Pressure Related Ocular Parameters in Caucasian Patients with Primary Open-Angle Glaucoma

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Abstract: *Objectives:* To investigate pressure related ocular parameters (intraocular pressure (IOP), estimated trans-lamina cribrosa pressure difference (TLPD) and ocular perfusion pressure (OPP) in Caucasian patients with primary open angle glaucoma (POAG) and control subjects.

Methods: This is an observational cross-section study that included 57 subjects (27 patients with open-angle glaucoma and 30 healthy control subjects). All subjects underwent ophthalmic and systemic measurements in order to evaluate pressure related ocular parameters – IOP (mmHg), OPP (mmHg), and TLPD (mmHg) based on established formulas. The differences in the IOP, OPP and TLPD values between patients with POAG and control subjects were evaluated.

Results: Intraocular pressure and TLPD were significantly higher in patients with glaucoma (mean IOP= 18.93 ± 4.53 mmHg; TLPD= 9.47 ± 5.02 mmHg), than in control subjects (IOP= 16.47 ± 2.60 mmHg; TLPD= 6.82 ± 3.60 mmHg) (p=0.017 and p=0.025 respectively). In univariate logistic progression, IOP and TLPD were significant predictors for POAG.

Conclusion: Our results suggest that in addition to IOP, TLPD is also significantly higher in Caucasian patients with POAG than in control subjects and both parameters are significant predictors of POAG. This suggests that TLPD may have a role in the pathogenesis of POAG.

Keywords: Intra-ocular pressure, Trans-lamina cribrosa pressure, Ocular perfusion pressure, Primary open angle glaucoma.

INTRODUCTION

Increased intraocular pressure (IOP) is considered as the major risk factor for developing primary open-angle glaucoma (POAG). However, glaucoma also affects patients with normal values of IOP (normotensive glaucoma). In addition to the IOP, other factors such as circulatory disturbances and blood pressure alterations were also suggested as possible pathogenic factors in POAG. In that context, ocular perfusion pressure (OPP) has also been suggested as a parameter that can be related to the incidence and progression of POAG [1]. There have been conflicting opinions concerning the effect of OPP on glaucoma [2]. An effect of intracranial pressure (ICP) on POAG has been suggested in previous studies, specifically the trans-lamina cribrosa pressure difference (TLPD) that is the difference between the IOP and the ICP [3].

Several studies reported association between the translaminar pressure difference and POAG [3-7]. It was suggested that rather than the transcorneal pressure difference, the pressure difference between the intraocular compartment and the pressure behind the lamina cribrosa (from the cerebrospinal fluid surrounding the optic nerve) may be more important for neurodegeneration in glaucoma. Increased translaminar pressure difference may affect the optic nerve fibers directly or by exerting pressure to their feeding blood vessels.

Direct measurement of intracranial pressure can be done by a standard lumbar puncture, which is invasive and not feasible for regular use in glaucoma subjects [6]. On the other hand, other indirect methods of intracranial pressure measurement showed variable reliability and may not be very practical for standard

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use [8]. In order to avoid an invasive procedure, an estimated intracranial pressure formula has been created and used to study Indian subjects with glaucoma [7]. Associations of glaucomatous optic neuropathy with the OPP, IOP and TLPD were evaluated and primary open-angle glaucoma was strongly correlated with TLPD, but not with OPP.

In this prospective cross-sectional study we aim to test the differences in OPP, IOP and TLPD between patients with already established POAG and control subjects from Caucasian descent.

METHODS

This is an observational, cross-section and controlled study that included 60 subjects (30 patients with POAG and 30 healthy control subjects). The study adhered to the tenets of The Declaration of Helsinki and the ethical standards of the procedures were approved by the institution where the study was performed (Medika Plus Polyclinic, Skopje, N Macedonia). The study was conducted from June 2019 to December 2019. All included subjects signed a written informed consent.

All included glaucoma patients had established POAG and received topical anti-glaucoma treatment. One eye per subject was included in the study (the right eye unless there was any exclusion criteria). Diagnosis of POAG was established according to the preferred practice pattern of the American Academy of Ophthalmology [9]. Exclusion criteria were: subjects younger than 50 years, intraocular surgical intervention (except for phacoemulsification that had been performed more than 6 months prior to the study), any retinal or neuro-ophthalmic pathology, significant ocular or orbital trauma and spherical equivalent of >6 D. All patients with glaucoma received topical therapy: 11 patients received beta blocker or prostaglandin monotherapy, 11 patients received therapy with beta blocker/prostaglandin and carbonic anhidrase inhibitor and 8 patients received prostaglandin, beta-blocker and a carbonic anhidrase inhibitor. The control subjects consisted of healthy volunteers without history of glaucoma or any other conditions mentioned in the exclusion criteria.

After signing informed consent and obtaining medical history all subjects underwent the following procedures: biomicroscopy, best corrected visual acuity (BCVA) by Snellen chart, intraocular pressure by Goldman applanation tonometer, auto kerato-refraktometry (Potec PRK – 5000, Korea), brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP) (SK Miniatur 300, Germany), weight and height. All measurements were done at a single visit of the patient. Intra cranial pressure (ICP) was calculated by the formula:

$$ICP\ (mmHg) = 0.44 \times BMI\ (kg/m^2) + 0.16 \times DBP\ (mmHg) - 0.18 \times age\ (years) - 1.91 \quad [1]$$

Translaminar pressure difference (TLPD) was calculated by the formula:

$$TLPD\ (mmHg) = IOP\ (mmHg) - ICP\ (mmHg) \quad [2]$$

Mean ocular perfusion pressure was calculated by the formula:

$$OPP\ (mmHg) = (2/3 \times MBP\ (mmHg)) - IOP\ (mmHg) \quad [3]$$

Mean blood pressure (MBP) was calculated by the formula:

$$MBP\ (mmHg) = ((2 \times DBP\ (mmHg)) + SBP\ (mmHg))/3 \quad [4]$$

Statistical Analysis

Data was categorized as categorical and measurement data. It was processed in Microsoft Excel 365 and using the statistical software package R (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics are presented with frequency tables, and mean, percentage and corresponding standard deviation (SD) and standard error (SE) are reported. For the test of difference of means, data was tested for normality and the Levene's test based on mean or median was applied. Based on the results we proceeded with the corresponding test (two sample t-test with equal variances, Welch t-test or Mann Whitney U test). The test for distribution of proportions was applied to categorical data. In the model of logistic regression we used Firth correction. The alpha level of statistical significance is set at 0.05.

RESULTS

A total of 57 subjects were included in the study. Three subjects from the POAG group were excluded (SE>6 D). The demographic and clinical characteristics of patients are presented on Table **1**. Best corrected visual acuity was significantly lower in patients with glaucoma than in control subjects (p=0.027). The other demographic and clinical characteristics of subjects did not differ significantly among the two groups.

Table 1: Demographic and Clinical Characteristics of Patients with POAG and Control Subjects

	POAG Group, n=27	Non Glaucoma Group, n=30	p Value
Age (years)	73.67 ± 7.98	69.58 ± 8.30	0.64 [a]
Sex	15 (55.6% female)	16 (53.3% female)	0.87 [c]
BMI (kg)	26.94 ± 5.31	25.65 ± 4.52	0.267 [d]
Systolic blood pressure (mm Hg)	132.04 ± 14.29	128.17 ± 16.05	0.270 [d]
Diastolic blood pressure (mm Hg)	79.85 ± 9.33	80 ± 8.30	0.522 [d]
Cerebrospinal pressure (mm Hg)	9.46 ± 2.96	9.65 ± 3.15	0.815 [a]
Best corrected visual acuity	0.72 ± 0.32	0.90 ± 0.19	0.027 [b]
Refractive error (D)	0.57 ± 2.09, n=25	0.51 ± 1.84	0.908 [a]
Mean keratometry (D)	43.75 ± 2.96, n=26	44.12 ± 1.94	0.448 [a]

[a] - two sample t-test with equal variances; [b] - Welch t-test; [c] – Chi Square test of independence; [d] – Mann Whittney U test.

The perfusion parameters – IOP, OPP and TLPD are presented on Table **2**. Intraocular pressure and TLPD were significantly higher in patients with glaucoma, than in control subjects (p=0.017 and p=0.025 respectively).

The univariate logistic regression analysis indicated that IOP (regression coefficient=0.183, OR=1.201, p=0.015) and TLPD (regression coefficient=0.140, OR=1.150, p=0.027) are significant predictors for POAG, but OPP was not (regression coefficient=-0.031, OR=0.969, p=0.392). (Table **3**).

DISCUSSION

In this current study IOP and TLPD of patients with open-angle glaucoma were significantly higher than in control subjects. In univariate analysis, both IOP and TLPD were significant predictors of glaucoma. OPP values did not differ between the two groups and OPP was not a significant predictor for glaucoma.

The results from this study confirm previous reports that TLPD is increased in patients with open angle glaucoma [3]. In previous studies TLPD has been calculated using measurements of intracranial pressure that were obtained with invasive and non-invasive methods. Invasive methods (lumbar puncture) are not ethical and feasible for routine use in patients with glaucoma. On the other hand, non-invasive methods (such as transcranial Doppler ultrasound, ophthalmodynamometry, MRI, tympanometry) had other limitations such as not being applicable for every patient or having low sensitivity. A formula for

Table 2: Differences in Pressure Related Parameters between Patients with POAG and Control Subjects

	POAG Group, n=27	Non Glaucoma Group, n=30	p Value
Ocular perfusion pressure (mmHg)	45.59 ± 7.35	47.57 ± 6.77	0.383 [a]
Intra-ocular pressure (mmHg)	18.93 ± 4.53	16.47 ± 2.60	0.017 [b]
Trans-lamina pressure difference (mm Hg)	9.47 ± 5.02	6.82 ± 3.60	0.025 [a]

[a] - two sample t-test with equal variances; [b] - Welch t-test.

Table 3: Association (Univariate Analysis) of Prevalence of Glaucoma with IOP, OPP and Translaminar Pressure Difference

	Regression Coefficient	p Value	OR	95% CI for OR left and Right	Cox & Snell R^2	Nagelkerke R^2
Intraocular pressure	0.183	0.015 [e]	1.201	(1.034, 1.439)	0.016	0.023
Ocular perfusion pressure	-0.031	0.392 [e]	0.969	(0.897, 1.041)	0.051	0.071
Trans lamina pressure difference	0.140	0.027 [e]	1.150	(1.015, 1.335)	0.083	0.116

[e] – logistic regression with Firth correction.

estimation of ICP based on body mass index and blood pressure was reported that highly correlated with measured lumbar cerebrospinal fluid pressure and was therefore used in order to estimate ICP in patients with glaucoma, myopia, diabetic retinopathy and retinal vein occlusions [4, 10-12]. In Indian patients with open angle glaucoma that were evaluated for intracranial pressure using this formula, higher IOP and TLPD were significantly associated with POAG [7]. Ocular perfusion pressure was not significantly associated with glaucoma [7]. This formula was also applied in the current study in order to test whether Caucasian patients with POAG differ in IOP, TLPD and OPP from control subjects. Although the mean age of our patient groups is higher than the one reported in Indian subjects, our results also suggest that IOP and TLPD are higher in patients with POAG than in control subjects. A similar study using the same formula in Caucasian patients has been recently reported [13]. Authors did not find significant difference in IOP and TLPD in their study, however, the patient and control groups significantly differed in age and refractive error both of which can affect ICP [10, 14]. Intracranial pressure decreases with age [13] that may cause TLPD to increase in older population [15]. This may be one of the factors for the increased risk of glaucoma with advanced age.

Decreased OPP has also been regarded as a risk factor for open-angle glaucoma. However, the calculated formula for OPP may not always represent the true OPP. Moreover, one study found that the majority of the reports on mean OPP used an incorrect formula [2]. The authors concluded that considerable heterogeneity existed in pressure related variables in glaucoma reports that can lead to disparities in various studies. In this current study, we used the formulas for mean arterial pressure and OPP suggested by Barbosa-Breda, *et al*. [2] that was also applied in the study that reported a formula based estimation of ICP [7]. In the current study there was not a significant difference in OPP between patients with open-angle glaucoma and control subjects. This result also confirms the report from the study of Indian patients with glaucoma [7], however differs from previous studies that found OPP to be significantly lower in patients with POAG than in control subjects [1]. The differences in OPP calculations, study design and inclusion criteria may be reasons for the discrepancy of the results.

Increased TLPD in glaucoma may have implications for the future care of patients, especially those with normal tension glaucoma or patients with good control of IOP who continue to have progression. Should we then implement this parameter in the protocol for evaluation of glaucoma? If yes, which method of ICP measurement would be most appropriate? In this study we aimed at evaluating TLPD using a formula based on estimation of intracranial pressure, which may be the most feasible method for a busy outpatient. The results from the current study are similar to those obtained by invasive and non-invasive evaluation of ICP [3], as well as from the study of patients with open-angle glaucoma in Indian patients that used a formula based estimation of ICP [7]. This suggests that the formula based estimation may be applicable for glaucoma management. In our study there was no significant difference in ICP between the groups, implying that the TLPD difference may occur only as a result of IOP difference, but this conclusion would be incorrect because the ICP values had considerable variations in each study group.

Regarding the limitations, as a preliminary pilot study, we did not include a large number of subjects. The study is observational and cross-sectional involving already established glaucoma patients, all of them receiving anti-glaucoma topical therapy. Therefore, we did not obtain all the parameters evaluated in glaucoma patients (such as visual field, optic nerve head evaluation of neuroretinal rim, cup area, retinal nerve fiber layer, etc.) at the time of their examination. We did not include central corneal thickness measurements because available formulae to correct IOP measurements for central corneal thickness were reported not to improve accuracy of the prediction model for the development of POAG [16]. Furthermore, the values of IOP corrected for central corneal thickness values did not differ from the uncorrected IOP values in patients with POAG that were evaluated for TLPD [7]. Also, racial differences in the ocular structure and function have been reported and the formula for estimating ICP may need adjustment for Caucasians. Regarding the fluctuations of BP and IOP, obtaining mean data may best be achieved by in-patient continuous IOP measurement or by using contact lens sensor and home-monitoring device for IOP measurement [17, 18], as well as holter BP monitors. However, in-patient monitoring of IOP was not feasible and continuous IOP monitoring devices have yet to be developed for their accuracy [18].

In conclusion, the results from this study suggest that in addition to IOP, TLPD is also higher in

Caucasian patients with POAG than in control subjects. TLPD was also a significant predictor of POAG. These results suggests a possible involvement of TLPD in the pathogenesis of POAG. Future longitudinal studies involving larger patient groups are necessary to establish the effect of TLPD on incidence and progression of POAG.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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