A comparative study between systemic hypertension, intraocular tension and ocular perfusion pressure in primary open angle glaucoma, normal tension glaucoma and normal population in a tertiary care centre

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Abstract

Introduction: Glaucoma is a chronic progressive optic neuropathy characterized by retinal ganglion cell death and associated visual field loss irrespective of intraocular pressure changes. The exact pathophysiological mechanism is not fully understood. The vascular hypothesis of OAG states that a low blood pressure (BP) relative to IOP can lead to low mean ocular perfusion pressure (MOPP), thus impairing perfusion of the Optic Nerve Head (ONH) with resultant glaucomatous cupping and visual field loss.

Objective: To find out any relationship between systemic hypertension, intraocular tension (IOP) and mean ocular perfusion pressure (MOPP) in primary open angle glaucoma (POAG), normal tension glaucoma and normal population.

Materials and Methods: It was a cross-sectional observational study. A total 125 patients attended in eye OPD at Calcutta National Medical College & Hospital, Kolkata, in one year having primary open angle glaucoma including normal tension glaucoma. Patients were distributed into three groups according to the technique of management. Applanation Tonometry and fundoscopic evaluation (+ 90 D lens) were done for all cases. Single recording of BP was taken. Gonioscopy, Humphrey's central visual fields and pachymetry were done. Data analyzed using standard statistical technique and a probability value ('p' value) of < 0.05 was considered as statistically significant.

Results: The average age of the study population was 54.38 ±8.92 years and ranging from 41 to 75 years. The study was male preponderant. The relationship between mean arterial pressure, intraocular pressure and mean ocular perfusion pressure was statistically significant in all subgroups.

Conclusion: There was a moderately strong correlation between MAP and MOPP whereas between MAP and IOP was weakly positive. The relationship between IOP and MOPP was inversely correlated.

Keywords: Ocular perfusion pressure, Open-angle glaucoma, Systemic hypertension.

Introduction

Glaucoma is a chronic progressive optic neuropathy characterized by retinal ganglion cell death and associated visual field loss.[1] The exact pathophysiological mechanism of optic nerve damage in glaucoma is not fully understood.[2] Besides the mechanical effect of raised intra ocular pressure (IOP) on optic nerve head (ONH),[3] several vascular risk factors such as systemic hypertension, atherosclerosis, vasospasm etc., have also been implicated as potential factors capable of increasing the risk of open angle glaucoma (OAG).[2,3] The vascular hypothesis of OAG states that a low blood pressure (BP) relative to IOP can lead to low mean ocular perfusion pressure (MOPP), thus impairing perfusion of the ONH with resultant glaucomatous cupping and visual field loss.[2,4-8] Assessment of the diurnal fluctuations in IOP and MOPP is, therefore, clinically relevant in glaucoma patients.[6] The term normal tension glaucoma refers to typical glaucomatous optic disc cupping and visual field loss in eyes that have normal IOP, open angles, and the absence of any contributing ocular or specific systemic disorders. This entity is often called 'low-tension glaucoma,' which is a misnomer because the IOP is usually at the upper end of the normal range and rarely low systemic hypertension as such may directly damage the small vessels of the optic disc and increase the risk of glaucoma. However, despite prior studies, the association between systemic hypertension, or perfusion pressure and OAG remains unclear. Understanding the relationship between these parameters is important to determine the risk factors influencing OAG development. This study examined a cohort of patients with systemic hypertension with the aim of studying its relationship with IOP and OAG and normal tension glaucoma (NTG) and compared it to a control group of normotensives in an adult Indian population.

Materials and Methods

Study area: The study was conducted at Calcutta National Medical College & Hospital, department of ophthalmology, Kolkata.

Study population: All patients attended in eye out-patient department (OPD) at Calcutta National Medical College & Hospital, Kolkata, in one year having primary open angle glaucoma including normal tension glaucoma.

Study period: One year (December 2015 to November 2016).

Sample size: A total number of 125 patients attended in eye OPD in one year having primary open angle glaucoma patient including normal tension glaucoma.
Sample design: Patients was distributed into three groups and subgroups according to the technique of management.
Group A: Patient with or without primary hypertension having primary open angle glaucoma.
Group B: Patient with or without primary hypertension having normotensive glaucoma
Group C: Patient age-matched controls without hypertension
Study design: It was a cross-sectional observational study
Study protocol: Single measurement of blood pressure was done for all the subjects in the right arm in sitting position using a mercury sphygmomanometer (auscultatory technique using the first, and fifth phases of the Korotkoff sounds as per the American Heart Association Blood pressure measurement recommendations).[10] IOP was measured in both the eyes using a applanation tonometry while dilated fundus examination performed using a +90 D lens for all the subjects. Mean arterial pressure (MAP) calculated as DBP + 1/3 (SBP–DBP). MOPP calculated using a standardized formula (MOPP = 2/3 × MAP–IOP).[11,12]
Study Tools: used were applanation tonometry, Gonioscope, Noncontact tonometer for measurement of Central corneal thickness, Humphrey field analyser, Optical coherence tomography, Ultrasound Tachymeter and Direct ophthalmoscope, Indirect ophthalmoscope +90D for fundoscopic examination.
Study techniques: Informed consent was taken from the patients and ethical clearance had been taken from ethic committee from this institution. Patients enrolled only within the first 6 months of the study and each patient followed up to 6 months after treatment.

Inclusion Criteria: Patients diagnosed to have essential hypertension, either self-reported hypertension or newly diagnosed cases (defined as ≥140 mm Hg systolic BP [SBP] and/or ≥90 mm Hg diastolic BP [DBP]), age above 40 years with primary open angle glaucoma and normal tension glaucoma and age above 40 years without hypertension having primary open angle glaucoma and normal tension glaucoma were included in this study.

Exclusion Criteria: Patients with hypertension due to secondary causes, age <40 years with or without primary open angle glaucoma, normal tension glaucoma and secondary glaucoma were excluded in this study.
Statistical Analysis: Data was collected and entered in Microsoft Excel then into statistical database SPSS (statistical package for social sciences, version 20.0, windows compatible). Data analysed using standard statistical technique like tabulation, proportions, percentage, mean and standard deviation. Suitable statistical test performed (Pearson's Chi square test, Kruskal-Wallis Test of significance, Spearman's rho correlation) A probability value ('p' value) of < 0.05 was considered as statistically significant.

Results

A total number of study population was 125 patients. The average age of the study population was 54.38 ±8.92 years and ranging from 41 to 77 years. The study was male preponderant. Maximum number of patient was from 41-50 years (48%) age groups. Maximum number of patients was primary open angle glaucoma (50.4%). SBP, DBP, MAP, IOP and VCDR were found to be statistically significant with different study group. (Table no: 1) SBP, DBP, MAP, IOP and VCDR were found to be statistically significant with different study subgroup (hypertensive vs non-hypertensive). (Table 2) There was strong correlation between MAP and MOPP amongst NTG group. (Table3) There was strong correlation between MAP and MOPP amongst NTG with hypertension group. (Table 4) In POAG with hypertensive group with medication, the correlation between MAP and MOPP was strong, while MOPP was inversely correlated with IOP showing strong association. The MAP was weakly correlated with IOP. In POAG with hypertensive group without medication, MAP was also strongly correlated with MOPP, while MOPP was inversely correlated with IOP showing strong association and MAP showed inverse correlation with IOP showing strong correlation. (Table 5) In NTG with hypertensive group with medication, MAP was strongly correlated with MOPP. While MOPP was inversely correlated with IOP showing strong association. In NTG with hypertensive group without medication, the result was same as NTG with hypertension with medication group. (Table 6)

Table 1: Relationship between different study group and study parameters

GROUP	SBP	DBP	MAP	IOP	MOPP	VCDR
POAG	144.19 ± 15.06	90.35 ± 9.03	107.49 ± 14.48	30.79 ± 7.20	51.67 ± 11.52	0.70 ± 0.11
NTG	130.00 ± 12.75	84.84 ± 5.81	99.89 ± 7.84	18.47 ± 1.82	54.28 ± 5.28	0.68 ± 0.07
NORMAL	125.16 ± 5.04	80.90 ± 3.39	95.66 ± 3.45	13.10 ± 1.65	55.04 ± 2.45	0.30 ± 0.06
	<0.001	<0.001	<0.001	<0.001	0.481	<0.001

Table 2: Relationship between different study group (hypertensive vs non-hypertensive) and study parameters

Subgroup	SBP	DBP	MAP	IOP	MOPP	VCDR
POAG with hypertension	157.03 ± 5.96	97.52 ± 3.94	117.35 ± 4.41	25.00 ± 2.90	61.57 ± 4.43	1`0.68 ± 0.09
POAG without hypertension	130.07 ± 7.36	82.47 ± 5.91	96.63 ± 13.94	37.17 ± 4.65	40.78 ± 5.41	0.73 ± 0.13
NTG with hypertension	150.50 ± 3.39	94.00 ± 1.46	112.83 ± 1.64	18.75 ± 1.00	62.72 ± 1.55	0.71 ± 0.06
NTG without hypertension	122.87 ± 3.90	81.65 ± 2.20	95.39 ± 1.50	18.37 ± 2.03	51.35 ± 1.68	0.66 ± 0.06
Normal	125.16 ± 5.04	80.90 ± 3.39	95.66 ± 3.45	13.10 ± 1.65	55.04 ± 2.45	0.30 ± 0.06
	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Table 3: According to different study group Spearman's Rank Correlation (ρ) in different study parameters.

GROUP				MAP	IOP	MOPP
POAG	Spearman's rho	MAP	Correlation Coefficient		-0.724	0.925
			p Value		<0.001	<0.001
		IOP	Correlation Coefficient	-0.724		-0.901
			p Value	<0.001		<0.001
		MOPP	Correlation Coefficient	0.925	-0.901	
			p Value	<0.001	<0.001	
NTG	Spearman's rho	MAP	Correlation Coefficient		0.009	0.886
			p Value		0.947	<0.001
		IOP	Correlation Coefficient	0.009		-0.379
			p Value	0.947		0.002
		MOPP	Correlation Coefficient	0.886	-0.379	
			p Value	<0.001	0.002	
NORMAL	Spearman's rho	MAP	Correlation Coefficient		0.085	0.858
			p Value		0.512	<0.001
		IOP	Correlation Coefficient	0.085		-0.391
			p Value	0.512		0.002
		MOPP	Correlation Coefficient	0.858	-0.391	
			p Value	<0.001	0.002	

Table 4: According to different study sub-groups Spearman's Rank Correlation (ρ) in different study parameters

Subgroup				MAP	IOP	MOPP
POAG with hypertension	Spearman's rho	MAP	Correlation Coefficient		0.004	0.756
			p Value		0.973	<0.001
		IOP	Correlation Coefficient	0.004		-0.618
			p Value	0.973		<0.001
		MOPP	Correlation Coefficient	0.756	-0.618	
			p Value	<0.001	<0.001	
POAG without hypertension	Spearman's rho	MAP	Correlation Coefficient		-0.196	0.667
			p Value		0.134	<0.001
		IOP	Correlation Coefficient	-0.196		-0.744
			p Value	0.134		<0.001
		MOPP	Correlation Coefficient	0.667	-0.744	
			p Value	<0.001	<0.001	
NTG with hypertension	Spearman's rho	MAP	Correlation Coefficient		-0.577	0.962
			p Value		0.019	<0.001
		IOP	Correlation Coefficient	-0.577		-0.760
			p Value	0.019		0.001
		MOPP	Correlation Coefficient	0.962	-0.760	

			p Value	<0.001	0.001	
NTG without hypertension	Spearman's rho	MAP	Correlation Coefficient		0.057	0.719
			p Value		0.705	<0.001
		IOP	Correlation Coefficient	0.057		-0.606
			p Value	0.705		<0.001
		MOPP	Correlation Coefficient	0.719	-0.606	
			p Value	<0.001	<0.001	
Normal	Spearman's rho	MAP	Correlation Coefficient		0.085	0.858
			p Value		0.512	<0.001
		IOP	Correlation Coefficient	0.085		-0.391
			p Value	0.512		0.002
		MOPP	Correlation Coefficient	0.858	-0.391	
			p Value	<0.001	0.002	

Table 5: Spearman's correlation coefficient (ρ) between POAG with hypertension with medication and POAG with Hypertension without medication

GROUP					**MAP**	**IOP**	**MOPP**
POAG	With medication	Spearman's rho	MAP	Correlation Coefficient	1.000	-0.175	0.808
				p Value		0.337	<0.001
			IOP	Correlation Coefficient		1.000	-0.682
				p Value			<0.001
			MOPP	Correlation Coefficient			1.000
				p Value			
	Without medication	Spearman's rho	MAP	Correlation Coefficient	1.000	0.191	0.696
				p Value		0.279	<0.001
			IOP	Correlation Coefficient		1.000	-0.551
				p Value			0.001
			MOPP	Correlation Coefficient		-0.551	1.000
				p Value		0.001	

Table 6: Spearman's correlation coefficient (ρ) between NTG with hypertension with medication and NTG with Hypertension without medication

GROUP					**MAP**	**IOP**	**MOPP**
NTG	With medication	Spearman's rho	MAP	Correlation Coefficient	1.000	-0.577	0.962
				p Value		0.134	<0.001
			IOP	Correlation Coefficient		1.000	-0.760
				p Value			0.029
			MOPP	Correlation Coefficient			1.000
				p Value			
	Without medication	Spearman's rho	MAP	Correlation Coefficient	1.000	-0.577	0.962
				p Value		0.134	<0.001
			IOP	Correlation Coefficient		1.000	-0.760
				p Value			0.029
			MOPP	Correlation Coefficient			1.000
				p Value			

Discussion

The present study groups were comparable to each other as they did not have any significant statistical difference with each other with respect to age and sex.

In present study, highest MAP found in POAG with hypertension group (i.e. 117.35) and lowest MAP found in NTG without hypertension (i.e. 95.39). Highest SBP was found in POAG with hypertension (i.e. 157.03mm Hg) and lowest in NTG without hypertension (i.e. 122mm Hg), highest DBP found in POAG with Hypertension group (i.e. 97.52 mm Hg) and lowest in normal group (80.90 mm hg). IOP was found highest in POAG without hypertension (i.e. 37.17) and lowest in normal group (i.e. 13.10). Highest MOPP was in NTG with hypertension (i.e. 62.72) and lowest in POAG without hypertension (40.78). VCDR found highest in POAG without hypertension (i.e. 0.73) and lowest in normal group (0.30). Several studies had been done to establish the relation between these criteria in various glaucomatous group. Association

between systemic hypertension and POAG had been evaluated in various population based studies that yield contradictory results. Population-based studies have consistently found an association between high blood pressure and IOP. In general, each 10 mmHg rise in systolic blood pressure is associated with only a small increase in IOP (approximately 0.27 mmHg). As these studies covered populations with different ethnic backgrounds including Caucasians (Egna Neumarkt Study, Rotterdam Study, Beaver Dam Study),[7-9] Africans (Barbados Eye Study)[8] and Asians (Tanjong Pagar Study)[9] it is likely that they are widely applicable. Indeed, some epidemiological studies (Table 1) like Rotterdam eye study,[11] Blue Mountain Eye study, Egna Neumarkt Glaucoma Study[10] suggest that systemic hypertension causes increase risk of primary open angle glaucoma while Thessaloniki Eye Study,[10] Early Manifest Glaucoma Trial[11] and the Barbados Eye Study[13] suggest that systemic hypertension have reduced risk factor for primary open angle glaucoma. Baltimore eye survey[12] suggest that age-dependent risk for younger and increased risk for older patients. In the Egna Neumarkt study,[10] the association was found between primary POAG and systemic hypertension. A positive correlation was also found between systemic BP and IOP.

In our study we found that all indices of hypertension (viz. SBP, DBP and MAP) between the groups who had POAG, NTG or normal groups.

On performing a Spearman's correlation in all groups we found a moderately strong correlation between MAP and MOPP (i.e. 0.676), whereas the correlation between MAP and IOP had weak positive value (i.e. 0.353). IOP and MOPP were inversely correlated and the value was weak -0.357. On further subgroup analysis strong negative correlation between MAP and IOP in POAG group (ρ = -0.724) but it was very weak in NTG (ρ = 0.009) and normal patient (ρ = 0.085).

When we study their correlation of MAP vs. MOPP the strongest correlation found in POAG groups (ρ = 0.925) it was found in NTG (ρ = 0.886) as well as in normal (ρ = 0.858) patients.

When we come to correlation of IOP with MOPP we found that there is strong inverse correlation in POAG groups (ρ = -0.901) the inverse correlation was seen in NTG and normal patient too but it was weak (-0.379 and -0.391 respectively).

When we study the correlation between the values after discriminating on the basis of hypertension in POAG patient being presence or absence we found that ρ for MAP vs. IOP with hypertension was very weak (0.004) and POAG without hypertension it was inverse correlation but weak (-0.196). Spearman's rho for MAP vs. MOPP in POAG group with or without hypertension was in positive correlation (0.756 and 0.667 respectively) showing slightly stronger in POAG with hypertension group. In IOP vs. MOPP found that ρ value was in inverse correlation in POAG with or without hypertension (-0.618 and -0.744 respectively) slightly more strong in POAG without hypertension group.

In the NTG group when we bring hypertension in the picture we found that ρ for MAP vs. IOP in hypertensive patient inverse strong correlation (-0.577) and without hypertension was very weak (0.057). Spearman's rho for MAP vs. MOPP in NTG with hypertensive group (0.962) and without hypertensive group (0.719) found to be in strong correlation. In IOP vs. MOPP found that ρ value in hypertensive (-0.760) and without hypertension (-0.606) which is marginally higher in hypertensive group.

In the POAG group with hypertension taking medication had a marginally higher ρ value for MAP vs MOPP (0.808) and ρ of IOP vs. MOPP (-0.682) both of which are statistically significant. This is contrast to study by Thessaloniki Eye Study.[**Error! Bookmark not defined.**,5]

We found that subjects on antihypertensive medications had increased likelihood of having glaucoma or glaucoma suspect. One potential reason may be related to the bedtime dosing of the antihypertensive medications which cause a drop in nocturnal BP and subsequent reduction in ONH perfusion. Pache and Flammer reported hypotension and in particular, a nocturnal drop in BP as an important risk factor for POAG.

Another possible explanation for the observed association between antihypertensive medications and OAG in our study is that the subjects on antihypertensive medications are likely to have more severe disease and hence, greater disruption of auto regulatory mechanisms of blood flow in the ONH. Chronically elevated BP results in arteriosclerosis, changes in the size of the precapillary arterioles and capillary dropout leading to increased resistance to blood flow and thus reduced perfusion.

Limitations

Calculation of mean OPP using theoretical formula may not reflect the real physiological status of ocular perfusion. Direct measurement of ocular blood flow could result in different outcomes. Furthermore, there are inevitable measurement inaccuracies during assessment of BP and IOP and also the scales of measurement differ (IOP values are in the range of 10-30 mm Hg while BP values approximate 100 mm Hg). Despite these limitations, several large studies have shown that calculated OPP is a highly relevant parameter in glaucoma. We acknowledge that BP and IOP are both influenced by diurnal variations; therefore, having a single elevated/normal BP or IOP reading may not be representative of an individual's true BP or IOP status. Therefore, though tedious, a study carried out with 24 hours ambulatory BP monitoring and recording of diurnal variation of IOP may be more appropriate. Continuous IOP monitoring technologies are currently

emerging that can contribute significantly to the study of IOP rhythms. They may provide an invaluable tool toward a better understanding of long and short term IOP fluctuations.

Conclusion

This study demonstrates that in all groups a moderately strong correlation existed between MAP and MOPP and IOP and MOPP were inversely correlated. On subgroup analysis strong negative correlation between MAP and IOP in POAG patients was noted but it was very weak in NTG and controls. The correlation of IOP with MOPP in POAG patients was strong and inverse while it was too weak in NTG and controls.

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