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Original Article

Ophthalmology Section

Evaluation of Ocular Perfusion Pressure in Migraine Patients: A Case-control Study

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ABSTRACT

Introduction: Vascular dysregulation is a common underlying factor between migraine and glaucoma. Fluctuations in Ocular Perfusion Pressure (OPP) can lead to ischaemia and damage to the optic nerve head. It is unclear if the risk of glaucoma in migraine patients is due to low OPP.

Aim: To compare the OPP of migraine patients with healthy controls and assess the role of OPP as a risk factor for glaucoma in migraine patients.

Materials and Methods: This case-control study was conducted from June 2019 to May 2020 at Yenepoya Medical College Hospital, Mangaluru, Karnataka, India. Adult patients of either gender, aged between 18 and 40 years, diagnosed with migraine, were included in the study. Intraocular Pressure (IOP), blood pressure, and OPP were measured in 94 migraine patients and compared with 94 age-matched controls. Data were analysed using Statistical Package for the Social Sciences (SPSS) version 23.0. Independent t-tests were used for comparison. Adjusted odds ratios were calculated using binary logistic regression, and a p-value <0.05 was considered statistically significant.

Results: The mean IOP was 13.27±2.02 mmHg among cases and 13.38±1.87 mmHg among controls. The mean Systolic Blood Pressure (SBP) was 118.91±4.67 mmHg among cases and 116.09±5.18 mmHg among controls. The mean Diastolic Blood Pressure (DBP) was 77.72±4.48 mmHg among cases and 75.77±4.89 mmHg among controls. The mean OPP was 47.69±2.43 mmHg among cases and 46.08±2.46 mmHg among controls. The t-test values showed a statistically significant difference in SBP, DBP, and OPP between the two groups (p-value <0.05).

Conclusion: The OPP in migraine patients differed significantly from that of the controls. However, further studies are needed to evaluate the relationship between perfusion pressure abnormalities and the risk of glaucoma in migraine patients.

Keywords: Blood pressure, Glaucoma, Intraocular pressure, Ischaemia

INTRODUCTION

Glaucoma, the leading cause of irreversible blindness worldwide, is a progressive optic neuropathy with a multifactorial aetiopathogenesis [1]. The most significant risk factor is high IOP, and it should be reduced to halt the progression. However, optic disc damage occurs in patients with normal tension glaucoma or low tension glaucoma even when the IOP is not elevated [2]. This suggests that there are mechanisms other than IOP that contribute to the occurrence and progression of glaucomatous disc damage. One such mechanism is vascular dysfunction, where there is diminished perfusion to the optic nerve head, leading to retinal ganglion cell stress and death [1].

The OPP is the perfusion pressure in the ocular vessels, calculated as the difference between blood pressure (BP) and IOP. The eye is supplied by the ophthalmic artery, in which the vessel BP is estimated to be two-thirds of the brachial arterial pressure. Therefore, OPP is defined as two-thirds of the mean arterial pressure minus IOP. Mean arterial pressure can be calculated as one-third SBP plus two-thirds DBP [2,3]. A lower OPP implies that either the IOP is high or the mean arterial BP is low. It is known that the optic nerve is vulnerable to ischaemia when the OPP is reduced. Thus, even with a normal IOP, the optic nerve is susceptible to damage, as seen in normal tension glaucoma. The vascular hypothesis suggests that abnormal perfusion to the optic nerve head is a strong factor in the pathogenesis of glaucomatous damage [2]. Low OPP is an important risk factor for the development and progression of glaucoma, particularly in patients with other risk factors. This is particularly true in normal tension glaucoma, where autoregulatory dysfunctions are implicated [1,3].

Migraine headache, a major global health issue, is a condition that involves the disturbance of the autonomic system. Vascular dysregulation is a common factor between glaucoma, migraine, and blood pressure abnormalities [4]. Studies have shown that patients with migraine are at a higher risk of developing glaucoma, including Primary Open-Angle Glaucoma (POAG) and normal tension glaucoma [5-7]. A possible common vascular aetiology is suggested for normal tension glaucoma and migraine [5]. The exact mechanism by which migraine predisposes to glaucoma is unclear. Very few studies have investigated migraine in terms of OPP, and the evidence is inconclusive [5-8]. In one study, no significant difference was found in the OPP of migraine patients and controls [8].

Hence, the present study was conducted with the hypothesis that the risk of glaucoma in migraine patients is due to low OPP. The study aimed to determine whether the OPP in migraine patients differed from that of healthy controls. The primary objective was to investigate potential differences in baseline IOP, SBP, DBP, and OPP between migraine patients during pain-free periods and healthy controls. The secondary objective was to determine the changes in these parameters during migraine attacks and pain-free periods.

MATERIALS AND METHODS

This observational case-control study was conducted at Yenepoya Medical College Hospital, Mangaluru, Karnataka, India, from June 2019 to May 2020. Approval from the Institutional Ethics Committee (IEC) was obtained (letter number YEC 1/238/2019 dated 8/7/2019).

Inclusion criteria: Adult patients of either gender between the age group of 18 and 40 years who were diagnosed with migraine (according to the International Headache Society criteria) [9] were included in the study. They were included irrespective of whether they were on or off prophylaxis for migraine. Also, all subcategories of migraine patients were included, irrespective of whether they

had migraine with aura or without aura. A total of 94 patients were included in this study.

Exclusion criteria: Patients who were already a glaucoma suspects or diagnosed with glaucoma were excluded. Hypertensive patients, pregnant women, patients with alcohol, tobacco, or any other substance (cocaine and other opioids) abuse were excluded. Patients with any other ocular or systemic diseases or previous ocular surgeries were excluded. Patients using systemic medications such as antidepressants, non-steroidal anti-inflammatory drugs, corticosteroids, immunosuppressives, bronchodilators, decongestants, phenylpropalamine, ephedrine, amphetamines, sibutramine, calcineurin inhibitors, erythropoietin, antihypertensives, oral hypoglycaemics, statins were also excluded from the study.

The purposive sampling technique was used to select the study participants from patients attending the ophthalmology outpatient department.

Sample size: The estimated global prevalence of migraine is 14.8% [10]. Considering this prevalence, the sample size for the present study was calculated to be 94, using the formula:

$$n=Z2\times p\times q/e2$$

where n is the required sample size, 'Z' is the standard normal deviate (which is equal to 1.96 at a 5% significance level), 'p' is the prevalence, and e is the allowable error (10%).

This study included 188 participants, of which 94 were cases (patients with migraine), and the remaining 94 were age-matched healthy controls. Among the total participants, 61 (32.45%) were males, and 127 (67.55%) were females.

Methodology and Parameters Studied

The specific outcomes intended to be measured were the mean IOP, mean SBP, mean DBP, and mean OPP in migraine patients (during headache-free periods) as well as in controls.

The blood pressure was measured in the sitting position on the right arm using a manual sphygmomanometer (Welch Allyn aneroid with an adult cuff). The IOP was measured using Goldman applanation tonometry (and corrected with central corneal thickness values by pachymetry) during the daytime between 10 am to 12 noon. This narrow time window was followed to maintain uniformity among all participants and to avoid bias due to diurnal variation of IOP [11].

Then, OPP was calculated as two-thirds of the mean arterial pressure minus IOP. The right eye IOP was considered for calculation purposes. The OPP of migraine patients was compared with that of normal age-matched controls. Regardless of whether a migraine patient was experiencing a headache attack or was headache-free at the time of presenting to the outpatient department, he or she was included in the study. If the participant reported having a migraine headache at the time of presentation, this factor was noted down along with the OPP measurement. Then, the patient was requested to come on any other day, if possible, during a migraine-free period for re-evaluation of OPP.

STATISTICAL ANALYSIS

The data were analysed using SPSS version 23. The mean values of IOP, SBP, DBP, and OPP in migraine patients during pain-free periods were compared with healthy controls using an Independent t-test. Furthermore, adjusted odds ratios were calculated using binary logistic regression, and a p-value <0.05 was considered statistically significant. For the purpose of analysis and calculating odds ratios, the following cut-off values for healthy controls from a research study were used [12]: mean IOP is more than 14.3±1.9, mean SBP is less than 118.7±9.4, mean DBP is less than 73.4±6.8, and mean OPP is less than 44.7±4.8.

RESULTS

Among patients with migraine, the mean age was 28.34±7.5 years, with a minimum age of 18 years and a maximum of 40 years. There were 31 (33%) males and 63 (67%) females. In the control group, the mean age was 27.94±7.29 years, with a minimum age of 18 years and a maximum of 40 years. There were 30 (31.9%) males and 64 (68.1%) females. The ages of the cases and controls were matched. An independent sample t-test was conducted to determine if the ages of the two groups were similar. The ages were found to be similar, with a test statistic of 0.375 and a p-value of 0.708.

The mean values of the parameters among cases (migraine patients during a headache-free period) and controls is shown in [Table/Fig-1]. There was a significant difference in SBP, DBP, and OPP between the two groups, as shown in [Table/Fig-1].

Variable (in mmHg)	Cases n=94 M±SD	Controls n=94 M±SD	t-test value	p-value
Mean IOP	13.27±2.02 Min10 Max17	13.38±1.87 Min 10 Max 18	-0.41	0.681
Mean Systolic BP (SBP)	118.91±4.67 Min110 Max126	116.09±5.18 Min 110 Max 124	3.93	<0.001*
Mean of Diastolic BP (DBP)	77.72±4.48 Min 70 Max 84	75.77±4.89 Min 70 Max 84	2.86	0.005*
Mean OPP	47.69±2.43 Min 41.6 Max 53	46.08±2.46 Min 41.6 Max 53.5	4.52	<0.001*

[Table/Fig-1]: Mean values of IOP, Systolic BP (SBP), Diastolic BP (DBP) and OPP (values are in mmHg) in patients with migraine during headache free period (n=94) and age matched controls (n=94). Independent t-test is used for comparison.
*Statistically significant association

For the purpose of analysis and calculating the odds ratio, the following cut-off values from a research study were used for the healthy controls [12]: mean IOP >14.3±1.9, mean SBP <118.7±9.4, mean DBP <73.4±6.8, and mean OPP <44.7±4.8. These values were considered as exposures since, according to the hypothesis, these factors in a migraine patient would increase the risk of developing ischaemia to the optic nerve head and glaucoma. In other words, the factors predisposing to glaucoma are high IOP, low SBP, low DBP, and low OPP. This is depicted in [Table/Fig-2].

There was no statistically significant association between the presence of high IOP and low DBP with the presence of migraine. However, a statistically significant association was found between

Parameters		Cases (migraine present)	Controls (migraine absent)	OR (95% CI)	p-value	aOR (95% CI)	p-value
IOP	IOP ≥14.3 mmHg, n=54	28 (51.9%)	26 (48.1%)	1.11 (0.59-2.09)	0.747	0.64 (0.31-1.33)	0.233
	IOP ≤14.2 mmHg, n=134	66 (49.3%)	68 (50.7%)				
SBP	SBP ≤118.6 mmHg, n=71	23 (32.4%)	48 (67.6%)	0.31 (0.17-0.58)	0.039*	0.26 (0.07-0.93)	0.039*
	SBP ≥118.7 mmHg, n=117	71 (60.7%)	46 (39.3%)				
DBP	DBP ≤73.3 mmHg, n=57	19 (33.3%)	38 (66.7%)	0.37 (0.19-0.71)	0.003*	3.67 (0.76-17.78)	0.106
	DBP ≥73.4 mmHg, n=131	75 (57.3%)	56 (42.7%)				
OPP	OPP ≤44.6 mmHg, n=48	11 (22.9%)	37 (77.1%)	0.20 (0.01-0.43)	<0.001*	0.17 (0.05-0.57)	0.004*
	OPP ≥44.7 mmHg, n=140	83 (59.3%)	57 (40.7%)				

[Table/Fig-2]: Association between IOP, SBP, DBP, OPP and presence of migraine.
*Statistically significant association
OR: Odds ratio; aOR: Adjusted odds ratio; CI: Confidence interval

the presence of low SBP and low OPP with the presence of migraine (p-value <0.05). The odds of being a migraine patient were 0.17 times higher among people exposed to OPP less than 44.6 mmHg.

Four patients underwent a second examination to compare the values during a migraine attack and a migraine-free period. However, this data was too small to draw any conclusions. The findings are shown in [Table/Fig-3]. During a migraine attack, the IOP did not change. However, the DBP fell, leading to a decrease in mean BP and a subsequent reduction in OPP.

Variable (mmHg)	During migraine attack	During migraine free period
Mean IOP	12.5±1.73	12.75±2.22
Mean Systolic BP (SBP)	121±2	120.5±1
Mean of Diastolic BP (DBP)	72±5.16	79±2.58
Mean OPP	46.38±1.60	48.65±1.58

[Table/Fig-3]: Mean OPP during acute migraine attack and pain free period among migraine patients (n=4).

DISCUSSION

Glaucoma is a progressive optic neuropathy characterised by disc changes and visual field abnormalities, where abnormal physiology in the optic disc interacts with the level of IOP [4]. The rate and extent of disc damage depend on the IOP and the underlying abnormal physiology. In normal-tension glaucoma, this abnormal physiology makes the optic disc vulnerable to damage, even in the absence of significantly elevated IOP [4]. Vascular dysregulation, including conditions such as hypertension, hypotension, migraine, and cold hands and feet, plays a role in causing disc damage in such cases [4]. The aim of the present study was to investigate OPP as an IOP-independent risk factor for glaucoma, specifically normal-tension glaucoma, in patients with migraine.

The association between migraine and glaucoma is well-established, although the exact mechanism remains unclear. Migraine is significantly associated with an increased risk of open-angle glaucoma and normal-tension glaucoma [6,13]. Findings from the Blue Mountains Eye Study also suggest a possible link between migraine headaches and open-angle glaucoma [14]. A higher frequency of migraine and vasospasm has been found to be associated with normal-tension glaucoma, particularly in females, and with a familial predisposition [5]. A supportive relationship between migraine and glaucoma was observed, as there was a reduction in the peripapillary retinal nerve fiber layer and choroidal thickness among migraine patients compared to controls (due to chronic ischaemic insult) [15]. The vascular hypothesis proposed in the pathogenesis of normal-tension glaucoma is further strengthened by the associations between multiple systemic vascular risk factors and low-tension glaucoma. These risk factors include systemic hypertension, diabetes mellitus, peripheral vascular disease, migraine headache, Raynaud syndrome, anaemia, systemic hypotension, and the use of calcium channel blockers [16].

The present study did not include hypertensive patients. However, in patients with hypertension, OPP may play a more significant role. A study found no difference in the glaucoma status of Indian subjects with or without hypertension. However, subjects on antihypertensive medications were almost twice as likely to have open-angle glaucoma. Interestingly, higher OPP was found to have a protective effect against glaucomatous disc damage. With every 1 mmHg increase in mean OPP, there was a 31% reduction in the risk of POAG [17]. Another study on Indian hypertensive patients receiving antihypertensive treatment and having POAG showed lower mean OPP compared to controls [18]. Although hypertensive patients had higher OPP compared to non hypertensives, they did not have a higher ocular blood flow, as measured by the pulsatile ocular blood flow tonograph. This may be due to chronic changes in vascular and haemodynamic factors in patients with hypertension [19].

A reduction in mean arterial pressure or an increase in OPP can lead to a decrease in ocular perfusion. If autoregulatory mechanisms are insufficient, then OPP may decrease due to vascular imbalances, leading to ischaemic damage of the optic nerve head. It is suggested that systemic blood pressure problems, particularly low blood pressure and low diastolic perfusion pressure, are risk factors in the pathogenesis of glaucoma. Nocturnal systemic hypotension, whether spontaneous or due to medications, has been found to increase the risk of glaucoma progression, specifically worsening of visual fields [20]. Patients with normal-tension glaucoma who exhibited more peripapillary choroidal microvasculature dropout, as assessed by optical coherence tomography angiography imaging (indicating compromised optic nerve head perfusion), were found to have a greater magnitude of night time diastolic blood pressure dip on continuous ambulatory blood pressure monitoring [21]. This is particularly significant in normal-tension glaucoma. In comparison to patients with POAG, patients with normal-tension glaucoma have lower mean arterial pressure (and experience more night time blood pressure dips), resulting in lower mean OPP, as shown in a South Indian study [22].

Regarding the changes occurring during a migraine attack, the present study found that during a migraine attack, IOP remains the same, while blood pressure decreases, leading to a decrease in OPP, specifically a decrease in DBP and OPP. These findings were consistent with studies that have measured blood pressure, IOP, and OPP in migraine patients [8,11,23]. Migraine headaches are associated with neurological, gastrointestinal, and autonomic system disturbances, which can cause blood pressure changes during a migraine attack. A study conducted on normotensive migraine patients noted a reduction in blood pressure, especially DBP. Diastolic hypotension was significant just before, during, and after an acute migraine attack [23]. IOP remains the same during an acute migraine attack. A study that assessed IOP in migraine patients found no significant changes in IOP during a migraine attack or pain-free period among migraine patients [8]. The present study also confirmed these findings. OPP remains the same in both the migraine and control groups. A study by Michael NDB et al., also found no difference in OPP between migraine patients and controls [8]. This is expected, as they did not calculate the fluctuations in OPP during migraine attacks and pain-free periods. In present study, there was also no difference in baseline OPP between migraine patients and controls. However, in the same study, the researchers noted significant thinning of the retinal nerve fiber layer in migraine patients compared to controls [8]. This indicates that the moments of insult are transient, but the damage is permanent.

Limitation(s)

The mechanism underlying headaches and auras in migraine patients is still not fully understood, although changes in vessel caliber are the most common occurrence. The present study did not take into consideration whether the patients had migraine with aura or without aura, which could be a confounding factor.

Another major limitation of this study was that OPP was assessed during the pain-free period. The baseline mean OPP of migraine patients appeared to be the same as that of healthy controls, or at least not lower. Therefore, it could not be proven that low OPP in migraine patients is a risk factor leading to glaucoma. In a small subset of four patients, it was found that during a migraine attack, the OPP reduced. This suggests that fluctuations in OPP occur before, during, or after a migraine attack. Reduced OPP or fluctuations in OPP can damage the optic nerve head and contribute to glaucoma progression. However, this finding was not conclusive due to the limited sample size, and a larger prospective trial would be needed to further investigate this relationship.

CONCLUSION(S)

The OPP among migraine patients differed significantly from that of the controls. However, further studies are needed to evaluate the relationship between perfusion pressure abnormalities and the risk of glaucoma in migraine patients. Considering OPP as a modifiable risk factor for glaucoma can provide opportunities for novel treatments of migraine.

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