Original Article

Ocular Pulse Amplitude in Non-Diabetic Patients with End Stage Renal Disease and Normal Individuals Using Dynamic Contour Tonometry

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Abstract

Introduction: Ocular Pulse Amplitude (OPA) is the fluctuation of IOP with the cardiac cycle which is equal to the difference between systolic and diastolic IOP. These variations in IOP are thought to be caused by the blood volume that is pumped into the eye, mainly the choroidal bed during each cardiac cycle. In patients with end stage renal disease (ESRD), Choroidal perfusion has been found to be reduced as determined by Indocyanine Green Angiography (ICG) which is an invasive procedure. OPA is recorded by Dynamic Contour Tonometer (DCT) which represents a potential new technology for measuring choroidal blood flow indirectly & non-invasively especially in patients with suspected compromise in perfusion as in ESRD. In this study we postulate that measurement of OPA can be used to assess the choroidal perfusion in patients with ESRD.

Objectives: To measure OPA in non-diabetic patients with ESRD on hemodialysis and to compare it with that of OPA in age matched normal individuals.

Materials & Methods: It was a prospective Cross-sectional study and was done in a clinical set up during the period of January 2013 to October 2013. OPA among 44 exposed and 44 non exposed individuals were measured using Dynamic Contour Tonometry (DCT) and analysis done.

Results: The mean OPA in non diabetic patients with ESRD was 1.945mm Hg (CI: 1.847 – 2.043) and the mean OPA in age matched normals was 2.16mm Hg (CI: 2.08 – 2.24).

Conclusion: OPA in non diabetic ESRD patients was statistically significantly lower than that of age matched normals (p=0.03). There was no correlation between OPA and other parameters like age, gender, intraocular pressure, blood pressure or serum creatinine levels.

Key words: Ocular Pulse Amplitude (OPA), End Stage Renal disease (ESRD), Dynamic Contour Tonometry (DCT), Non-diabetic patients, Indocyanine Green Angiography (ICG).

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Introduction

Ocular Pulse Amplitude (OPA) is the fluctuation of intraocular pressure (IOP) with the heart rate, which is equal to the difference between systolic and diastolic IOP (Knecht PB et al, 2012). OPA is an indirect indicator of the choroidal perfusion and reflects the ocular blood flow corresponding to the pulse as a function of time. These pulsatile variations in IOP are thought to be caused by the blood volume that is pumped into the eye, mainly the choroidal bed during each cardiac cycle. Simultaneous measurement of OPA and IOP is done with the help of Dynamic Contour Tonometer (DCT) which is a potential new technology for measuring choroidal blood flow indirectly & non-invasively. Moreover OPA has been studied in normals (Kaufmann C et al, 2006) as well as in patients with glaucoma (Stalmans I et al, 2008) and vascular disorders (Grieshaber MC et al, 2009). A reduction of the blood flow may cause hypoxia and further cell death and therefore may also initiate diseases like normal tension glaucoma and diabetic retinopathy.

In earlier studies with pneumotonometry (Kaufmann C et al, 2006), the mean OPA was found to be 1.5 ± 0.11 mmHg and with ocular blood flow analyzers, the OPA ranged from 2.2 ± 0.8 to 3.0 ± 0.92 mmHg. In a study of 223 normal eyes using DCT, Kaufmann C et al (2006) found a median OPA value of 3.0 mmHg (10th -90th percentile range, 1.8-4.3 mmHg). Indocyanine green angiography (ICG) was the only method available to assess choroidal perfusion and related abnormalities till recently (Ito YN et al, 2001). Also, choroidal perfusion is found to be reduced in patients with diabetes (Ciulla TA et al, 2002).

According to glomerular filtration rate (GFR) categories, chronic kidney disease is divided into 6 categories from G3a to G5 and the patients who come under G5 category with a GFR of < 15 ml/min/1.73m² is known as end stage renal disease (ESRD) patients or kidney failure patients who are on dialysis. In ESRD patients, choroidal perfusion has been found to be reduced as determined by ICG (Klein GJ et al, 1990). However ICG is an invasive procedure. But a precise evaluation of the changes in the choroidal circulation is mandatory to prevent visual function impairment during the management of these patients. So OPA could be used to give indirect evidence to the choroidal perfusion and may be used as an accurate noninvasive tool to assess ocular perfusion especially in patients with suspected compromise in perfusion as in ESRD.

Materials and Methods

A cross sectional, observational study was conducted in the Department of Ophthalmology from January 2013 to October 2013. The exposed group consisted of patients with non-diabetic ESRD on hemodialysis who had history of hypertension. Age matched individuals with no systemic illnesses formed the non-exposed group. Patients with ESRD on hemodialysis were recruited from the Department of Nephrology. Age matched subjects were selected from patients who came for ophthalmic evaluation to the Department of Ophthalmology. The study protocol was approved by the Institutional review board (IRB) and ethical committee which constituted members outside the institution as per ICMR guidelines required for any study conducted in the institution. Informed consent for the research was also obtained from the patients included in the study.

Non diabetic patients (Fasting plasma glucose (FPG) ≤ 126 mg% with no calorie intake for at least 8 hours prior according to American Diabetes Association (ADA) guidelines) ≥ 18 years of age with ESRD referred from the dialysis unit willing to give informed consent were included in the exposed group. Non hypertensives (Systolic

BP < 120 mm Hg and diastolic BP < 80 mm Hg without any anti-hypertensive medications according to Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure [JNC7] guidelines) and non-diabetics ≥ 18 years of age willing to give informed consent were included in the non-exposed group. OPA readings with quality factor of 1 or 2 measured by DCT were taken for both exposed and non-exposed group for the study. Patients with glaucoma (IOP > 24 mm Hg or suspicious discs), history of transient ischemic attacks or cerebrovascular accidents, patients with any corneal pathology with preclude the accurate measurement of OPA using DCT, patients with vascular disorders like coronary artery disease (CAD), carotid stenosis, carotidocavernous fistulas and autoimmune disorders were excluded from the study.

Laboratory investigations like Fasting Plasma Glucose (FPG) and Serum Creatinine were checked for those patients in the exposed group and FPG alone was checked for the non-exposed group. Fasting plasma glucose was done in the lab according to American Diabetic association guidelines 2013 (Executive summary: Standards of medical care in diabetes–2013). Patients who had FPG ≤ 126 mg/dl (ADA 2013 guidelines) were diagnosed as non-diabetics and were included in the study. Routine ocular examination was done in all the patients including visual acuity test using Snellen's chart, torch light examination, slit lamp examination, Intraocular Pressure measurement using Goldmann Applanation Tonometry and detailed fundus evaluation. In addition, OPA measurement using DCT was also done in all patients in both exposed and non-exposed group.

Given the non-availability of literature on OPA in ESRD, we conducted a pilot study to calculate the sample size. The pilot study consisted of 8 patients each in exposed and non-exposed group. Using DCT, we measured the OPA of all the patients. The measurements with quality factor 1 or 2 were taken and compared. When we compared the values that we obtained during the pilot study, we found that the OPA of patients in exposed group were lower than that of non-exposed group. 2 mean hypothesis test was used for obtaining the sample size and we got a sample size of 44 in each arm using the following formula,

$n = \frac{(Z_{\alpha/2}+Z_{1-\beta})^2 * 2 * s^2}{d^2} n = \frac{(Z_{\alpha/2}+Z_{1-\beta})^2 * 2 * s^2}{d^2}$ where 'n' is the sample size, 'α' is the error, '1-β' is the power, 'S' is the standard error and 'd' is the clinically meaningful difference between the 2 groups.

Data entry was done in an excel sheet and analyzed using SPSS version 17. The OPA in both eyes were averaged separately for all 88 subjects (44 exposed and 44 non-exposed) and used for analysis using Mann Whitney U test. Student t test was also used to look at statistical significance on parameters such as OPA and IOP in the exposed and the non-exposed groups. We also looked at correlation between OPA and parameters like age, gender, IOP and BP and serum creatinine levels in patients with ESRD, using Pearson's correlation coefficient (r).

Results

The data collected from 44 patients among the exposed and 44 patients among the non-exposed group were analyzed. Among the exposed group, 30 male patients and 14 female patients participated in the study whereas among the non-exposed group, 13 male patients and 31 female patients took part in the study. OPA measured twice in both eyes separately and the averaged OPA in the right and left eyes of each patient was used for analysis. In the exposed group we had patients from 18 years to 67 years of age. Hence, we recruited age matched individuals from 18 to 64 years to form the non-exposed group. Among the exposed group, 16 patients were under the age group of 18-28

years, 13 patients were under the age group of 29-38 years, 9 patients were under the age group of 39-48 years, 3 patients were under the age group of 49-58 and 3 patients were under the age group of 59-68 years. Among the non-exposed group, 18 patients were under the age group of 18-28 years, 12 patients were under the age group of 29-38years, 9 patients were under the age group of 39-48 years, 3 patients were under the age group of 49-58 years and 2 patients were under the age group of 59-68 years.

Among the exposed group in the right eye, the mean OPA in the right eye in exposed group was 1.945 ± 0.65 mm Hg (CI: 1.847 - 2.043, SE - 0.098). Mean OPA among the non-exposed in the right eye was 2.16 ± 0.58 mm Hg (CI: 2.08 - 2.24, SE - 0.087). When the mean OPA in the exposed group and non-exposed group were compared, OPA among the exposed group was lower than the non-exposed group. There was a statistically significant difference between the 2 groups (p = 0.03) and the confidence interval do not overlap.

The mean OPA in the left eye in exposed group was 2.10 ± 0.80 mm Hg (CI: 1.98 - 2.22, SE - 0.12). The mean OPA in the left eye in non-exposed group was 2.35 ± 0.53 mm Hg (CI: 2.28-2.42, SE - 0.07). The exposed group had lower OPA as compared to non-exposed group. There was a statistically significant difference between the 2 groups (p = 0.02) and the confidence intervals do not overlap. There was a strong positive correlation between OPA in right and left eye (r = 0.79) among the exposed group (Figure 1).

There was only a moderate correlation between OPA in the right and left eyes (r = 0.32) among the non-exposed (Figure 2).

The median age of subjects in the exposed and non-exposed groups was 30. Hence we looked at OPA in those patients who were ≤ 30 years and those who were > 30 years.

OPA in the right eye in the age group ≤ 30 years (n = 21) was slightly lower in exposed group compared to non-exposed group and it was not statistically significant. OPA in the right eye in patients with age > 30 years of age was lower among the exposed compared to non-exposed group, but it was not statistically significant.

OPA in both eyes in male and female patients were compared. OPA in female patients was lower among the exposed compared to non-exposed group and it was not statistically significant. OPA in both eyes in male patients was lower among the exposed compared to non-exposed group but was not statistically significant. However OPA in female patients were more compared to male patients in both exposed and non-exposed group but was not statistically significant.

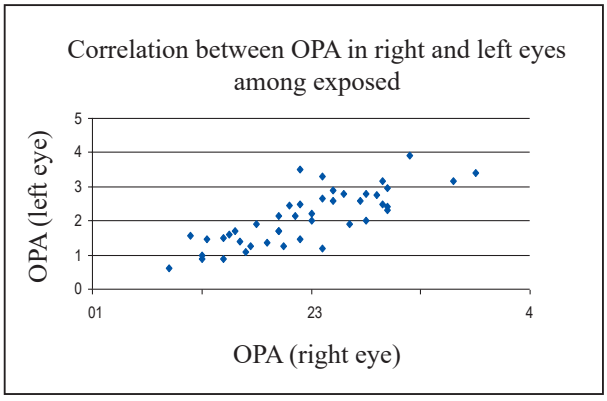

Figure 1

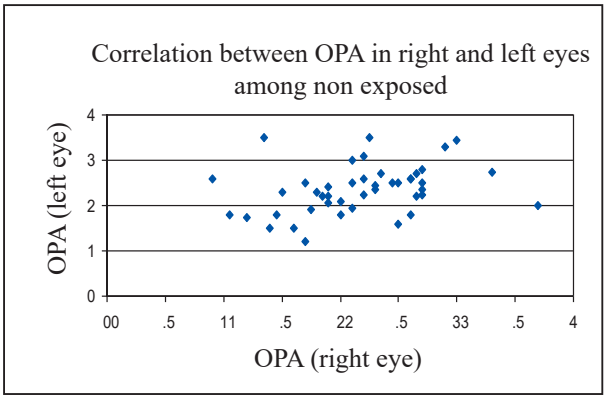

Figure 2

Discussion

Patients with ESRD who are on hemodialysis are always at a risk of developing eye diseases. Choroidopathy is a main complication that occurs in these patients and the only method to study the severity of the disorders of the choroid is ICG. Given the invasive nature of ICG, it is life threatening and hence contraindicated in ESRD (Brancato R et al, 1998). OPA is the fluctuation of IOP with heart rate and it is an indirect indicator of the choroidal perfusion. OPA can be measured with the help of DCT which helps in the simultaneous recording of OPA and IOP.

According to literature, normal OPA ranges from 1-3.4 mm Hg and there was positive correlation between OPA and IOP (Pourjavan S et al, 2007). We measured OPA to look at choroidal perfusion in patients with ESRD on hemodialysis and compared them with age matched normals. We chose patients with ESRD with no diabetes to ensure that OPA is not affected by diabetes and retinopathy if any. Since the patients were undergoing hemodialysis their blood pressures were also normal.

Analyzing the OPA in the right and left eyes separately would ensure that measurement errors and biases are eliminated. 2 values of OPA with quality factor 2 or less also minimized errors in measurement. In both right and left eyes the OPA in patients with

ESRD was statistically significantly lower than age matched normals. In the right eye the mean OPA was 1.945 mm Hg (CI: 1.847 - 2.043) and 2.16 mm Hg (CI: 2.08-2.24) in the ESRD group and normals respectively. There was a statistically significant difference between the 2 groups ($p = 0.03$). The fact that the confidence intervals do not overlap clearly indicates that there is a difference between the 2 groups. The mean

OPA in the exposed group and non-exposed groups in the left eye were also statistically significantly different ($p = 0.02$).

Similar to the study by Purjavan et al (2007), there was a very strong positive correlation

(Pearson's correlation coefficient $r= 0.79$) between OPA in the right and left eyes in patients with ESRD thus showing that both eyes have similar OPA ($p=0.03$). Similar correlation existed between IOP ($r=0.74$) in both eyes in patients with ESRD.

Studies by Kaufmann et al (2006), Stalmans et al (2008) and Purjavan et al (2007) found positive correlation between OPA and IOP as measured using DCT in normal subjects. However in our study we found no correlation between OPA and IOP using DCT in patients with ESRD as well as normal subjects.

In our study, we found that the mean OPA in non-diabetic patients with end stage kidney disease was 1.945 mm Hg (CI: 1.847 - 2.043) and the mean OPA in age matched normals was 2.16 mm Hg (CI: 2.08-2.24). The OPA in non-diabetic patients with end stage renal disease was found to be statistically significantly lower than that of age matched normals ($p = 0.03$). We also found that there was no correlation between OPA and other parameters like age, gender, intraocular pressure, blood pressure or serum creatinine levels.

With the assumption that age related changes in the choroidal blood flow can affect the

OPA we divided the patients into those who were 30 years or less and those more than

30 years. 30 years being the median age, was chosen as the cut off. With age considered as a confounding factor we assumed a considerable difference in OPA between exposed and non-exposed patients in the younger subset of patients. Age however, did not seem to account for changes in OPA in patients with ESRD in this study. The patients recruited for our study were

those undergoing hemodialysis and hence had normal blood pressure at the time of measuring OPA. Therefore the influence of high blood pressure on OPA could not be studied. The OPA would probably have been lower if we had recruited patients who were not on dialysis or if these measurements were taken just before the dialysis and compared with the values of the OPA after dialysis. This probably would have given us a better insight into the ocular blood flow in these patients. However, this was not within the scope of our study. Moreover, doubling the sample size would have been helpful in detecting the effect of age on measured OPA.

Conclusion

In this study, we postulate that measurement of OPA can be used as a simple non-invasive test to assess the choroidal perfusion in patients with end stage renal disease. In patients with ESRD on dialysis we found decreased OPA indicating decreased choroidal perfusion in ESRD. Following up and measuring the OPA in patients with ESRD prior to dialysis, immediately after dialysis and after renal transplantation would help us understand the changes in OPA and choroidal perfusion with treatment. This knowledge may also help us use OPA as a tool to detect the success of renal transplantation as it could potentially improve choroidal perfusion.

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