A COMPARATIVE STUDY OF OCULAR BLOOD FLOW PARAMETERS IN POAG, PACG AND CONTROLS IN A TERTIARY CARE EYE CENTRE

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ABSTRACT

AIM

To measure ocular blood flow (OBF) in glaucoma patients using Color Doppler Imaging (CDI) and to compare theOBFparameters with age- matched controls.

METHOD

17 patients (34 eyes) with Primary open angle glaucoma (POAG), 14 patients (20 eyes) with Primary angle closure glaucoma(PACG) and 17 (34 eyes) controls were recruited. Peak systolic velocities (PSVs), end diastolic velocities (EDVs) and resistive indices (RIs) for the ophthalmic artery (OA), the central retinal artery (CRA) and the short posterior ciliary arteries (SPCAs) were measured using CDI.

RESULT

Mean age, mean Intraocular pressure (IOP), mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP) were comparable among the groups ($p<0.05$). In OA, mean PSVs (in cm/s) were 22.81 ± 6.89, 23.72 ± 3.31, 25.83 ± 2.59; mean EDVs (cm/s) were 6.03 ± 2.72 ,7.87 ± 1.35 ,10.90 ± 1.88 and mean RIs were 0.73 ± 0.07, 0.66 ± 0.04, $0.58\ \pm0.06$ in POAG, PACG and Controls respectively. The difference in mean PSVs, mean EDVs and mean RIs was statistically significant between POAG vs controls ($p<0.05$) and between PACG vs controls but insignificant between POAG vs PACG.

In CRA, mean PSVs (cm/s) were 11.12 ± 3.10, 9.27 ± 2.35, 12.87 ± 2.52; Mean EDVs (cm/s) were 3.33 ± 1.18, 2.993 ± 0.95, 5.75 ± 0.88 and Mean RIs were 0.69 ± 0.08, 0.68 ± 0.04, and 0.53 ± 0.05 in POAG, PACG and controls, respectively. The difference in mean PSVs, mean EDVs and mean RIs was statistically significant between POAG vs controls and PACG vs controls. The difference was statistically insignificant when same parameters were compared between POAG vs PACG.

In SPCAs, mean PSVs (cm/s) were 9.85 ± 2.73, 9.58 ± 1.85, 11.61 ± 2.76; mean EDVs were 3.05 ± 1.26, 4.21 ± 1.26, 6.59 ± 1.93 and mean RIs were 0.70 ± 0.07, 0.56 ± 0.08, 0.41 ± 0.14 in POAG, PACG and controls respectively. The difference in mean PSVs, mean EDVs and mean RIs was statistically significant between POAG vs controls and between PACG vs controls.

CONCLUSION

Both POAG and PACG wereconsistently associated with decreased blood flow velocities andincreased RIs in retrobulbar vessels. This association is more prominently seen in POAG as compared to PACG.

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Key words:

Ocular blood flow, color Doppler imaging, peak systolic velocity, end diastolic velocity

INTRODUCTION

Glaucoma is the leading cause of irreversible blindness affecting more than 60 million people worldwide.[1]

It is a progressive optic neuropathyinvolving characteristic structural changes of theoptic nerve and characteristic visual field defects.[2]Raised IOP is regarded as the most important risk factor in the development and progression of glaucoma. But reducing the IOP does not ensure the cessation of the disease progression.[3-7]That is why other risk factors are thought to contribute in glaucomatous optic neuropathy.

Vascular factors have also been implicated in the development of glaucomatous optic nerve damage.[8] The vascular hypothesis suggests a primary problem in the optic nerve circulation as a result of localized organic changes in the blood vessels of the nerve. [9]Inability to adapt to tissue blood flow requirementsmay lead to chronically low or unstable ocular perfusion,[10]which in turn may cause ischemia, oxidative stress or both, possibly leading to glaucomatous damage to the optic nerve head.

Various techniques have been used to evaluate OBF in patients with POAG, such as scanning ophthalmoscopy,[11] scanning laser Doppler flowmetry[12, 13] and pulsatile ocular blood flow.[14, 15]Compared with these techniques, CDI has particular advantages in that it is non-invasive, is not affected by poor ocular media, requires no contrast or radiation, and has been used in ophthalmology for 20 years.[16,17] This ultrasound technique combines simultaneous B-mode ultrasound imaging with colors representing movement based on Doppler frequency shifts. It allows the assessment of blood flow velocities including PSV and EDV in the OA, the CRA and the SPCAs. In addition, RI, a measure of peripheral vascular resistance, can be calculated for each retrobulbar vessel.

SUBJECTS AND METHODS-

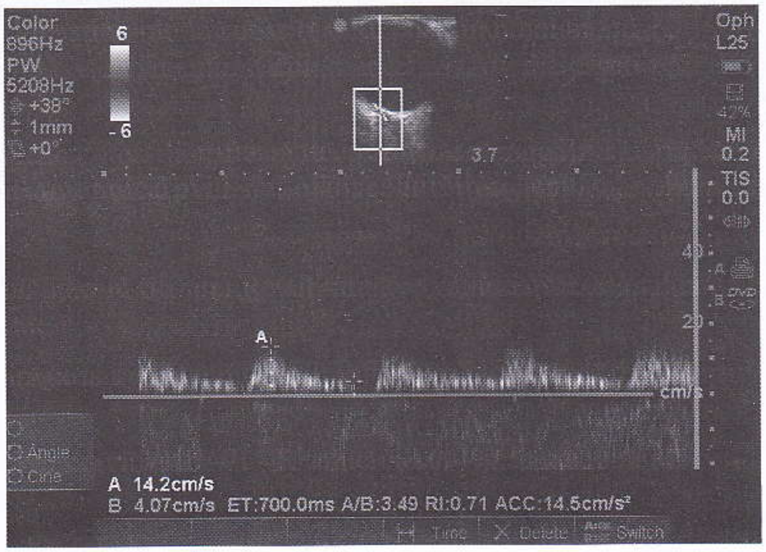
A hospital-based cross-sectional, observational study was done over a period of 1 year (January 2016 to December 2016).

Patients with a diagnosis of POAGor PACG under topical anti glaucoma medication with adequately controlled IOP i.e. <21 mmHg (measured on two consecutive occasions separated by an interval of at least 2 hours) were included. Patients with isolated raised IOP, secondary causes of glaucoma, trabeculectomy surgery, on Carbonic Anhydrase Inhibitors/systemic antihypertensive medications and not on topical anti- glaucoma medication and/or uncontrolled intraocular pressureswere excluded from our study.

Subjects attending the outpatient clinic and having an IOP<21 mm Hg (i.e. Measured on two consecutive occasions separated by an interval of at least 2 hours, but not more than 12 weeks) with a normal optic disc were taken as controls.

The study subjects were divided into three groups i.e. POAG group (17 patients, 34eyes), PACG group (14 patients, 20 eyes) and Controls (17 patients, 34 eyes).

IOP using Goldman Applanation tonometry (GAT), SBP and DBP in the sitting posture (mean of two consecutive measurements) using a mercury sphygmomanometerwere measured for each study subject.Orbital CDI was performedusing M- Turbo Ultrasound System (Sonosite,Inc. Bothell, WA, US) in the supine position.OA, CRA, andSPCAs were examined following a standard protocol.[18, 19] OA was located by scanning medial to the optic nerve approximately 15mm posterior to the globe.CRA measurements were taken in the middle of optic nerve 2-3 mm behind the surface of the optic disc. SPCAswere located on both sides of the optic nerve and were measured at a position that was close to the optic nerve and as anterior as possible without receiving interference from the choroid.



OBFparameters, i.e. PSV, EDV and (RI=PSV-EDV/PSV) for OA, CRA and SPCAs were recorded (**Figure 1**).

All the parameters were entered in excel sheet and were compared among these three groups.

Graph Pad Prism 7 (California, USA, version 7.00)was used for statistical analysis. Continuous data were presented as mean with a standard deviation. To compare continuous data, unpaired t-test (2 comparisons) and One way ANOVA (3 comparisons) were used. Statistical significance was set at $p < 0.05$.

RESULTS

Demographic and general characteristics of study participants are shown in table 1, table 2 and table 3. Mean age and mean IOP were comparable among the groups (p=0.412, 0.50). The difference in mean SBP, as well as mean DBP, was also statistically insignificant (p=0.962, 0.927).

OBF parameters and their comparisons are depicted in table 4 and table 5. In **OA,** mean PSV and mean EDV were significantly decreased in POAG (p=0.018, 0.0001) and PACG (p=0.01, 0.0001) groups as compared to controls. Similarly, mean RI was significantly raised in both POAG (p=0.0001) and PACG (p=0.0001) patients compared to controls.

When POAG and PACG groups were compared, mean EDV was significantly reduced in the POAG group (p=0.0006). Also, mean RI was significantly raised in the POAG group (p=0.0002).No significant difference was seen in mean PSVs between the two groups (p=0.58).

In **CRA,** mean PSV and mean EDV were significantly reduced in POAG (p=0.01, 0.0001) and PACG (p=0.0001, 0.0001) patients as compared to controls. RIs were also significantly raised in both the groups when compared with controls (p=0.0001, 0.0001).

When POAG and PACG groups were compared mean PSV was significantly higher in POAG patients (p=0.02) as compared to PACG patients. The difference in the rest of the parameters (mean EDV and mean RI) was statistically insignificant (p=0.278, 0.64).

In **SPCAs,** mean PSV and mean EDV were significantly reduced in POAG (p= 0.01, 0.0001) as well as PACG (p=0.003, 0.0001) patients as compared to controls. Mean RIs were significantly raised in both the groups as compared to controls (p= 0.0001, 0.0001)

On comparison between POAG and PACG groups, we found significantly reduced mean EDV (p=0.002) and significantly raised RI (p=0.0001) in POAG group. The difference in mean PSVs between the two groups did not reach up to the level of statistical significance (p=0.62).

DISCUSSION

The definition of glaucoma states that the most important risk factor is the raised IOP for occurrence and progression of glaucomatous optic neuropathy. But many randomized controlled trials have shown that despite controlling IOP many patients of glaucoma keep on progressing.[20-24]

Therefore, it was thought that besides uncontrolled IOP, there are other risk factors that interplay to cause glaucoma damage and subsequentprogression. The vascular theory of glaucoma emphasizes the role of compromised OBF as one of the important factors in glaucoma progression. Therefore, this cross-sectional study was done to find out the role of vascular factors in patients with glaucoma.

In all the three vessels studied, blood flow velocities were significantly decreased and RIs were significantly increased in POAG as well as PACG patients as compared to controls.

NC Sharma, D Bangiya*et al* [25] also studied OBF parameters by CDI in healthy and glaucomatous eyes and found that mean EDV was significantly decreased and mean RI was increased in both POAG and PACG patients in CRA and SPCAs. In OA, only mean PSV was significantly decreased in POAG and PACG patients.

HakkıBirinci *et al* [26]in their study also found out that OBF velocities were significantly decreased in all the three retrobulbar vessels i.e. OA, CRA and SPCAs in POAG patients. Similarly, RIs in POAG patients were significantly raised as compared to normal subjects.

Simon J. A. Rankin *et al*[27]studied OBF in CRA and SPCAs in glaucomatous patients and found that compared with the normal subjects, the patients with chronic OAG showed a statistically significant decrease in the mean EDV and an increase in the mean RI in all vessels studied.

PrinRojanapongpun*et al*[28]studied these parameters using CDI in OA only and found out that blood flow velocities were significantly decreased in POAG patients as compared to normal subjects.

Our study also revealed that in OA and SPCAs, mean EDVswere significantly reduced in POAG patients as compared to PACG patients. Similarly, mean RIs were significantly raised in POAG patients as compared to PACG patients. While in CRA, mean PSV was significantly lower in PACG patients as compared to POAG patients. The difference in the rest of the parameters did not reach up to the level of statistical significance.

Optic nerve head is mainly supplied by the SPCAs which are branches of the OA. The contributionsfrom the CRA and the pial vessels are very small.[29] Moreover, the most reliable parameters of ONH perfusion are EDV and RI. EDV, reflecting the average blood flow during the longest phase of the cardiac cycle, seems to be more suitable than PSV, which represents only an instantaneous variation of blood flow. [30] Thus we can infer that retrobulbarhemodynamics is more altered in POAG patients than PACG patients.

Similar to our study **NC Sharma, D Bangiya*et al***[25] also in their study found that most of the blood flow parameters were more altered in POAG patients as compared to PACG patients.

Therefore, our study supports all these aforementioned studies in that retrobulbarhemodynamics is altered to a significant degree in the glaucoma patients. Although from this study, it is difficult to infer whether it is the cause or the effect of glaucomatous optic neuropathy. More extensive longitudinal studies are needed for that purpose.

In our study, we only recruited patients under glaucoma medications with well-controlled IOP. Increased IOP is the major cause of glaucomatous optic neuropathy and also a known factor affecting the blood flow velocities. So, we have excluded an important confounding factor from this study thus reducing the bias. We can say that this finding of altered retrobulbarhemodynamics is not the result of increased IOP. Moreover, the difference in SBP and DBP was also not significant among the groups excluding the possibility that this finding of decreased retrobulbar flow might be the result of decreased systemic blood pressures.

Therefore, in the diagnosis and therapy of POAG and PACG,it is necessary to know not only the IOP, but there is alsothe importance of the OBF velocities. If we do not take into account these additional risk factors, then glaucoma might progress despite achieving target IOP in many patients.

But it is important to mention here that these OBF velocities measured by CDI are not reflections of actual OBF. For that, we would need diameters of these vessels which are practicallyimpossible with this technique. Moreover,SPCAs being the major blood supply to ONH are the most important vessels to be studied. But CDI cannot separately measure the parameters in each of these vessels. The values obtained represent the mass effect produced by a bundle of vessels, rather than from individual ciliary vessels. Therefore, we would need a better alternative in the futurewith the same advantages as CDI.

CONCLUSION

1) Both POAG and PACG are consistently associated with decreased blood flow velocities and increased RI in OA, CRA and SPCAs compared to normal subjects.
2) There is a more significant association of decreased velocities and raised RI in retrobulbar vessels with POAG patients as compared to PACG patients.

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Legends:

Table 1- Number of study participants.

Table 2- Sex distribution of study subjects.

Table 3-General Characteristics of Study Subjects

Table 4- Blood Flow Parameters in Retrobulbar Vessels Using CDI

Table 5- Comparison of Blood Flow Parameters among the Groups: Statistical Significance (p Values)

Figure1: Ocular Blood flow Parameters

A= PSV, Peak Systolic velocity

B= EDV, End diastolic velocity

A/B = RI, Resistivity Index

Table 1Number of Participants

	POAG*	PACG†	CONTROLS‡
Number of subjects	17	14	17
Number of eyes	34	20	34

*Both eyes were affected in all the participants.
†One patient was uniocular and only one eye was affected in 6 patients.
‡Both eyes of all the subjects were included.

Table 2Sex Distributions*

	Male	Female
POAG	10(58.82%)	7(41.17%)
PACG	7(50.0%)	7(50.0%)
Control	11(64.70%)	6(35.29%)

* Male to female ratio was 1.4:1, 1:1, and 1.8:1 in POAG, PACG and control groups respectively.

Table 3General Characteristics

	POAG (17 patients)	PACG (14 patients)	Controls (17 patients)	P value*
Age (years) Mean ± SD	60.29 ± 8.06	59.14±6.34	57.18± 5.75	0.412
IOP (mm Hg) Mean ± SD	15.52 ± 4.27	15.80 ± 2.62	14.82 ± 2.08	0.50
SBP(mm Hg) Mean ± SD	136.35± 8.22	135.71±14.09	136.82±11.024	0.962
DBP(mm Hg) Mean ± SD	85.82±5.22	85.85±8.28	86.58±5.64	0.927

Table 4 Blood Flow Parameters

		POAG	PACG	Controls
OA	PSV (cm/s)	22.81 ± 6.89	23.71 ± 3.30	25.85 ± 2.58
	EDV(cm/s)	6.03 ± 2.72	7.88 ± 1.35	10.89 ± 1.87
	RI	0.73 ± 0.07	0.66 ± 0.04	0.57 ± 0.06
CRA	PSV(cm/s)	11.11 ± 3.10	9.27 ± 2.35	12.87 ± 2.51
	EDV(cm/s)	3.33 ± 1.18	2.99 ± 0.95	5.74 ± 0.88
	RI	0.69 ± 0.08	0.69 ± 0.04	0.52 ± 0.05
SPCAs	PSV(cm/s)	9.84 ± 2.73	9.58 ± 1.85	11.60 ± 2.75
	EDV(cm/s)	3.05 ± 1.25	4.21 ± 1.25	6.58 ± 1.93
	RI	0.70 ± 0.07	0.56 ± 0.08	0.410.13)

Table 5Statistical Significance (p Values)*

		OA	CRA	SPCAs
POAG vs. Controls	PSV	0.018	0.01	0.01
	EDV	0.0001	0.0001	0.0001
	RI	0.0001	0.0001	0.0001
PACG vs. Controls	PSV	0.01	0.0001	0.003
	EDV	0.0001	0.0001	0.0001
	RI	0.0001	0.0001	0.0001
POAG vs. PACG	PSV	0.58	0.026	0.62
	EDV	0.006	0.278	0.002
	RI	0.0002	0.64	0.0001

*Unpaired t-test has been used for statistical analysis.