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ORIGINAL ARTICLE

A comparative study of ocular blood flow in untreated patients of primary open-angle glaucoma, normal-tension glaucoma, and ocular hypertension

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Abstract

Background: Primary open-angle glaucoma (POAG) is characterized by a multifactorial optic neuropathy. Existence of normal-tension glaucoma (NTG) and ocular hypertension treatment (OHT) indicates that other factors must also be involved in their pathogenesis beyond intraocular pressure (IOP). An ocular blood flow (OBF) study can provide information about vascular resistance which can provide useful information in patients progressing despite an adequate IOP control. Our study compared OBF characteristics between treatment-naïve patients of POAG, NTG, and OHT.

Methods: Forty-five POAG, NTG, and OHT patients (15 in each group) were subjected to ophthalmic and glaucoma evaluation followed by color Doppler imaging of bilateral ophthalmic arteries. The outcome variables were peak systolic velocity, end diastolic velocity, and resistivity index.

Results: Mean peak systolic velocity (PSV) (cm/s ± SD) of NTG, OHT, and POAG groups were 28.05 ± 8.99, 36.06 ± 11.82, and 26.26 ± 9.46 cm/s, respectively, and mean end diastolic velocity (EDV) (cm/s ± SD) were 5.74 ± 1.21, 9.66 ± 4.38, and 7.24 ± 2.75 cm/s, respectively. Mean resistivity index (RI) (RI ± SD) of NTG, OHT, and POAG groups were 0.77 ± 0.06, 0.72 ± 0.09, and 0.71 ± 0.06, respectively. PSV and EDV of OHT were statistically significantly higher than in NTG and POAG. RI of NTG group was statistically significantly higher than in OHT and POAG. High RI implies an increased peripheral resistance to flow.

Conclusion: OBF was significantly reduced in patients with NTG and POAG which may play a role in disease progression. OBF and patient's hemodynamic status should be considered in glaucoma management especially when the disease is progressing inspite adequate IOP control.

Introduction

Primary open-angle glaucoma (POAG) is characterized by a multifactorial optic neuropathy with a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons, developing in the presence of open anterior chamber angles, and manifesting with characteristic visual field defects.[1,2] It is estimated that worldwide, there are more than 80 million cases of glaucoma and this will increase to almost 110 million by year 2040.[3,4]

The ocular hypertension treatment study has provided the best evidence to suggest that intraocular pressure (IOP) is an independent risk factor for glaucoma development.[5] A landmark study demonstrated that patients with higher baseline IOP had increased risk of glaucoma progression.[6] IOP is currently the only modifiable risk factor to prevent glaucoma progression. Two principal theories have been described which explains the pathogenesis of glaucomatous optic neuropathy (GON) – a mechanical theory and a vascular theory. Mechanical theory suggests that retinal

ganglion cell loss occurs as a result of direct axonal damage secondary to elevated IOP. The vascular theory of glaucoma considers GON as a sequel of insufficient blood supply secondary to either increased IOP or other risk factors which may directly or indirectly reduce ocular blood flow (OBF).

Blood supply to the optic nerve head (ONH) is very unique. The superficial layer of the ONH is supplied mainly by small branches of the central retinal artery. The prelaminar region, a small area anterior to the laminar cribrosa, and laminar region of ONH are mainly supplied by branches from recurrent choroid arterioles and short posterior ciliary arteries which often form a complete or incomplete vascular ring around the ONH. Venous drainage of the ONH occurs through the central retinal vein. The ONH seems to be the only part of the central nervous system which has no proper blood–brain barrier, with the capillaries lacking blood–brain barrier properties.[7] The retina is supplied by central retinal artery, an end branch of the ophthalmic artery (OA). Retinal circulation is characterized by a low level of flow and high level of oxygen extraction. Circulation is autoregulated, meaning that the flow is independent of perfusion pressure within a certain range.[8] In contrast, the choroidal circulation is characterized by relatively high flow and low oxygen extraction. Poor autoregulation renders choroidal blood flow more dependent on perfusion pressure.[9] The existence of normal-tension glaucoma (NTG) on one hand and ocular hypertension (increased IOP without glaucomatous damage, ocular hypertension treatment [OHT]) on the other, indicates that other factors must also be involved in the pathogenesis of GON which may render the eye more sensitive to IOP. Some patients show progression of glaucomatous damage despite maintaining IOP at target levels. All these observations cannot be satisfactorily explained by the pressure theory alone, indicating that increased IOP, although clearly sufficient, is not necessary for the development of GON.[10]

OBF is highly regulated to adapt to changing metabolic needs of the retina, to compensate for changing perfusion pressures, and also to keep the temperature at the back of the eye constant.[11] Various methods to evaluate OBF include color Doppler imaging (CDI), scanning laser Doppler flowmetry, retinal vessel analyzer, laser speckle flowgraphy, digital scanning laser ophthalmoscope angiography, and retinal oximetry. During CDI of the eye, a desired blood vessel is selected by the operator using anatomical location. Quantification of blood flow velocities is done by calculating Doppler shift between the frequencies of sound waves striking moving reflective sources.[12] The peak and trough of the velocity waveform are then identified by the computer. Most commonly, CDI is used to measure blood flow parameters of retrobulbar vessels, namely, OA, central retinal artery, and short posterior ciliary arteries. Various scanners and transducers (5–14 MHz) can be used depending on tissue depth desired. CDI studies provide information about the vascular resistance offered by these vessels which can provide useful information in patients who show visual field progression despite adequate IOP control. Important parameters are the end diastolic velocity (EDV), peak systolic velocity (PSV) and a calculated (PSV-EDV/PSV) vascular resistivity index originally described by Pourcelot.[13] Various IOP lowering agents are known to alter the blood flow to the optic nerve and choroid which has been demonstrated using OBF studies.[14] Various studies have measured the vascular resistance in POAG patients, but there is lack of data in untreated patients of glaucoma which reflects the baseline or untreated state of OBF.[15-17]

Our study aims to compare OBF characteristics between newly diagnosed patients of primary open-angle glaucoma, normal-tension glaucoma, and ocular hypertension.

Methods

In this prospective observational study, 45 newly diagnosed POAG, NTG, and OHT patients, aged more than 18 years, visiting the glaucoma clinic of a tertiary eye care center were selected. The Institutional Ethical Committee approval was obtained before data collection. There were 15 patients in each of the three study groups: POAG, NTG, and OHT. The duration of the study was from December 2018 to June 2020.

The exclusion criteria were patients with previous history of any medical treatment or surgical intervention for glaucoma, angle-closure disease, congenital or juvenile glaucoma, secondary glaucoma, patients known to have any systemic disease likely to influence the hemodynamics, for example, hypertension and cardiac disease, concomitant use of any medications likely to have an influence on the cardiovascular function, hemodynamics or blood circulation, and patients who were unwilling to participate.

Written informed consent was obtained from the patients. Best-corrected visual acuity using Snellen's chart, anterior segment examination using slit lamp, IOP measurement using Goldman applanation tonometer, gonioscopy using Goldmann 4 mirror gonioprism, dilated stereoscopic fundus examination using +90 D lens, visual field assessment using octopus 900 visual field analyzer, central corneal thickness measurement using ultrasonic pachymeter, and diurnal variation of IOP if required (8 am. to 8 pm. using Goldman applanation tonometer) were done for all the patients.

Finally, color Doppler imaging of bilateral ophthalmic arteries was performed on ultrasound machine (Philips HD 15, USA) by a single experienced sonographer who was unaware of the subject's clinical status. High-frequency linear probe of 7.5 MHz was used. All examinations were carried out in the supine position with eyes closed. Blood flow in the retro bulbar orbit was detected by production of color pixels on visual display unit. In general, optic nerve was identified using a B-scan, which is an important landmark for the detection of OA. The outcome variables of the OBF study were the basic hemodynamic parameters: peak systolic velocity (PSV), which is the highest velocity of blood flow during the systolic phase of cardiac cycle, EDV, which is the velocity of blood flow at the end of diastolic

phase of cardiac cycle, and resistivity index (RI), which is derived as PSV-EDV/PSV.

The results were entered into Microsoft Excel sheet for further analysis. Kruskal–Wallis test was used for statistical analysis of data wherever applicable. Tables and graphs were used to present findings of the study.

Results

A total of 90 eyes of 45 patients were enrolled in the study, 30 eyes belonging to each of three study groups – POAG, OHT, and NTG. Baseline data of the patients are shown in Table 1.

All the parameters for the three groups are shown in Table 2.

Mean PSV (cm/s ± SD) of NTG, OHT, and POAG groups were 28.05 ± 8.99, 36.06 ± 11.82, and 26.26 ± 9.46 cm/s, respectively. PSV of OHT was statistically significantly higher than NTG group and POAG groups ($P = 0.00127$) [Figure 1].

Mean EDV (cm/s ± SD) of NTG, OHT, and POAG groups were 5.74 ± 1.21, 9.66 ± 4.38, and 7.24 ± 2.75 cm/s, respectively. EDV of NTG group and POAG group was statistically significantly lower than OHT group ($P = 0.00234$) [Figure 2].

Value of RI does not depend on Doppler angle as compared to PSV and EDV; this is because RI is a ratio, and therefore, its absolute value can be used to compare the results among studies as the values remain constant irrespective of Doppler angle change. High RI implies an increased peripheral resistance to flow causing direct impedance to blood flow in the retinal circulation. Mean RI (RI ± SD) of NTG, OHT, and POAG groups were 0.77 ± 0.06, 0.72 ± 0.09, and 0.71 ± 0.06, respectively. RI of NTG group was found to be statistically significantly higher than OHT and POAG group ($P = 0.00281$) [Figure 3].

Discussion

Localized organic changes in the blood vessels of the nerve with or without a low perfusion pressure causing a primary problem in the optic nerve circulation are one of the likely mechanisms implicated in the pathogenesis of glaucomatous damage. The OA, central retinal artery, and the short posterior ciliary artery are important vessels in influencing the pathogenesis of GON. Doppler velocimetry is a reproducible technique for evaluation of ocular vessels. Different studies using different types of instruments point indicate that on average, blood flow is decreased in some glaucoma patients, especially in NTG patients and in patients that progress despite normalized IOP. Furthermore, this decrease in blood flow, although related to the extent of damage, can precede GON and is not confined to the eye alone. This indicates that at least, one component of the blood flow reduction in glaucoma is of primary nature.

A study was done on indigenous African population which proved that OBF varied significantly between eyes with glaucoma and normal eyes.[16]

Significantly slower mean blood flow velocities (e.g., PSV and EDV) were recorded in the OA and CRA of POAG patients as compared with the control group in this study. This finding was similar to a previous report which reported slower mean PSV and EDV of the OA in comparison with that in the control group in the same Asian population. They reported mean PSV of 43.86 ± 1.32 cm/s and EDV of 11.92 ± 0.44 cm/s in the control group as compared to PSV of 39.04 ± 1.00 cm/s and EDV of 10.25 ± 0.33 cm/s, in glaucoma cases. Similarly, slower OA as well as central retinal artery PSV and EDV have been reported by different studies.[18] Another study done in Egypt showed higher PSV values in glaucoma patients as compared to control population.[19]

The increases in RI in both OA and CRA in glaucoma patients as compared to the control group have been reported previously. Value of RI does not depend on Doppler angle as compared to PSV and EDV; this is because RI is a ratio and therefore its absolute value can be used to compare the results among studies as the values remain constant irrespective of Doppler angle change. High RI implies an increased peripheral resistance to flow in causing direct impedance to blood flow in the retinal circulation. A study showed increased RI seen in the CRA in glaucoma patients and suggested that it may have been caused by longstanding raised IOP that caused direct impedance to blood flow in the retinal circulation.[20]

Another independent study showed that the alteration in OBF noted, that is reduction in PSV and EDV as well as increase in RI of the OA and CRA in POAG in the tropical African population, was similar to previous reports in other Caucasian and Asian populations.[21] Baseline OBF values in POAG patient may be useful in determining the severity of damage as well as monitor disease progress in addition to visual field analysis.

Table 1: Baseline demographic and ocular data of the patients

Doppler parameter	NTG	OHT	POAG
Age (years±SD)	55.93±7.06	55.73±11.2	55.93±6.04
BCVA (LogMAR±SD)	0.67±0.83	0.26±0.25	0.53±0.83
IOP (mm Hg±SD)	12.96±2.12	16.6±5.2	16±3.95
VCDR (± SD)	0.79±0.12	0.43±0.12	0.75±0.13
Central corneal thickness (microns mean±SD)	514±24.19	533.26±36.74	529.33±17.91
Diurnal variation test (mm Hg mean±SD)	3.86±1.35	7.4±2.25	6.9±2.03

NTG: Normal-tension glaucoma, OHT: Ocular hypertension treatment, POAG: Primary open-angle glaucoma

In our study, NTG group had the lowest mean EDV while OHT group had the highest PSV and EDV values. Mean RI was highest of 0.77 in NTG group, followed by 0.72 and 0.71 in OHT and POAG groups, respectively. This data suggests that NTG is more associated with decreased OBF, followed by POAG and OHT. The EDV values in NTG and POAG patients are significantly lower than the mean EDV value in normal population (7.95 cm/s).[14] Lower EDV values suggest sluggish OBF in these patients which may probably be the reason for the progression of optic neuropathy. The mechanisms underlying the abnormal OBF in NTG remain unclear, but oxidative stress, vasospasm, and endothelial dysfunction appear to be the likely risk factors.[22] Current evidence[23] suggests that a major risk factor is a general vascular dysregulation called vasospastic syndrome which leads to low blood pressure and thus low perfusion pressure on one hand and disturbed autoregulation and an inability to adapt to increased IOP or decreased blood pressure on the other. This results in unstable ocular perfusion.

A study done by Kaiser *et al*. suggested that in OAG patients, an increase in perfusion pressure is paralleled by an increase in PSV and EDV of the OA and central retinal artery.[15] Another study suggested that in OAG patients, there is only a little autoregulation in posterior ciliary arteries in response to perfusion pressure as compared to the retinal vasculature making the optic nerve vulnerable to IOP and blood pressure fluctuations.[11] Significantly slower mean blood flow velocities (e.g., PSV and EDV) were recorded in the OA and central retinal artery of POAG patients as compared with the control group in a study done by Buhrmann RR.[16] Another independent study showed alterations in OBF through reduction in PSV and EDV as well as increase in RI of the OA and CRA in POAG in the tropical African population, which was similar to previous reports in other Caucasian and Asian populations.[17]

Therefore, only lowering the IOP for the treatment of glaucoma may not be enough; the therapeutic strategy should also include optic neuroprotection in which improving OBF should be critical. In addition to OBF improvement, glaucoma patients with altered OBF should also undergo further hemodynamic evaluation including 24 h blood pressure monitoring, electrocardiography, and a thorough cardiovascular evaluation to uncover underlying hemodynamic disorders or to modify the treatments for their established vascular diseases.

Our study did have some limitations like a limited sample size and patients who did not provide a history of systemic

Table 2: Doppler parameters for the three patient groups

Doppler parameter	OHT	NTG	POAG
Peak systolic velocity (PSV) (cm/s)			
10–20	2	10	3
20–30	8	12	17
30–40	13	5	8
40–50	3	3	1
50–60	4	0	1
End diastolic velocity (EDV) (cm/s)			
2.5–5.0	5	9	6
5.1–7.5	7	21	12
7.6–10.0	7	0	8
10.1–12.50	1	0	3
12.6–15.0	6	0	1
15.1–20.0	3	0	0
Resistive index (RI)			
0.50–0.59	2	2	1
0.60–0.69	8	15	7
0.70–0.79	11	12	18
0.80–0.90	9	1	4

NTG: Normal-tension glaucoma, OHT: Ocular hypertension treatment, POAG: Primary open-angle glaucoma

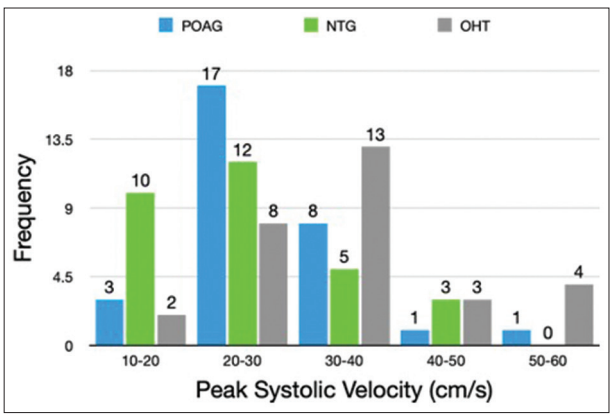

Figure 1: Comparison of peak systolic velocity among primary open-angle glaucoma, normal-tension glaucoma, and ocular hypertension treatment patient groups

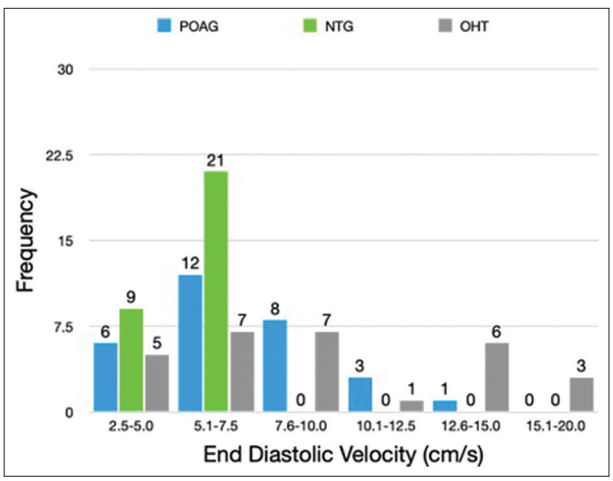

Figure 2: Comparison of end diastolic velocity among primary open-angle glaucoma, normal-tension glaucoma, and ocular hypertension treatment patient groups

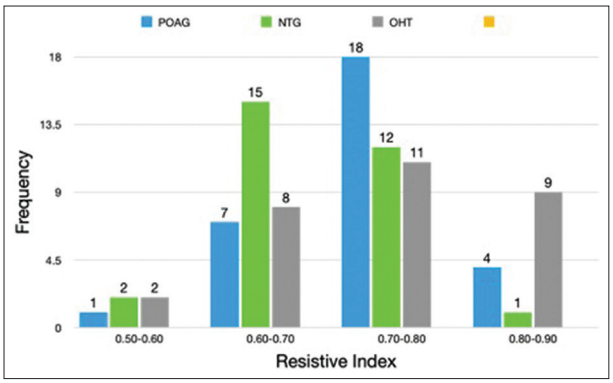

Figure 3: Comparison of resistive index among primary open-angle glaucoma, normal-tension glaucoma, and ocular hypertension treatment patient group

illness were not specifically investigated to rule out those diseases but since we included only treatment-naive patients we could eliminate any anti-glaucoma drugs induced alterations in the OBF, thereby providing the true hemodynamic data of different types of glaucoma. Our study compared the resistive index (RI) between study groups eliminating measurement bias. Assessment and correlation of underlying hemodynamic abnormalities by measuring 24 h blood pressure monitoring and electrocardiography with the clinical progression can be done in future studies.

Conclusion

At present, the accepted form of treatment for glaucoma remains IOP reduction. Despite evidence of a vascular component in glaucoma for decades, additional treatment of blood flow in glaucoma is only just starting to be accepted as a possibility. The result is that new treatment options are now being investigated which include improving ocular perfusion dynamics, influencing vascular dysregulation, or protecting neural cells directly. By virtue of the growing body of evidence supporting the role of ocular hemodynamics in glaucoma, it would be desirable to study OBF in glaucoma patients. Our study could conclude that OBF was significantly reduced in patients with NTG and POAG which may have its own role in progression of GON independent of IOP. The OBF and patient's hemodynamic status should be considered in overall management of a glaucoma patient especially when the disease is progressing in spite of seemingly adequate IOP control.

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