Role of Central Corneal Thickness in Circadian Intraocular Pressure Fluctuations among Patients with Primary Open Angle Glaucoma

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ABSTRACT

Objectives: To determine how central corneal thickness in patients with primary open-angle glaucoma correlates with intraocular pressure diurnal fluctuations. This study also verifies the effect of positioning (supine or sitting) on intraocular pressure.

Methods: This study was conducted on a 38 subjects with mild to moderate primary open angle glaucoma were recruited and evaluated for 24 hours in a controlled environment, having their intraocular pressure measured. During the hours of 7:00 AM to 9:00 PM, intraocular pressure was measured in the sitting and supine positions, while in the hours of 11:00 PM to 5:00 AM they were made in the supine position only. Patients were maintained on their normal medication schedules. Baseline information was gathered from clinical charts in addition to a detailed patient history.

Results: The mean circadian intraocular pressure fluctuation was 8.8 (3.2) mmHg ($p<0.0001$). Night time intraocular pressures were on an average 2.3 (2.6) mmHg higher than day time pressures ($p<0.0001$). Daytime supine pressures were significantly higher than sitting by 2.8 (1.1) mmHg, ($p<0.0001$), but daytime supine mean IOP 19.9 (4.0) mmHg was lower than night time supine intraocular pressure of 20.8(4.3), ($p=0.04$). Intraocular pressure fluctuations were greater among patients with thinner central corneas. Inverse relationship was observed between central corneal thickness and daytime supine intraocular pressure flux (Spearman rho= -0.39, $p=0.02$) and between central corneal thickness and night time supine intraocular pressure flux (rho = -0.37, $p=0.02$).

Conclusion: This study has shown that significant fluctuations in intraocular pressure still occur in clinically controlled patients with primary open-angle glaucoma. And that those patients with thinner corneas show greater diurnal intraocular pressure fluctuations than patients with thicker corneas. Furthermore, supine intraocular pressure measurement may provide a more clinically relevant picture in those patients, as compared to sitting pressures.

Key words: Central corneal thickness, Intraocular pressure, Primary open angle glaucoma.

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Introduction

Glaucoma is the second leading cause of blindness worldwide and in the USA in individuals over the age of 50 years and is expected to become a major health issue as individuals live longer.[1]

Primary Open-Angle Glaucoma (POAG), which is the most common type of glaucoma, is considered to be a multifactorial progressive optic neuropathy with an intricate interplay of both ocular and systemic risk factors.[2] Intraocular Pressure (IOP) fluctuations and thin Central Corneal Thickness (CCT) are considered independent risk factors for glaucoma

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progression.[3,4] Wide fluctuations in IOP are recognized to be major factors in the progression of glaucoma.[5] These fluctuations, including diurnal changes of IOP, may be important considerations in managing patients with glaucoma. Elevated IOP and CCT are considered powerful predictors for the development of POAG.

Individuals with thicker corneas have poorer IOP responses to ocular hypotensive medications than those with normal or thin corneas.[6,7] But it is unknown if IOP fluctuations are influenced by CCT.

This study was designed to determine the relationship of CCT to diurnal IOP fluctuations.

Methods

A total of 38 patients from the UT Southwestern James W. Aston Ambulatory Care Center with mild to moderate POAG between the ages of 50 and 80 years were recruited for participation in this study.

Inclusion criteria were: typical glaucomatous optic nerve cupping, corresponding visual field damage (-2 to -12 mean deviation) in the worse eye, open irido-corneal angles by gonioscopy, reliable Humphrey visual field tests (fixation losses less than 20%, false positive and false negative errors less than 30%) and visual acuity of 20/100 or better in the worse eye. Patients with prior glaucoma surgeries were permitted.

Baseline information was gathered from clinic charts and a detailed patient history including patient age, gender, race, systemic medications, systemic illnesses, duration of glaucoma, glaucoma medications, status of optic nerves including cup-to-disc ratio, past ocular surgeries, visual acuity, Humphrey visual field, average of last two IOP (Goldmann Applanation Tonometer, Haag-Streit, Mason, OH) measurements, slit lamp findings, average nerve fiber layer thickness by ocular coherence tomography or Heidelberg retinal tomography, and CCT (Corneo-Gage Plus pachymeter, Sonogage Inc., Cleveland, OH) was also collected.

Patients were admitted two at a time to the General Clinical Research Center located in Parkland Memorial Hospital on Friday evenings.

The patients were provided with nursing supervision and full meals (limited free-water intake of 3000 ml for the 24-hours of data collection and no caffeine or tobacco). They were instructed to take their medications, both ocular and systemic, at their normal at-home schedule.

After calibration according to manufacturer's specifications, IOP measurements were taken during the study using the Mentor Model 30 Classic Pneumotonometer (Mentor O&O, Inc., Norwll, MA). IOP measurements were performed bi-hourly from 7:00 AM on Saturday till 7:00 AM the next day. Three measurements were made each time on each eye and then averaged. The right eye was always measured first. Topical 0.5% proparcaine was used for anesthesia.

During daytime hours of 7:00 AM to 9:00 PM, IOP was measured in the sitting and supine positions. During night time hours of 11:00 PM to 5:00 AM, IOP measurements were made in the supine position only.

The POAG patients were compared with two-sample t-tests for continuous variables and Fischer's Exact test for categorical variables. Comparisons within subjects (e.g., day versus night) were made with paired t-tests. Spearman correlation coefficients were used to assess the association between CCT and IOP circadian fluctuations.

Results are expressed and mean and standard deviation unless otherwise indicated. Statistical analysis was performed using SAS v9.1.3 software (SAS Institute, Cary, NC).

Results

In total, there were 38 subjects in the study. The mean age of all subjects was: 67.7 years (SD±8.9) with 23 (61%) female and 15 (39%) male.

Sixteen subjects (42%) were Caucasian, 14 (37%) were African-American, 5 (13%) were Hispanic, and 3 (8%) were of another ethnicity. Notably, only 54% reported any family history of glaucoma. Thirteen subjects (34%) had previous glaucoma surgery. At baseline IOP was 15.4 (3.9) mmHg and CCT was 547 (26).

IOP measurements during the day and night time periods and in sitting and supine positions are summarized in Table I. The mean circadian IOP fluctuation was 8.88(3.2) mmHg from maximum to minimum ($p<0.0001$, paired t-test). Night time IOPs were an average of 2.14(2.6) mmHg higher than day time pressures ($p<0.0001$). Daytime supine pressures were significantly higher than sitting by 2.8(1.1) mm Hg, ($p<0.0001$).

Daytime supine pressures were significantly lower than night time supine pressures by 0.9(2.5) mm Hg, $p=0.04$. (Fig. 1)

No significant difference was observed between peak daytime IOP, 22.5(4.5) mm Hg and peak night time IOP, 22.6(5.1) mm Hg.

IOP fluctuations were greater in patients with thinner central corneas.

Table I. IOP in 38 subjects with POAG

	24-hr		Day	Night
	Minimum	Maximum		
All readings, mmHg	14.8 (3.4)	23.7 (5.3)	18.5 (3.8)	20.8 (4.3)
Sitting, mmHg	14.9 (3.5)	22.5 (4.5)	17.1 (3.7)	-
Supine, mmHg	17.0 (3.8)	23.5 (5.2)	19.9 (4.0)	20.8 (4.3)

Results are expressed as mean (SD).

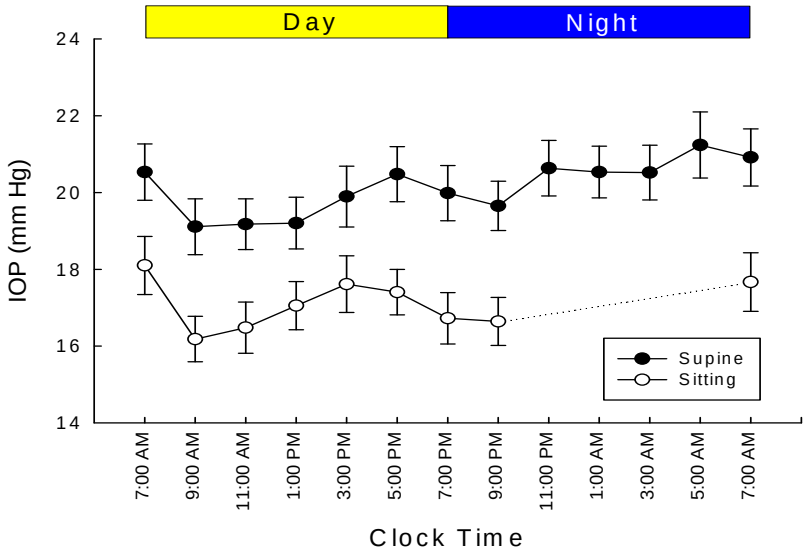

Fig. 1. Circadian intraocular pressure, sitting and supine. A graph displaying the circadian trend in IOPs at bi-hourly intervals. Supine pressures are consistently higher than sitting pressures, which were not taken during sleeping hours (11:00PM – 5:00AM).

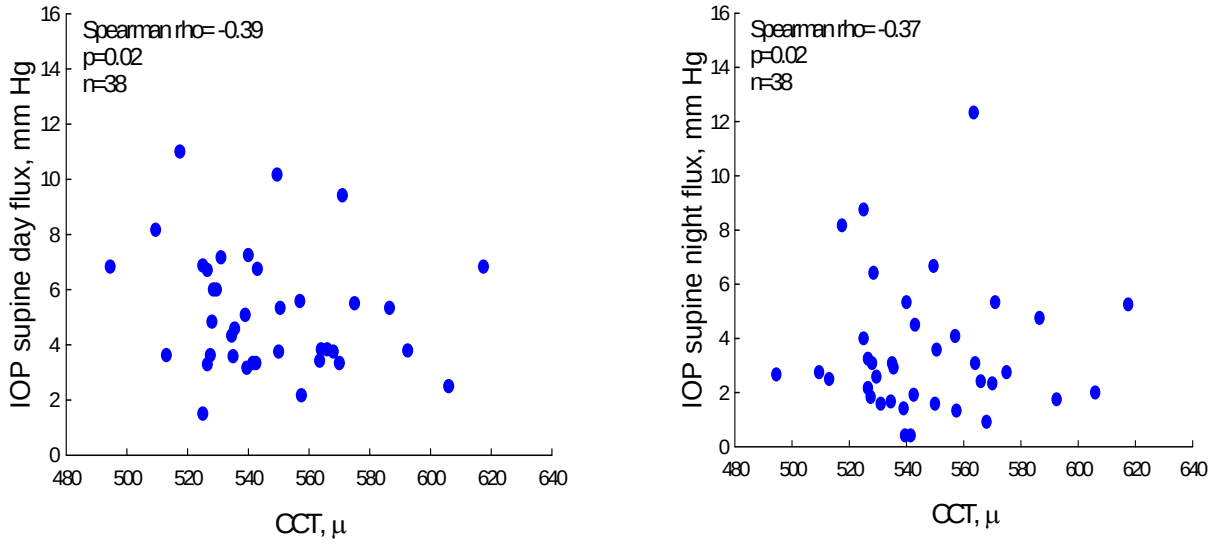

Fig. 2a & 2b. Central corneal thickness vs. day/night IOP fluctuation. A plot of the negative trend between CCT and IOP fluctuation during daytime hours (2a) and night time hours (2b)

Significant inverse association were observed between CCT and daytime supine IOP flux (figure 2a, rho=-0.39, p=0.02) and between CCT and night time supine IOP flux (figure 2b, rho=-0.37, p=0.02).

Discussion

IOP control is the mainstay of clinical glaucoma management.[2] In this well controlled group of patients, significant IOP fluctuations were clearly

evident during day and night. Even though daytime supine values were greater than daytime sitting values, as expected, the maximum supine values between day and night were not significantly different. Thus, maintaining the patient's daytime IOP peak within the target IOP range would give a clinician confidence that the night time peak may not exceed the target IOP.

Notably, the biphasic peak IOPs tended to occur at 5:00 PM and 5:00 AM, outside of typical clinic hours. Considering that daytime and night time peaks are similar, managing the average fluctuation of a patient's daytime IOP would suffice in trying to achieve 24-hour IOP control.

The average diurnal fluctuation of 8.88 mmHg could mean that a single in-office IOP measurement is not enough. An innocuous IOP taken at 9.00 AM office visit could increase beyond the acceptable upper threshold later in the day. Therefore, for optimal care, both the patient's daytime IOP peak and range of IOP fluctuations may need to be assessed.

CCT may play a larger role, directly or indirectly, in IOP fluctuation than previously described.[8-10] Our data shows that CCT may explain up to 15% of the variance in fluctuation between patients with thinner and thicker CCTs. This may explain the importance of CCT in progression of glaucoma. CCT is a simple and non-invasive method to assess risk of progression.

This reinforces the conclusion recently published in a report by the Academy of Ophthalmology,[11] that stated: "measuring CCT is an important component of a complete ocular examination, particularly for patients being evaluated for the risk of developing POAG. Therefore, CCT measurement should be included in the examination of all patients with ocular hypertension. Although the evidence supporting the necessity of measuring CCT as part of screening for POAG or as a risk factor for glaucoma progression is not as strong, IOP is the only modifiable risk factor in the treatment of glaucoma, and CCT has the potential to significantly impact IOP measurement by applanation tonometry in all patients."

Also, a study by Liu *et al.*[12] found that glaucomatous eyes have higher mean diurnal IOP compared with healthy eyes, their diurnal-to-nocturnal change of habitual IOP is smaller, and the posture-independent IOP pattern around normal awakening time is different in eyes with early glaucomatous changes.

These represent a growing body of evidence that CCT plays an important role in diurnal IOP and long-term effects on optic disc damage. Patients with thin CCTs may require a much lower target IOP than previously described.

Conclusion

This study has shown that diurnal IOP fluctuations are common even in clinically controlled patients with glaucoma (8.88 mmHg) of whom patients with POAG and thinner central corneas showed greater diurnal IOP fluctuations. They are at a greater risk of further damage to the optic disc than individuals with thicker CCTs. CCT may be very useful risk factor to consider when creating a target IOP range for adequate control.

The postural influence on IOP is also relevant in clinical practice. Supine pressures, such as those found during nocturnal sleep, are significantly higher than the typical daytime sitting pressure taken during clinic hours.

It is also important, as this study has demonstrated, to assess the peak IOPs in any given patient before calculating the intended target pressure. As daytime peaks mimic night time peak IOP, it may not be as necessary to seek a 24-hour analysis of pressures as long as the daytime peak has been measured.

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