Intraocular Pressure Fluctuations in Medical versus Surgically Treated Glaucomatous Patients

FELIPE A. MEDEIROS, ALEXANDRE PINHEIRO, FREDERICO C. MOURA, BRUNO C. LEAL, and REMO SUSANNA JR.

Department of Ophthalmology, University of São Paulo, São Paulo, Brazil

ABSTRACT

The purpose of this study was to compare the IOP fluctuations in the daytime tension curves of glaucoma patients under ocular hypotensive therapy with those of patients previously submitted to trabeculectomy. We also evaluated the IOP peaks and fluctuations for the same patients in response to the water-drinking test (WDT).

The study included 30 primary open-angle glaucoma (POAG) patients using ocular hypotensive medications and with no history of previous intraocular surgery (medical group), and 30 POAG patients previously submitted to one or more trabeculectomies though taking no medication at the time of the study (surgical group). All patients were submitted to a diurnal tension curve—DTC (8:30–17:00/3-hour intervals) followed by the WDT.

The IOP peak and IOP fluctuation during the diurnal tension curve were significantly greater in the medical group than in the surgical group. The same was observed following the WDT. From an overall baseline IOP of 10.6 mmHg, the mean IOP change following the WDT was 13% in the surgical group and 40% in the medical group.

Patients submitted to trabeculectomy have less IOP fluctuations during the diurnal tension curve and following a water-drinking provocative test. This effect could represent an additional benefit of surgery in controlling the intraocular pressure of glaucomatous patients.

INTRODUCTION

Primary open-angle glaucoma (POAG) is generally managed by decreasing the intraocular pressure (IOP) to a level that the physician believes will prevent further glaucomatous damage. However, in a significant proportion of patients, the visual fields continue to deteriorate in spite of office pressures within the range of normal values (1–4). It has been suggested that the progressive damage in some cases could be caused by peaks of IOP or diurnal IOP variability not detected by tonometry during office hours (5–7). This has prompted clinicians to monitor the IOP more closely with diurnal tension curves (DTC) or by home tonometry (8–10).
Drance (5) showed that one third of glaucoma patients with apparently well-controlled intraocular pressures during office hours had IOP peaks detected during a 24-h pressure curve. Intraocular pressure peaks and variability during the day have been correlated with visual field progression in several clinical reports. In a prospective study, Bergea et al. (11) suggested that an IOP curve is preferable to single IOP measurements at IOP levels below 24 mmHg in providing information on the impact of IOP regulation upon visual field progression. In another study, Asrani et al. (10) showed that IOP fluctuations are an independent risk factor in patients with glaucoma and as such may need to be treated specifically. It is possible that certain drugs or surgical interventions are more effective than others in dampening these fluctuations. It is important to ascertain whether the treatment provided is adequately reducing mean IOP, peak IOP and fluctuations in a given patient. The best way to assess this is by performing a diurnal tension curve or monitoring the patient with home tonometry.

However, the costs and labor involved in this make the determination of the 24 h IOP course difficult, whether by DTC or home tonometry. Many studies have been aimed at finding some way of predicting the peak diurnal IOP. The water-drinking provocative test (WDT) has been proposed as a practical test to predict the IOP peak of the diurnal tension curve. Previous studies have found a high correlation between the IOP peak in the DTC and in the WDT (12–16). Furthermore, changes in IOP as a response to the water-drinking test have previously been implicated as a risk factor to progressive visual field loss in open-angle glaucoma (17–18). The application of this test for the evaluation of trabeculectomy patency has also been recently reported (19).

The primary purpose of the present study was to compare the intraocular pressure fluctuations in the daytime tension curves of glaucoma patients under ocular hypotensive therapy with those of patients previously submitted to trabeculectomy. As a secondary purpose, we evaluated the intraocular pressure peaks and fluctuations for the same patients in response to the water-drinking test, and correlated these variables to the IOP measurements obtained through the daytime tension curves.

MATERIALS AND METHODS

This study was conducted at the Glaucoma Service, Department of Ophthalmology, University of São Paulo. The study included primary open-angle glaucoma patients using ocular hypotensive medications and with no history of previous intraocular surgery (medical group), and patients previously submitted to one or more trabeculectomies though taking no medication at the time of the study (surgical group). All patients had typical glaucomatous optic disc and visual field defects, as defined by previously published criteria (20). In the medical group, the patients had been on a stable ocular hypotensive medication regimen for at least 1 month and the eye drops were taken normally on the day of examination. Patients with previous history of intraocular surgery other than trabeculectomy were excluded from both groups. In the surgical group, trabeculectomy had been performed at least 3 months prior to inclusion in the study. All trabeculectomies were performed using antimetabolites.

All patients were submitted to a diurnal tension curve which consisted of four IOP measurements at 3-hour intervals (8:00 to 17:00). To be eligible, the mean IOP of the DTC (arithmetic mean of the four measurements) had to be less than or equal to 15 mmHg. After the DTC, the patients were submitted to the water-drinking provocative test. The patients were instructed not to eat or drink during the four-hour period antecedent the test. The test was carried out as follows: the patient was required to drink 1 liter of tap water in 5 minutes. The IOP was measured 3 times at 15-minute intervals. The maximum value of the three measurements was considered as the maximum IOP during the WDT. The IOP fluctuation during the WDT was calculated as the maximum IOP minus the baseline IOP. The baseline IOP was considered as the IOP measured immediately before water ingestion. All IOP measurements were performed with a Goldmann applanation tonometer.

The patients were consecutively selected until we obtained 30 patients in each group matched by mean IOP of the DTC (± 1 mmHg) and by age (± 5 years). When both eyes of a patient were eligible for the study, one of these was randomly assigned for inclusion.
The statistical analyses of the differences between the matched groups in this study were performed with a two-tailed Student’s \( t \) test for age and intraocular pressure values of the diurnal tension curve (mean, peak and fluctuations). An analysis of covariance (ANCOVA) was performed using mean IOP fluctuation after the WDT as response variable, treatment group (medical or surgical) as factor and baseline IOP as covariate. A similar analysis was made with maximum IOP during the WDT as the response variable. Pearson’s linear correlation was used to verify the correlation between intraocular pressure peaks in the DTC and those in the WDT. The difference between the maximum IOP in the DTC and in the WDT in each group was assessed by a paired Student’s \( t \) test.

**RESULTS**

Thirty patients were included in the medical group and 30 patients in the surgical group. The mean age of the patients was 67 ± 12 years and 63 ± 11 years in the medical and surgical groups, respectively (\( P = 0.22 \), Student’s \( t \) test). In the medical group, 5 patients were taking one drug (latanoprost), 8 patients were taking two drugs (latanoprost and timolol); 11 patients were taking three drugs (latanoprost, timolol and dorzolamide) and 6 patients were taking four drugs (latanoprost, timolol, dorzolamide and brimonidine). In the surgical group, 5 patients had trabeculectomy using adjunctive 5-fluorouracil and 25 patients had trabeculectomy using Mitomycin-C.

The mean IOP of the diurnal tension curve was 11.2 ± 1.9 mmHg in the medical group and 10.5 ± 2.3 mmHg in the surgical group. There was no statistically significant difference between the two groups (\( P = 0.20 \)). The IOP fluctuation during the diurnal tension curve was significantly greater in the medical group than in the surgical group \([3.2 ± 1.5 (SD) \text{ vs. } 2.2 ± 1.7 \text{ mmHg}, P = 0.027, \text{ Student’s } t \text{ test}]\). The mean ± SD of the IOP peak of the diurnal tension curve was 12.9 ± 2.2 mmHg and 11.6 ± 2.4 mmHg in the medical and surgical groups, respectively (\( P = 0.04 \), Student’s \( t \) test).

The difference between the mean baseline IOP values of the two groups (defined as the IOP before the water ingestion) was not statistically significant (Table 1). From an overall baseline IOP of 10.6 mmHg, the mean ± standard error of the mean (SEM) of the IOP fluctuation during the WDT was 1.4 ± 0.4 mmHg in the surgical group and 3.7 ± 0.4 mmHg in the medical group. The value of 10.6 mmHg was obtained from analysis of covariance and represents the grand mean value of the covariate (baseline IOP), i.e., the point where the two groups (medical and surgical) are most equivalent with respect to the covariate. Although the mean value of the baseline IOP was not significantly different between the two groups, we have used analysis of covariance (including baseline IOP as a covariate) to provide further adjustment for the possible confounding effect of this variable. The adjusted means of the IOP fluctuation in the WDT were then calculated taking into account the overall baseline IOP. The difference of 2.3 ± 0.5 mmHg was statistically significant in favor of the surgical group (\( P < 0.0001 \), ANCOVA; 95% confidence interval [CI]: 1.3 to 3.3). The mean percentile change

<table>
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<th>Medical group (n = 30)</th>
<th>Surgical group (n = 30)</th>
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<tbody>
<tr>
<td>DTC mean IOP</td>
<td>11.2 ± 1.9</td>
<td>10.5 ± 2.3</td>
<td>0.20</td>
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<tr>
<td>DTC maximum IOP</td>
<td>12.9 ± 2.2</td>
<td>11.6 ± 2.4</td>
<td>0.04</td>
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<tr>
<td>DTC IOP Fluctuation</td>
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<td>0.027</td>
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<tr>
<td>Baseline IOP</td>
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<td>10.2 ± 2.7</td>
<td>0.21</td>
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<tr>
<td>WDT maximum IOP*</td>
<td>14.6 ± 0.4</td>
<td>12.0 ± 0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>WDT IOP change*</td>
<td>3.7 ± 0.4</td>
<td>1.4 ± 0.4</td>
<td>&lt;0.0001</td>
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*calculated from an overall baseline IOP of 10.6 mmHg (analysis of covariance)
in IOP was 13% in the surgical group and 40% in the medical group. Figure 1 shows the scatter-plot of the IOP variation values during the WDT versus the baseline IOP for each patient in both groups. The mean (± SEM) of the maximum IOP during the WDT was 12.0 ± 0.4 mmHg in the surgical group and 14.6 ± 0.4 mmHg in the medically treated patients (P < 0.0001, ANCOVA). Figure 2 shows the scatter-plot of the maximum IOP values during the WDT versus the baseline IOP for each patient in both groups. At each time point after the water ingestion, the mean IOP was significantly
greater in the medical group than in the surgical group (Table 2). There was a statistically significant correlation between the IOP peak in the DTC and the maximum IOP obtained during the water-drinking test, both in the medical group ($r = 0.378$, $P = 0.039$; Pearson’s correlation coefficient) and in the surgical group ($r = 0.733$, $P < 0.001$; Pearson’s correlation coefficient). Figure 3 shows the scatter-plot of the peak IOP values in the diurnal tension curve versus the peak IOP values in the water-drinking provocative test. The maximum IOP values in the water-test and those in the diurnal tension curve were not significantly different in the surgical group (mean ± SD of difference: $0 ± 2.2$ mmHg; $P = 0.935$, paired Student’s $t$ test). In the medically treated patients, the maximum IOP during the WDT was significantly greater than the maximum IOP in the DTC (mean ± SD of difference: $2.1 ± 2.6$ mmHg; $P < 0.001$, paired Student’s $t$ test).

**DISCUSSION**

Previous studies have demonstrated the importance of reduced mean intraocular pressure in halting the progression of glaucomatous damage. However, a lower mean IOP did not uniformly prevent progression, and the importance of peaks and diurnal variation of IOP as risk factors for glaucoma-

![Figure 3](image-url)
tous progression has been well established. Stewart et al. (21) demonstrated that a low variance in IOP over time is important in preserving visual function in advanced glaucoma. Only 1 of 72 patients with advanced glaucoma included in their study with a square root of variance of 4 mmHg or less had lost vision. In another study, the only IOP parameter that correlated with visual field outcome was the magnitude of IOP fluctuation in normal-tension glaucoma eyes (22). Evidence for the importance of pressure variations also comes from a study by Asrani et al. (10) evaluating 64 patients (105 eyes) with home tonometry. The large fluctuations in diurnal IOP were the most important risk factor associated with visual field loss in glaucoma patients, whereas office IOP measurements had no predictive value. Their findings indicate that because the fluctuations of IOP per se are an independent risk factor for glaucoma progression, they may need to be treated specifically. As suggested by the authors, it is possible that certain drugs or treatments are more effective than others in dampening the fluctuations.

The present study demonstrates that patients previously submitted to trabeculectomy showed less variability in terms of the intraocular pressure than patients under ocular hypotensive medical treatment. The smaller IOP variability of the surgical group was observable both in the diurnal tension curve and in the patients’ response to the water-drinking test. Although the water-drinking test has been shown to be a poor diagnostic tool in glaucoma (23), the emphasis on the value of this test has changed. Recently, Brubaker (24) proposed that the WDT could be used as an indirect measurement of outflow facility to compare the intraocular pressure responses of glaucoma eyes to different drugs. The mechanism of IOP elevation after water drinking remains unclear. However, the ability of the eye to recover from a transient rise of intraocular pressure following water ingestion depends on the pressure sensitivity of the aqueous humor outflow, the so-called outflow facility. Low facility of outflow seems to account, at least in part, for the instability and larger circadian rhythm of the IOP in glaucoma patients. A treatment that improves the outflow facility can be expected to show less IOP variation secondary to water challenge as well as a smaller IOP variation during the day. In our work, we showed that at each time point after drinking water, the IOP was significantly greater in the medical group than in the surgical group. In accordance with this, we also showed that the IOP variation during the DTC was greater in the medical group than in the surgical group, with both groups paired by mean intraocular pressure. As the patients in our study were using a variety of medications which may have different actions on the outflow facility, it is possible that some drugs or combinations of drugs may be more effective than others in dampening the fluctuations. This issue needs further investigation.

The change in IOP in response to the water-drinking provocative test has been implicated as a risk factor for progressive visual field loss in glaucoma. In a large prospective study of 5000 patients with open-angle glaucoma, Armaly et al. (18) found five of 26 potential risk factors for glaucoma to be significantly related to the development of glaucomatous visual field defects—outflow facility, age, intraocular pressure, cup-to-disk ratio and pressure change after drinking water. In another study, Yoshikawa et al. (17) evaluated several clinical tests for predicting the progression of visual field loss in NTG patients. They showed that the maximum IOP levels after the WDT in patients with NTG and progressive visual field loss was significantly greater than the levels observed for the non-progressive group. They concluded that the WDT was the most useful clinical predictor of progression of visual field defects in NTG eyes. The transitory variation of IOP caused by ingestion of liquids during meals was also suggested as playing an aggravating role in cases of optic nerve glaucomatous damage (25).

The peaks of intraocular pressure are also associated with visual field progression in glaucoma patients. Zeimer et al. (6) found that 29% of patients with progressive visual field loss had IOP peaks during home tonometry as compared with 5% of patients with stable visual fields. In a prospective study, Martinez-Belló et al. (26) found that the peak intraocular pressure of patients with progressive visual field loss was significantly different from that of stable patients, but were unable to find any difference in mean levels of intraocular pressure between the progressive and non-progressive glaucoma patients. In our study, the maximum IOP in the diurnal tension curve was significantly greater
in the medical group than in the surgical group. The maximum IOP in response to the WDT was also greater among the medically treated patients. There was a significant correlation between the IOP peaks in the DTC and WDT in both groups. Previous studies have also found a significant correlation between these two variables in glaucoma patients (12–16). In trying to explore the relationship of peak tension provoked by the water-drinking test and the peak diurnal tension, the biggest problem is to determine the true diurnal peak tension. One of the shortcomings of our study is that we did not perform a complete 24-h IOP curve. Although most glaucoma patients have their maximum IOP readings in the morning period (7,27), we may have failed to detect the maximum IOP in some cases. In fact, the maximum IOP values in the WDT were significantly greater than in the diurnal tension curve among the medically treated patients. There are studies suggesting that some glaucoma patients under medical treatment have a tendency for higher IOP values at night (28). By performing a 24-h IOP curve and thereby improving the chances for detecting higher intraocular pressures, we could probably have strengthened the relationship between the peak diurnal tension and the peak tension obtained in response to the water-drinking test while lessening the difference between these two variables.

Our findings are in accordance with earlier studies showing a relatively small range of diurnal IOP variation in trabeculectomized patients. Wilensky et al. (29) showed that filtration surgery may have an enhanced effect in reducing the diurnal IOP variation as compared to drugs. Saiz et al. (30) reported the results of a 5-year study of the influence of trabeculectomy on the maximum IOP and amplitude of diurnal IOP fluctuation in 26 eyes of glaucoma patients. Twenty-four hour pressure curves were recorded before surgery and at 1 year and 5 years after surgery. There was a significant reduction of both the maximum IOP and the amplitude of the IOP variation during the day as compared to preoperative values. The authors suggest that the recording of pressure curves after surgery is probably less important for patients with controlled IOP than it is for non-surgical patients.

Several reports have noted that filtration surgery produces a lower IOP than medical treatment and that this is associated with a better long-term visual function. However, the data available in the literature remains insufficient for evaluating whether surgical or medical therapy is more effective in preventing glaucoma progression in patients treated by reducing the IOP to the same level. Stewart et al. (31) studied the visual field outcome of surgical and medically treated patients, matching the groups by age, race and mean intraocular pressure. They were unable to demonstrate any difference between the two groups in terms of long-term visual function, although in their study some patients in the surgical group were also using medications and in these cases the surgery might not have been completely effective. In our study, we paired the patients by mean intraocular pressure while restricting inclusion to patients with a mean IOP of no more than 15 mmHg. The reason for adoption of this criterion was that we were interested in analyzing the IOP peaks and fluctuations of patients with apparently well-controlled mean intraocular pressure. The clinical significance of a higher IOP fluctuation or presence of IOP peaks in a similar scenario is not known. A recent report by the Advanced Glaucoma Intervention Study (AGIS) Group suggested that the mean IOP should be kept in the low teens and IOP peaks maintained below 18 mmHg to prevent further visual field deterioration in patients with moderate to advanced glaucomatous damage (32). In this situation, it would be desirable to have as small an IOP fluctuation as possible. We have demonstrated that surgery is more effective than medical treatment in this regard. However, further studies are required to determine whether the reduction of IOP fluctuation with filtration surgery is more effective in preventing further glaucomatous damage than medical treatment in patients with apparently well-controlled mean intraocular pressures.

The water-drinking test seems to be a useful tool for evaluating the IOP fluctuations and peaks in glaucoma patients, and has provided some insights into how the eye is able to recover from pressure perturbations of the kind which occur in everyday situations. However, further studies are required before any correlation of the results obtained in response to the water-drinking test and through functional measurements in glaucoma patients can be shown.
REFERENCES


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Reprint Requests: Felipe A. Medeiros, M.D.
5350 Toscana Way #E-111
San Diego, CA 92122
E-mail: fmedeiros@uol.com.br
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