IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 22, Issue 6 Ser.10 (June. 2023), PP 38-44
www.iosrjournals.org

A Comparative Type Of Cross-Sectional Study Of Optic Nerve Head Perfusion In Normal Eyes And Eyes With Glaucoma Using Optical Coherence Tomography Based Microangiography

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Abstract:
Background*: To examine the difference in optic nerve head perfusion parameters between normal eyes and eyes with primary open angle glaucoma using optical coherence tomography based microangiography.*
Materials and Methods*: A case group of 30 patients with early primary open angle glaucoma and control group of 30 normal subjects were taken. OCTA scans were performed along with detailed ocular examination including BCVA, measurement of IOP and mean ocular perfusion pressure (MOPP), gonioscopy, optic disc evaluation and perimetry. Parameters noted using OCTA included structural parameters like CD ratio, rim Area and RNFL thickness and functional parameters like perfusion percentage and flux index.*
Results*: One eye of each subject from both case (30) and control group (30) were included in this study. The mean age difference between the two groups was non significant with p value of 0.340. Perimetry showed statistically significant difference in the visual field mean deviation between the two study groups (p<0.001). MOPP showed no statistically significant difference (p=0.423). OCTA showed statistically significant difference in fundus CD ratio (p<0.001); rim area (p<0.001); RNFL thickness (p<0.001); perfusion percentage (p<0.001) and flux index (p,0.001).*
Conclusion: *The perfusion parameters (perfusion percentage and flux index) and RNFL thickness and rim area were less in POAG group as compared to control group whereas the fundus CD ratio was more in POAG group compared to control group. Hence along with structural parameters, functional parameters can also be used for screening of glaucoma suspects which may facilitate in early diagnosis and initiation of therapy in glaucoma.*
Key Word*: Optic Nerve Head Perfusion ; Optic Coherence Tomography Based Microangiography ; Cup Disc Ratio ; Rim Area ; Retinal Nerve Fibre Layer Thickness ; Perfusion Percentage ; Flux Index.*

Date of Submission: 11-06-2023 Date of Acceptance: 21-06-2023

I. Introduction

Glaucoma is one of the leading causes of permanent adult blindness according to research conducted globally.[1] 10% of people over the age of 70 and close to 1% to 2% of people over the age of 40 are affected.[2] Even in developing nations like India, where glaucoma is the second-leading cause of blindness, statistics are evolving. It was predicted that India would house 20% of the world's glaucoma patients by the year 2020.[2]

Glaucomatous optic neuropathy is a sign of primary open angle glaucoma (POAG), which lacks a secondary etiology that can be determined. Chronic progressive optic neuropathy is associated with optic disc cupping and visual field (VF) changes with no obvious systemic or ocular causative factors.[3] Structural changes in POAG take place in the optic nerve head and retinal nerve fibre layer (RNFL) surrounding the optic disc. Glaucoma development is significantly influenced by abnormalities in vascular function in the Optic Nerve Head region.[4],[5] Vascular dysfunction was identified prior to the onset of visual neuropathy brought on by glaucoma.[5] According to earlier research, glaucomatous eyes have a considerable reduction in ocular perfusion as compared to the general population.[6],[7] Additionally, glaucomatous eyes with disease progression see a greater drop in blood flow than eyes without disease progression.[6]–[9]

A recently created novel diagnostic tool called optical coherence tomography based angiography (OCTA) uses a non-invasive imaging technique to assess blood flow by analysing the motion contrast of red blood

cells. As a result, we may use this to quantitatively evaluate the retina's microcirculation. Therefore, this unique imaging technique is capable of detecting any abnormalities in the microcirculation.

In order to achieve non-invasive three-dimensional (3-D) in vivo microcirculatory visualization in the eye with microscopic resolution, we will be using optical coherence tomography based microangiography (OCTA) in this study. This novel optical microangiography imaging technique is based on Fourier-domain optical coherence tomography (FD-OCT).[10] In order to distinguish between areas of static tissue and areas of blood flow, OCTA uses low-coherence interferometry to assess variations in backscattered signal. It does this by comparing successive B scans taken at the same cross-sectional position to find moving particles (red blood cells).

DEFINITIONS OF OPTIC NERVE HEAD PERFUSION PARAMETERS:

1. PERFUSION PERCENTAGE (%): The total area of perfused vasculature per unit area in a region of interest (ROI). This metric is calculated by summing up the number of pixels which contain perfused vasculature, and dividing the sum by the total number of pixels in the considered region and lastly calculating its percentage.

2. FLUX DENSITY (unitless): The total area of perfused vasculature per unit area in a region of interest (ROI), weighted by the brightness (intensity) of the flow signal. FI quantifies the number of blood cells passing through a retinal vessel cross sectional area per unit of time. It is a unitless parameter.

II. Aims And Objectives

To assess the ability of Optical Coherence Tomography based Microangiography in differentiating between primary open angle glaucoma and healthy eyes of normal subjects using optic nerve head perfusion parameters . Structural parameters have also been compared.

III. Material And Methods

This prospective comparative study was carried out on patients of Department of Ophthalmology at S.M.S. Medical Hospital, Jaipur, Rajasthan from 1st May 2021 to 30th April 2022. A total 60 adult subjects (both male and females) of aged ≥ 20 years were for in this study.

Study Design: Cross sectional study.

Study Location: The study was conducted in Upgraded Department of Ophthalmology, S.M.S. medical college and attached group of hospitals, Jaipur, Rajasthan.

Study Duration: 1st May 2021 to 30th April 2022.

Sample size: 60 patients.

Sample size calculation: Sample size was calculated at 95% confidence level and study power of 80% assuming the mean difference of 0.06 ± 0.06 in the normalized flux of healthy study group and glaucoma study group. For the detection of mean difference of 0.06 +/- 0.06 , the required sample size for this study is 30 cases in each study group.

Subjects & selection method: All men and women who meets the inclusion and exclusion criteria attending the OPD in Ophthalmology department of SMS Medical College & Hospital , Jaipur, during the study period were enrolled in the study. Subjects were divided into two groups (each group had 30 participants) on the basis of criterias for case group and control group.

Group A (N= 30 patients) - Case Group consisting of patients with primary open angle glaucoma.

Group B (N= 30 patients) - Control Group consisting of healthy subjects.

Inclusion criteria:

1. Subjects were either healthy volunteers or early open-angle glaucoma patients of age 20 years or older.
2. For healthy subjects:
   (a) IOP of 21 mmHg or less with no history of raised IOP.
   (b) Healthy appearance of optic disc.
   (c) No abnormality in visual field.
   (d) Best Corrected Visual Acuity (BCVA) of 20/40 (6/12) or better.
   (e) Open angles.
   (f) Willing to participate in study.
   (g) Normal retinal nerve fiber layer (RNFL) thickness.

3. For Primary Open Angle Glaucoma subjects:
   (a) Intra ocular pressure >21 mm Hg on more than two occasion with Goldmann applanation tonometer.
   (b) BCVA of 20/40 (6/12) or better.
   (c) Refractive error between -6 and +3D spherical equivalent.
   (d) Willing to participate in study.
   (e) Presence of glaucomatous optic neuropathy with corresponding RNFL defects.

Exclusion criteria:
1. Uncooperative patients.
2. Any ocular disease other than glaucoma and cataract.
3. Any corneal pathology.
4. Significant media opacity preventing high quality images.
5. Primary angle closure glaucoma.
6. Ocular trauma.
7. Surgery other than uneventful cataract extraction or glaucoma surgery in affected or contralateral eye .

Procedure methodology

The hospital based comparative observational study was performed with the approval of the Institutional Ethics Committee. Written informed consent was obtained from all the patients after giving them a full explanation of the study. The study has recruited subjects with primary open angle glaucoma (POAG) or normal optic discs. One eye from each subject was included in this study. A single eye was randomly selected and imaged if both are eligible.

Detailed history was taken regarding past ocular history, medical history like diabetes and hypertension . All subjects underwent a comprehensive ophthalmologic examination at time of enrolment. The diagnosis of POAG was based on the presence of glaucomatous optic neuropathy with corresponding RNFL defects, and a history of intraocular pressure (IOP) greater than 22 mm Hg. Mean ocular perfusion pressure was calculated and then visual field examination was done.

Thereafter, we calculated the optic nerve head structural biometric measurements like rim area, average cup-to-disc ratio and retinal nerve fiber layer thickness . Then, we measured the optic nerve head perfusion by perfusion parameters like perfusion percentage and flux index using optical microangiographic imaging technique of OCTA .

Firstly we compared the perfusion parameters of the two study groups and then we compared this perfusion parameters with structural biometric parameters of ONH.

Statistical analysis was done using suitable test of significance.

Statistical analysis

The questionnaires were initially checked for completeness, and data was cleaned for errors and missing values. The corrected data was then entered into Microsoft Excel after preparing a Master-chart. After data entry of every ten questionnaires, one random form was picked and data entry was re-checked. An independent person verified data entry of two randomly chosen forms after entry of every fiftieth questionnaire.

Data analysis was done using licensed SPSS software version 21.0 (Chicago, Illinois). Univariate analyses was done initially and the results were presented with the help of tables, text, bar-diagrams and pie-charts. Descriptive statistics were used to calculate frequencies of categorical variables, and measures of central tendencies and dispersion were used to describe continuous variables. Independent t-test and ANOVA test were used to compare the continuous variable and chi-square test was used for categorical variables. Non parametric Mann Whitney test and Kruskal Wallis test were used in case of data did not follow a normal distribution. Data are presented as mean (standard deviation) or number or proportions.
A p-value <0.05 was considered as statistically significant.

IV. Result

Our study population consisted of 30 patients and 30 controls with mean age of 50.97 ± 12.65 years and 50.63 ± 14.45 years respectively. Youngest participant in case group was 34 years old while oldest participant was 79. In control group youngest and oldest participants was 22 years and 78 years old. There was no statistically significant age difference among both groups.

Male participants in case group and control group was 60.0% and 50.0% respectively and female participants in case and control groups was 40.0% and 50.0% respectively, this gender distribution was not statistically significant.

Mean Intra Ocular Pressure value in case group and control group was 23.87± 2.16 mmHg and 12.33±2.47 mmHg respectively and this difference was statistically significant.

Mean Ocular Perfusion Pressure (mm Hg) in case group and control group was 49.58±5.73 and 50.76±5.61 respectively which was not statistically significant.

Mean Visual Field Mean Deviation (in dB) in case group and control group was -5.10± 0.89 dB and -1.08±1.37 dB respectively and this difference was statistically significant.

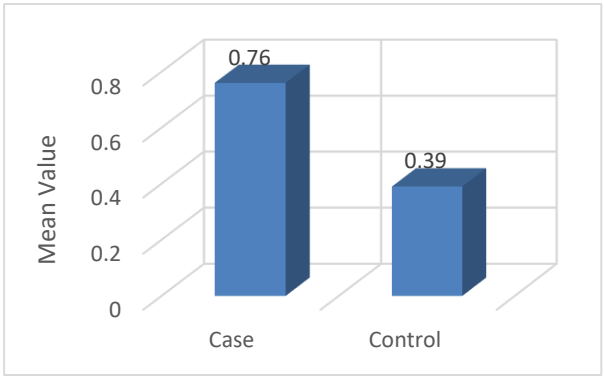
Table 1 shows the comparison of optic nerve head structural parameters between POAG case group and control group using OCTA.

Table no 1: Comparison of optic nerve head structural parameters.

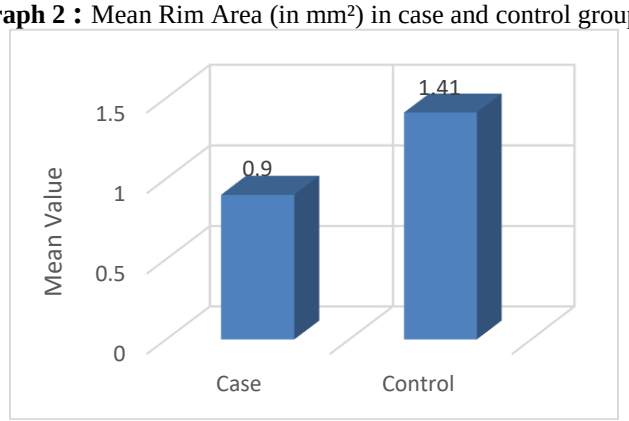
Structural Parameters	Case Group (Mean ± SD)	Control Group (Mean ± SD)	p-value
Cup Disc Ratio (unitless)	0.76 ± 0.11	0.39 ± 0.09	<0.001
Rim Area (in mm^2)	0.90 ± 0.23	1.41 ± 0.12	<0.001
RNFL Thickness (in µm)	70.73 ± 11.72	98.13 ± 9.08	<0.001

From Table 1 , we can see that mean fundus Cup to Disc Ratio in case group and control group was 0.76±0.11 and 0.39±0.09 respectively. Mean Rim Area (in mm^2) in case and control group was 0.90±0.23 millimetre² and 1.41±0.12 millimetre² respectively. Mean RNFL Thickness (in µm) in case group and control group was 70.73±11.72 µm and 98.13±9.08 µm respectively and these differences were statistically significant (p<0.001).

Graph 1 : Fundus- Mean Cup to Disc Ratio in case and control groups.



Graph 2 : Mean Rim Area (in mm^2) in case and control groups.



Graph 3 : Mean RNFL Thickness (in µm) in case and control groups.

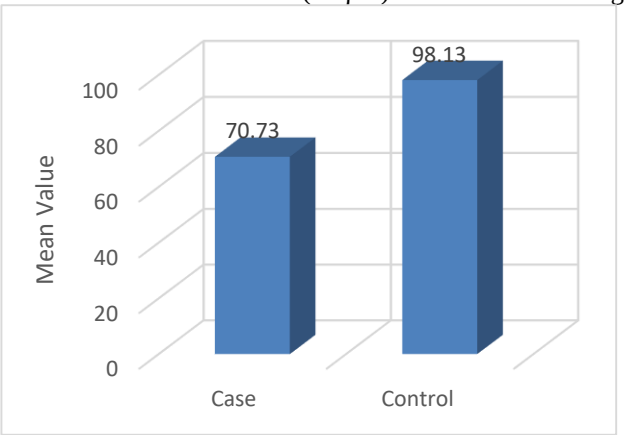


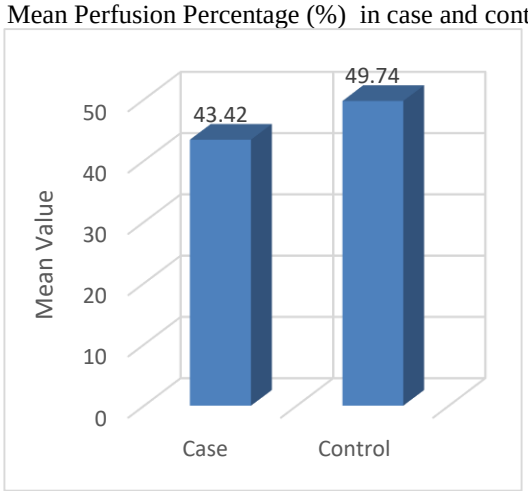
Table 2 shows the comparison of functional (vascular) parameters of optic nerve head between POAG case group and control group using OCTA.

Table no 2 : Comparison of optic nerve head functional parameters.

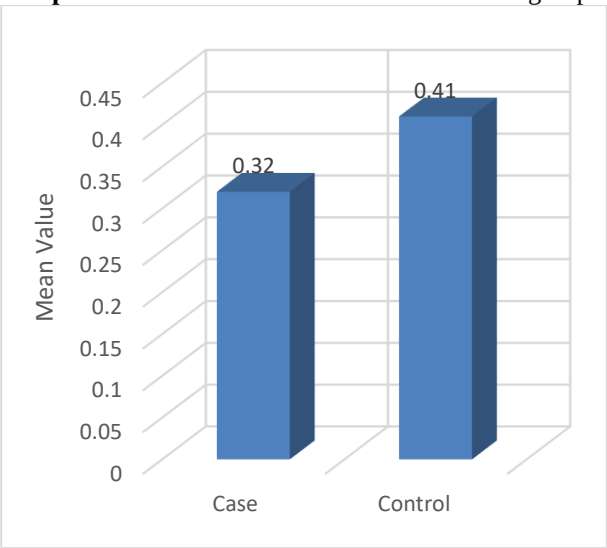
Functional Parameters	**Case Group (Mean ± SD)**	**Control Group (Mean ± SD)**	**p value**
Perfusion percentage (%)	43.42 ± 1.79	49.74 ± 2.59	<0.001
Flux Index (ratio)	0.32 ± 0.05	0.41 ± 0.02	<0.001

From Table 2 we can say that mean Perfusion Percentage in case and control group was 43.42 ± 1.79 % and 49.74 ± 2.59 % respectively and this difference was statistically significant. Also mean Flux Index value in case and control group was 0.32 ± 0.05 and 0.41 ± 0.02 respectively which was also statistically significant.

Graph 4 : Mean Perfusion Percentage (%) in case and control group.



Graph 5 : Mean Flux Index in case and control groups



V. Discussion

In this hospital based observational study, 60 participants were included for the analysis. They were divided in two groups, case group comprising of 30 participants with early primary open angle glaucoma and control group comprising of 30 normal participants (as per inclusion criteria).

In our study comparison between glaucoma patients and healthy controls regarding the age distribution illustrated no statistically significant difference (p=0.340). The mean age of the participants of case and control group was 50.97± 12.65 and 50.63±14.45 respectively. Similarly, study of Chen et al[11] showed that the mean age of patients was 62.9±11.4 years and mean age of control was 68.1±7.3 years which demonstrated no statistically significant difference. But in the study of Jia et al[12], the mean age in the normal group, 52 ± 10 years, was 16 years younger than the glaucoma group.

In current study, the gender distribution was not statistically significant (p=0.604). The percentage of male participants in case group and control group was 60.0% and 50.0% and that of female was 40.0% and 50.0% respectively. Study done by Chen et al[11] showed that male were 11 (52.4%) and female were 10 (47.6%) in patients and 12 (60.0%) male and 8 (40.0%) female in control group and the gender distribution was statistically non-significant. However, Jia et al[12] did not consider the gender distribution in their study.

Current study showed the mean IOP in case group and control group was 23.87±2.16and 12.33±2.47 mmHg respectively and this difference was statistically significant (p<0.001). This result was contrasting to the result found in the study of Chen et al[11] where the mean values for IOP were 15.0±4.0 mm Hg for patient group and 13.6±3.5 mm Hg for control group which was statistically non significant. Jia et al[12] also shows non significant difference in the IOP between the control group and glaucoma group with a p value of 0.118.

In our study, the mean values of mean ocular perfusion pressure in case and control group was 49.58±5.73 mm Hg and 50.76±5.61 mm Hg respectively. This difference was not clinically significant (p=0.423). Similar result was found in the study of Chen et al[11] where the mean values of MOPP were 48.1±9.1 mm Hg for patient group and 53.1±9.2 mmHg for control group. Also, Jia et al[12] showed non significant relation in values of MOPP between control group and glaucoma group with a p value of 0.662.

In current study, mean VFMD in case group and control group was -5.10± 0.89 dB and -1.08 ± 1.37 dB respectively and this difference was statistically significant (p<0.001). In the study of Chen et al[11], the values for VFMD were not compared. Even in that study, only VFMD value for glaucoma group is calculated. But, Jia et al[12] studied the difference in mean value of VFMD between the control group 0.20±0.87 dB and the glaucoma group -3.28±4.12 dB which came out to be statistically significant with a p value of 0.003.

Present study showed Fundus CD Ratio in case group and control group was 0.76± 0.11 and 0.39±0.09 respectively (p< 0.001). It clearly indicates that this difference was clinically significant. Results of Chen et al[11] study showed that normal controls had significantly lower CD Ratio when compared with glaucoma. In that study, the averaged CD Ratio was 0.44±0.18 for normal and 0.71±0.11 for glaucomatous patients. This result was statistically significant (p<0.0001). Jia et al[12] study showed the mean Cup/Disc area ratio of control group and glaucoma group to be 0.11±0.10 and 0.37±0.17 respectively with a p value of 0.012 which was statistically significant.

Current study showed averaged RNFL thickness in case group and control group was 70.73±11.72 µm and 98.13±9.08 µm respectively (p< 0.001). It clearly indicates that this difference was clinically significant.

Results of Chen et al study also showed that normal controls had significantly higher averaged RNFL thickness values when compared with values of patients with glaucoma. [11] In that study, the averaged RNFL thickness was 89.7±9.9 µm for normal and 66.5±8.5 µm for glaucomatous patients. This result was statistically significant ($p<0.0001$). In the study of Jia et al[12], the mean NFL thickness was 107.9±9.9 in the control group and 82.0±17.0 in the glaucoma group with a p value of 0.000 which was statistically significant.

In our study, the rim area in control group and case group have values 1.41±0.12 mm² and 0.90±0.23 mm² respectively ($p<0.001$). This result is statistically significant. This result is in match with the result of Chen et al[11] study where the rim area was 1.30±0.16 mm² in control group and 0.82±0.19 mm² in glaucoma group which was also statistically significant ($p<0.0001$). Both studies pointed towards the fact that rim area is significantly lower in glaucomatous group as compared to normal group. Also, Jia et al[12] study showed similar results with mean value of rim area 1.55±0.34 mm² in the control group and 1.13±0.25 mm² in the glaucoma group which was statistically significant with a p value of 0.007.

When we compared functional parameters of optic nerve head between control and glaucomatous group in our study , we found that both the parameters were significantly reduced in glaucomatous group as compared to the control group. The mean value of perfusion percentage was 43.42±1.79 % in case group and 49.74±2.59 % in the control group with p value of <0.001. Also, the mean value of flux index was 0.32±0.05 in case group and 0.41±0.02 in control group with a p value of <0.001. Both results are statistically significant.

This is in harmony with the study of Chen et al[11] which was done to investigate the differences of perfusion in the optic nerve head between glaucomatous eyes and normal eyes. In that study, compared with normal eyes , glaucomatous eyes had a significantly lower flux in preLC (0.32±0.04 in normal and 0.25±0.07 in glaucoma with a p value of 0.0002), lower vessel area density (0.76±0.02 in normal and 0.70±0.06 in glaucoma with a p value of <0.0001) , lower normalized flux (0.36±0.04 in normal and 0.30±0.06 in glaucoma with a p value of 0.0003). All the results were statistically significant.

Jia et al[12] study also showed statistically significant difference in the flux index with a p value of 0.003 between the control group and glaucoma group with mean values of 0.161±0.008 and 0.121±0.0263 respectively.

VI. Conclusion

To conclude, we found that in our study perfusion parameters which we used in our study (perfusion percentage and flux index) and RNFL thickness and rim area were less in POAG group and fundus CD ratio were more in POAG group as compared to control group.

Hence, we recommend that the evaluation of ocular perfusion parameters using optical coherence tomography based microangiography may be used in the screening of glaucoma suspects. This will facilitate in the early diagnosis of glaucoma and initiation of therapy at an early stage.

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