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STUDY OF AUTONOMIC FUNCTIONS IN PRIMARY OPEN ANGLE GLAUCOMA PATIENTS USING COLD PRESSOR TEST AND TO COMPARE THE RESULTS WITH AGE AND SEX MATCHED CONTROLS

Harminder Singh[1], Indu Khurana[2] and Itika Singh[3]*

[1]Specialist Govt. Regional Hospital Rohtak, [2]Dean Cum Principal and Professor, Dept. of Physiology, WCMSRH, Jhajjar, [3]Demonstrator, Dept. of Physiology, B.P.S Govt. Medical College (W), Khanpur Kalan, Sonipat.

***Corresponding Author: Itika Singh**
Specialist Govt Regional Hospital Rohtak, Dept of Physiology, B.P.S Govt Medical College (W), Khanpur Kalan, Sonipat.

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ABSTRACT

Introduction: Primary open angle glaucoma (POAG) is a chronic condition characterized by visual loss, glaucomatous optic atrophy, and elevated intraocular pressure in presence of open iridio-corneal angle or vascular dysregulation leading to visual impairment. Cold pressor test (CPT) measures function of sympathetic neural control of cardiovascular system. In CPT heart rate increases indicating cardiac sympathetic activation and rise of blood pressure is due to a wide spread vasopressor reaction initiated through a neurogenic reflex arc. **Material and method:** Study was carried out on 30 POAG patients and 30 controls. Basal intraocular pressure(IOP), mean arterial blood pressure (MAP) and mean ocular perfusion pressure (MOPP) was tabulated. Cold pressor test was done and changes in MAP and MOPP were compared in both the groups. Statistical analysis was done using student t test. **Results:** Immediate response to CPTresulted in statistically significant rise in MAP, $p < 0.05$. Insignificant decrease in MOPP was observed in POAG patients than in controls. Statistically significant rise in MOPP in POAG patients as compared to controls ($p<0.05$) was observed inrecovery period. **Conclusion:** Autonomic dysfunction plays significant role in pathophysiology of POAG specially sympathetic overdrive. CPT can be used as a diagnostic tool to detect POAG in early stages to prevent ocular morbidity.

KEYWORDS: Primary Open Angle Glaucoma, Intraocular pressure, Cold pressor test, Mean arterial pressure, Mean ocular perfusion pressure.

INTRODUCTION

Glaucoma is an optic neuropathy characterized by progressive retinal ganglion cells death and visual field loss.[1] Glaucoma affects 1 in 200 people aged 50 years and /or even younger, and in 1 in 10 over the age of 80 years.[2] POAG is diagnosed by the presence of "classical triad"; characterstic pattern of visual field defects, morphological changes in optic disc (cupping) and raised intraocular pressure (IOP) >21mm Hg.[3] In the initial stages IOP may not be raised permanently but there is an exaggeration of the normal diurnal variation. A diurnal variation of 5 mm Hg of IOP is suspicious and over 8 mm Hg is diagnostic of glaucoma and in late stages IOP is permanently raised above 21 mm Hg.[4] Multiple risk factors have been implicated in the development of glaucoma. The most acknowledge of which include advancing age, elevated IOP and positive family history. By definition IOP is a mechanical entity, referring to the force exerted by intraocular fluid per unit area on the tissue which contain them.[5] With an increase in IOP by 1 mm Hg there is 10% increased risk of development of POAG, but 30-50% glaucoma patients have IOP within statistically normal range.[6] The elevation of IOP occurs due to reduction of aqueous outflow due to blockage at trabecular meshwork level.[7] Autonomic dysfunction has been thought to be contributory factor due to autonomic neuropathy in pathophysiology of both open angle and normal pressure glaucoma.[8] The mean ocular perfusion pressure (MOPP) is defined as mean arterial pressure (MAP) minus IOP, therefore, either fall in MAP or rise in IOP decreases the ocular perfusion. There is strong positive relationship between MAP and IOP in patients with baroreflex failure with intact efferent sympathetic and parasympathetic innervations. The instability of blood flow i.e primary vascular dysregulation leads to repeated mild perfusion which contributes via oxidative stress to glaucomatous damage.[9]

The haemodynamic situation of the body is supervised and influenced by ANS via control of blood pressure (BP). High sympathetic drive may constrict the microvasculature nourishing the optic nerve head and leads to decreased ocular blood flow.[10] Cold pressor test (CPT) measures the function of sympathetic neural control of the cardiovascular system. In CPT heart rate

increases which indicates cardiac sympathetic activation and rise of blood pressure is due to a wide spread vasopressor reaction initiated through a neurogenic reflex arc.[11] The hand is immersed in ice water for one minute and changes in blood pressure and heart rate are measured, relating to vascular response and excitability of pulse.[12] In healthy subjects the cold pressor test (CPT)triggers a vascular sympathetic activation resulting in increase in blood pressure. Immersion of hands or feet for about 60–90 s in cold water (4°C) due to activation of thermoreceptors and nociceptors afferents as well as emotional arousal, lead to sympathetic activation and rise in blood pressure and heart rate. An increase in BP may be due to an increased cardiac output during the initial period of the test with little increase in muscle sympathetic nerve activity, in the later period an increase in this activity elevates peripheral resistance. Pulse pressure also increases, mainly at the end of the test. Rise in diastolic blood pressure normally exceeds 15 mm Hg.[11,13]

MATERIAL AND METHOD

The prospective study was conducted in the department of Physiology in collaboration with Regional Institute of Ophthalmology (R.I.O), Pt. B. D. Sharma, PGIMS Rohtak. The study sample was comprised of two groups. Group I- Thirty newly diagnosed patients with POAG. Groups II-Thirty age and sex matched healthy controls.

Inclusion criteria for group I (POAG)

- Intraocular pressure > 21 mm Hg without treatment.
- Optic disc changes suggestive of glaucomatous damage including one or more of these signs : neuroretinal rim notching, optic disc excavation, vertical or horizontal cup to disk (C/D) ratio >0.5 or C/D asymmetry between 2 eyes greater than 0.2, peripapillary splinter haemorrhages.
- Visual field outside normal limits on Humphery automated perimetry on three perimetry readings.
- All angles (360^0) open on gonioscopy.
- Pupil diameter ≥ 3mm without mydriatic or miotic drugs.

Inclusion criteria for group II (controls): No suspicion of any form of glaucoma or any other eye disease.

Exclusion criteria

- Patients with secondary causes of glaucoma, hazy media, optic neuritis, any disease involving the macula, retina, or visual pathway, high myopia (>6D), previous intraocular surgery and on drugs known to cause optic neuropathy.
- Patients suffering with diabetes mellitus, hypertension and history of smoking.

Ophthalmogical Work Up- A prior informed consent was taken. Complete ophthalmological examination of each patient with POAG was done in Glaucoma Clinic of R.I.O. including uncorrected and best corrected visual acuity, slit lamp examination, detailed fundus examination, IOP measurement with Goldmann applanation tonometer, gonioscopy and visual field analysis.

Preliminary Preparation- The whole procedure was explained in detail to each subject in his/her own language to allay any fear or apprehension. Consent was taken from every individual to undergo whole procedure. The tests were conducted during working hours (9am-1pm) to avoid diurnal variation. All the subjects were tested under similar laboratory conditions and allowed to acclimatize themselves to the experimental and environmental conditions.

Procedure- The basal recording of blood pressure was taken by tying the sphygmomanometer cuff on the right arm. Then the subject's left hand upto wrist was immersed into cold water (8^0C) for 2 minutes and blood pressure was recorded immediately after removal of the hand from the cold water and then after 5 minutes.[11]

Basal mean ocular perfusion pressure (MOPP) was calculated from the value of IOP and mean arterial pressure (MAP) as.

- MOPP = (MAP- IOP).
- MAP =Diastolic pressure+1/3 Pulse pressure,[14] and.
- Pulse pressure (PP) = Systolic pressure – Diastolic pressure.

Statistical analysis- The data obtained was compiled, tabulated and statistically analysed. Observations of group I (patients with POAG) were compared with group II (controls) using student t-test.

OBSERVATIONS

The present study was conducted in Department of Physiology in collaboration with Department of Regional Institute of Ophthalmology (R.I.O) Pt. B.D. Sharma University of Health Sciences, Rohtak. The study was carried out on 30 patients with Primary open angle glaucoma (group I) and 30 age and sex matched healthy controls (group II). Out of 30 POAG patients (group I), 53.33% were males and 46.66% were females whereas in controls (group II) 17 (56.66%) were males and 13 (43.33%) were females. The mean basal value of IOP (table I) in patients with POAG was statistically very high in group I (22.51 ± 1.45) as compared to group II (15.82±1.09 p value 0.0001) and the mean value of MOPP was statistically lower in group I (75.13 ± 7.61 p <0.04) as compared to group II (78.93 ± 6.12). However, the mean value of MAP were comparable in both groups. The immediate changes in MAP and MOPP in response to cold pressor test in group I and group II was compared in figure 1. The mean value of MAP was insignificantly increased in group I (101.25 ± 7.08) than group II (97.79 ± 6.38). MOPP was decreased in group I (78.94 ± 7.18) as compared to group II (81.98 ± 6.43). The changes in MAP and MOPP during the recovery period after the cold pressor test in group I and group II were compared

in table II. In group I, the mean values of MOPP were significantly lower (75.15± 6.43 p 0.04) as compared to group II (78.99 ±6.16).

Table I: Basal IOP, MAP and MOPP in group I and group II.

Parameter (mmHg)	Group I (Mean ± SD)	Group II (Mean ± SD)	p value
IOP	22.51 ± 1.45	15.82 ± 1.09	****0.0001**
MAP	97.44 ± 7.22	94.64 ± 6.14	0.11
MOPP	75.13 ± 7.61	78.93 ± 6.12	***0.04**

** very highly significant(p<0.001) *statistical significance (p<0.05).

Table II: MAP and MOPP after 5 minutes (recovery period) of CPT in group I and group II.

Parameter (mm Hg)	Group I (Mean ± SD)	Group II (Mean ± SD)	p value
MAP	97.53 ± 7.29	94.71 ± 6.18	0.11
MOPP	75.15 ± 6.43	78.99 ±6.16	***0.04**

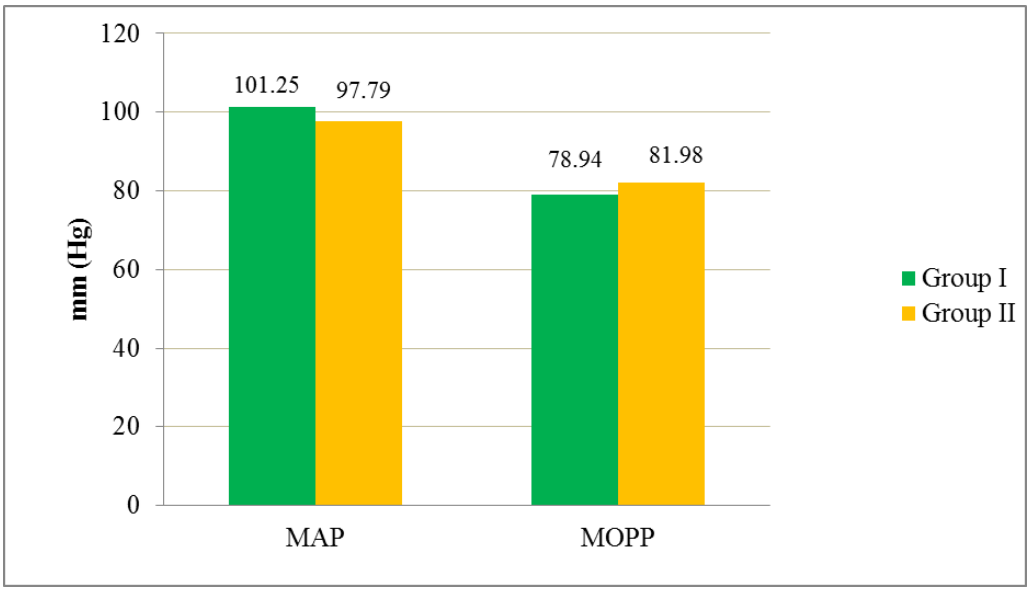

Figure 1: Comparison of immediate response to CPT on MAP and MOPP in group I and group II.

DISCUSSION

The study was carried out on 30 patients with primary open angle glaucoma (group I) and 30 healthy age and sex matched controls (group II). In both the groups status of autonomic activity was studied by following tests and compared. Mean arterial pressure (MAP) was recorded and mean ocular perfusion pressure (MOPP) was calculated and changes in response to cold pressor test were studied. Cold Pressor Test triggers activation of vascular sympathetics and causes rise in blood pressure. Any condition associated with deficient sympathetic outflow, CPT expected to show smaller rise. Immediate Response to CPT showed statistically significant rise in MAP, ($p < 0.05$) and an insignificant decrease in MOPP was observed in group I (78.99 ± 7.18) than in group II (81.98 ± 6.43). Zhang M et al conducted GenSalt study in rural north China and studied the factors associated with blood pressure response to the CPT. They found that females, old age and elevated baseline BP levels are associated with greater BP response.[15] The observed response to cold pressor test on MAP and MOPP signifies that systemic sympathetic activation affects ocular blood flow. High sympathetic derive may constrict the microvasculature nourshing the optic nerve head (ONH) and leads to diminished ocular blood flow. A study by Joanna Wiezbowska et al 'Cardiac autonomic dysfunctions in patients with normal tension glaucoma : 24 hours heart rate and blood pressure' has suggested that increased sympathetic nervous system activation results in increased vascular resistance and may have implication by altered blood flow and ocular perfusion pressure on pathogenesis of glaucoma.[16]

CONCLUSION

In POAG primary effect appears to occur as optic nerve head ischemia. The auto regulatory mechanisms predominantly maintains the ocular blood flow, however if ocular perfusion falls below the limit of autoregulation, then neurovascular mechanism unable to maintain the blood flow. Therefore autonomic dysfunction specially with sympathetic overdrive causes resistance in the microvasculature. The resultant reduced ocular blood flow plays a role in pathophysiology of glaucoma (optic neuropathy due to ischemia leading to ganglion cell

death).[10] The findings of the preset study in response to CPT conclude that autonomic dysfunction may play role in pathogenesis of POAG by reducing ocular blood flow.

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