treated XFG patients. Recently, Mocan et al. (2016) reported that untreated XFG patients who underwent a WDT had maximum IOP levels between 32 and 54 mmHg. Intraocular pressure (IOP) elevations of this magnitude during the WDT could be detrimental to optic nerve health; this is why we did not include untreated XFG patients in the current study.

In summary, the IOP peaks and fluctuations detected during the WDT

presented good reproducibility in both XFS and XFG. All IOP peak differences and the majority of the fluctuation differences fell within our predefined limits.

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