Retinal Venous Occlusive Diseases and Study of their Risk Factors

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ABSTRACT

Introduction: Retinal vein occlusion (RVO) is a major cause of vision loss. Of the two main types of RVO, Branch Retinal Vein Occlusion (BRVO) is 4 to 6 times more prevalent than Central Retinal Vein Occlusion (CRVO), and is the most common type of RVO. Risk factors evaluated in this study include Age, Sex, Hypertension, Diabetes Mellitus, Primary Open Angle Glaucoma (POAG), Tobacco consumption in any form, Dyslipidemia, Hyperhomocysteinemia and Iron deficiency Anaemia (IDA). Current research aimed to study the risk factors associated with Retinal Venous Occlusive diseases and to study correlation of occurrence of lesions with these risk factors.

Material and methods: This was a hospital based cross-sectional study involving 60 cases diagnosed with Retinal Venous Occlusions who were further evaluated for the above mentioned risk factors. Results were evaluated by Unpaired t test, Fisher test, student 't' test and Chi-Square test. 'p' value less than 0.05 was taken as significant**.**

Results: BRVO (n=49), CRVO (n=11). Most common co-morbidity was hypertension, which was found to be significant ($p<0.05$). Diabetes, dyslipidemia, tobacco in any form, iron deficiency anaemia were not found to be significant. Hyperhomocystemia was found to be significant ($p<0.05$) under 40 years of age and insignificant risk factor above 40 years. Presence of POAG with a duration of more than 5years was significant factor in CRVO but not in BRVO.

Conclusion: Age and hypertension are significant risk factors for RVO. Hyperhomocysteinemia is a significant risk factor for RVO in patients below 40 years on age. POAG is a risk factor for development of CRVO. Presence of multiple risk factors increases the chances of development of RVO.

Keywords: Central Retinal Vein Occlusion, Branch Retinal Vein Occlusion, Hypertension, Hyperhomocysteinemia, Primary Open Angle Glaucoma

INTRODUCTION

The dramatic picture of retinal vein obstruction, initially described as retinal apoplexy by Liebreich (1854) and hemorrhagic retinitis by Leber (1878), was first established as a clinical entity due to thrombosis by Julius von Michel (1878),who recognized that the relatively common appearances of gross venous disturbances and profuse retinal haemorrhages were due to this cause.

Retinal vein occlusions (RVOs) are the second most common retinal vascular diseases after diabetic retinopathy[1]; and a major cause of vision loss.[2]

Classification of retinal venous occlusive diseases:

- Central retinal vein occlusion (CRVO)
- Hemiretinal vein occlusion (HRVO)
- Branch retinal vein occlusion (BRVO)
- Papillophlebitis[3]

Untreated RVO often results in vision impairment and significant ocular complications in a substantial proportion of patients. Retinal venous occlusive disease typically occurs at arteriovenous crossing in BRVO or at the Lamina cribrosa in CRVO and HRVO (anatomical variant of CRVO).[4,5]

Retinal venous occlusions have a characteristic appearance with intra-retinal haemorrhages, cotton wool spots, tortuous and dilated retinal veins, retinal oedema and occasionally optic disc swelling. These findings are present segmentally in BRVO, in either the superior or inferior half in HRVO, and in all quadrants of the retina in CRVO. Some mild CRVOs in patients younger than 50 years are classified as papillophlebitis.

Vision loss can vary from minimal vision loss to complete blindness.Causes of vision loss associated with RVO include macular oedema, macular non-perfusion, epiretinal membrane, vitreous hemorrhage, neovascular glaucoma or tractional retinal detatchment.[5-9]

RVO affects both the sexes equally[8,9] and is more frequent in older age (over 65 years)[5]. Systemic risk factors include Hypertension, Diabetes Mellitus, Dyslipidemia, Atherosclerotic associated diseases like ischemic heart disease, and cigarette smoking,

Systemic vasculitis including systemic lupus erythematosus, sarcoidosis, and syphilis; Hypercoagulation diseases like antiphospholipid syndrome[10-11], protein S deficiency and thrombophilia.[12-14] Hematologic neoplasia including polycythaemia vera, multiple myeloma, and leukemia. Drugs like oral contraceptives, diuretics and Hepatitis B vaccine are also known to cause RVOs. Individuals less than 60 years of age may have a greater association with hypercoagulable states and inflammatory conditions, compared to older persons with a higher incidence of systemic vascular disease risk factors.[15,16]

Ocular risk factors include POAG, ischemic optic neuropathy,

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pseudotumor cerebri, tilted optic nerve heads and optic nerve head drusen.[5,17,18]

Current research aimed to study the risk factors associated with Retinal Venous Occlusive diseases and to study correlation of occurrence of lesions with these risk factors.

MATERIAL AND METHODS

A total of 60 patients diagnosed with RVOs irrespective of age and sex were studied from the period of December 2015 to May 2017 at the Krishna Institute of Medical Sciences Hospital, Karad. A valid consent of the patients was obtained prior to the examination. Detailed history was noted. Ocular examination including Best Corrected Visual Acuity, Anterior segment on Slit lamp Biomicroscopy, Intraocular pressure on Goldmann's Applanation Tonometer and Gonioscopy was done. Posterior segment examination by Indirect and Direct ophthalmoscopy after dilatation with 0.8% tropicamide and 5% phenylephrine eye drops (if not contraindicated) was done and Fundus photograph was taken. Blood Pressure was noted and laboratory investigations including Blood Glucose, Haemoglobin, Lipid Profile, Serum Homocysteine were done. Patients with co-morbidities were further classified into newly diagnosed and known cases. Known cases were further classified into controlled and uncontrolled cases.

RESULTS

BRVO was found in 52 eyes of 49 patients and CRVO was found in 14 eyes of 11 patients.

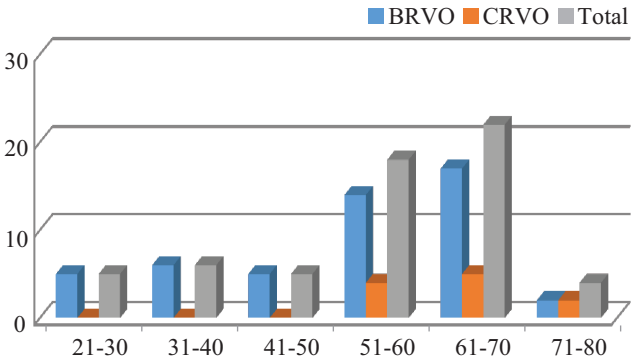
Distribution of patients according to Age

Majority of the patients (36.7%) were in the age group of 61-70 year; with an average age of 65 years. (Graph 1)

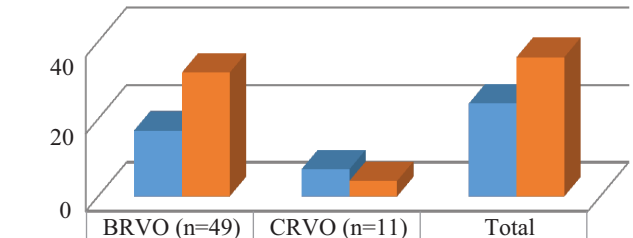
Distribution of patients according to Sex

There was female preponderance (60%) in the group while male patients constituted 40% of the study group. (Graph 2)

Majority of patients had Hypertension (69.4% of BRVO

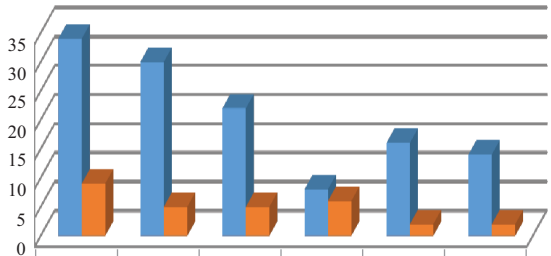


Graph-1: Distribution according to age



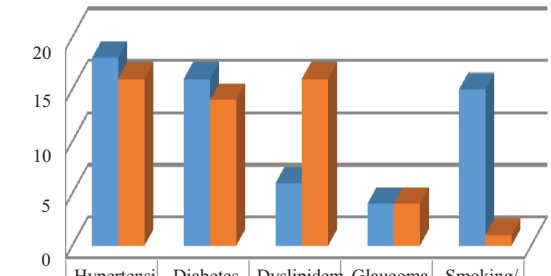
	BRVO (n=49)	CRVO (n=11)	Total
Male	17	7	24
Female	32	4	36

Graph-2: Distribution according to sex



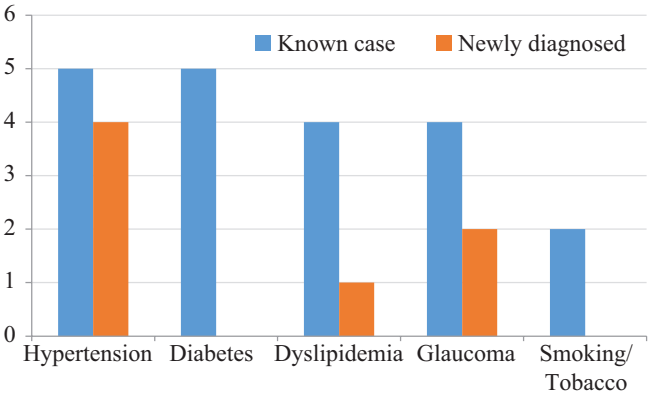
	Hypertension	Diabetes Mellitus	Dyslipidemia	Glaucoma	Smoking/ Mishri	Hyperhomocysteinemia
BRVO (n=49)	34	30	22	8	16	14
CRVO (n=11)	9	5	5	6	2	10

Graph-3: Distribution of patients according to Co-morbidities

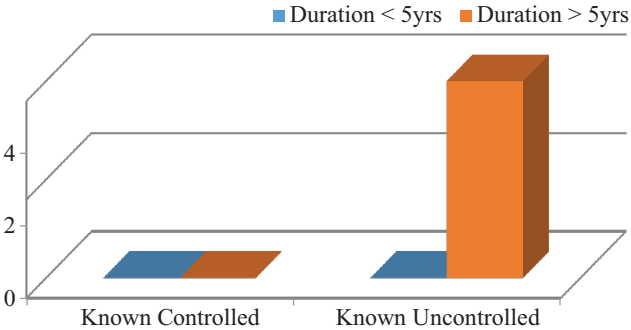


	Hypertension	Diabetes Mellitus	Dyslipidemia	Glaucoma	Smoking/ Mishri
Known	18	16	6	4	15
Newly Diagnosed	16	14	16	4	1

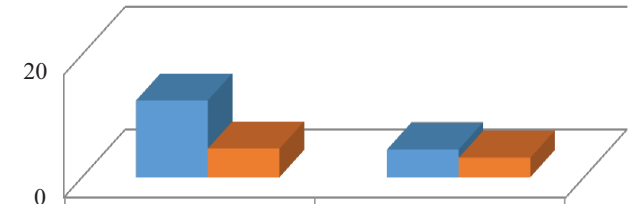
Graph-4A: Correlation of Known and Newly Diagnosed Cases with BRVO



Graph-4B: Correlation of Known and Newly Diagnosed Cases with CRVO

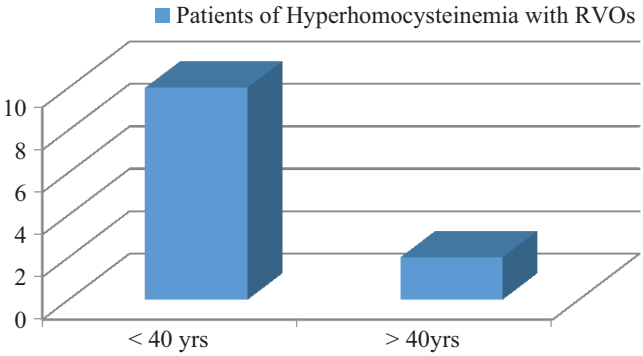


Graph-5: Association of duration of Glaucoma and CRVO



	Mean	SD
≤40	12.48	4.5
>40	4.64	3.15

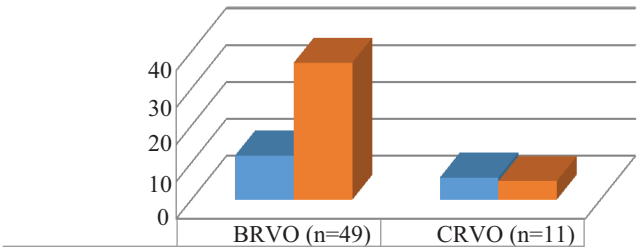
Graph-6A: Association of Age and Homocysteine in patients



Graph-6B: Patients of Hyperhomocysteinemia with RVOs

Right Eye	16.66	5.29	27.36	11.26
Left Eye	16.16	3.3	21.69	6.91

Graph-7A: Intra-ocular pressure (mmHg) in patients with BRVO and CRVO



Single Risk Factor	12	6
Multiple Risk Factors	37	5

Graph-8: Association of Single and Multiple Risk Factors with Retinal Venous Occlusive Diseases

cases and 81.8% of CRVO cases)followed by Diabetes Mellitus(61.2% of BRVO cases and 45.5% of CRVO cases). (Graph 3)

Correlation of Known and Newly Diagnosed Cases with RVOs:

The correlation of known and newly diagnosed cases with BRVO and CRVO was statistically significant as per Chi-Square test ($p<0.05$). (Graph 4a)

Association of Duration of POAG with CRVO

The association of duration of POAG with CRVO was found to be statistically significant as per Chi-Square test ($p<0.05$). (Graph 5)

Association of Age and Homocysteine in patients

This difference is statistically significant between the homocysteine levels of the patients under the age of 40 years and those above the age of 40 years; as per Student t-test (**$p<0.05$**). (Graph 6a)

The study showed 10 patients with Hyperhomocysteinemia under the age of 40 years and 2 patients above the age of 40 years.This difference is statistically significant as per Student t-test ($p<0.05$).(Graph 6b)

Graph 6b

Intra-ocular pressure (mmHg) in patients with BRVO and CRVO

It was observed that there is significant difference in the mean intra-ocular pressure in patients with BRVO and CRVO for both the eyes as per Student t-test (**$p<0.05$**). (Graph 7a)

Association of Duration of Glaucoma with CRVO

All Known cases of Glaucoma having CRVO were uncontrolled cases with duration of glaucoma more than 5 years. The association of duration of glaucoma with CRVO was found to be statistically significant as per Chi-Square test ($p<0.05$).

Association of Single and Multiple Risk Factors with Retinal Venous Occlusive Diseases There is significant association of single and multiple risk factors with retinal venous occlusive diseases as per Chi-Square test ($p<0.05$). (Graph 8)

Association of duration of Hypertension, Diabetes Mellitus and Dyslipidemia with RVO was not found to be significant and nor was the association between occurrence of RVO among known and newly diagnosed cases of the above. Diastolic hypertension was found to be more significant than Systolic hypertension in causation of RVO. Neither Tobacco chewing in any form; nor its duration was found to be associated with RVO. POAG was not found to be significant in the development of BRVO. When Hyperhomocysteinemia was considered as a risk factor irrespective of age; it was not significant. IDA was not found to be a significant risk factor.

DISCUSSION

Many studies and case reports regarding risk factors for RVOs are present in the literature.

Advancing age is an important risk factor for RVO (Table-1). Age-related retinal arterial stiffening compresses the underlying vein at the arteriovenous crossing leading to venous obstruction.

Prakhar S et al[19] 2015, in a tertiary eye center based prospective, interventional study observed Hypertension, diabetes mellitus and dyslipidemia in 35 (85%), 15 (37.5%) and 8 (20%) patients, respectively. Homocysteine level was found to be raised in 11 (27.5%) patients.

Cahill M et al[20] 2011, in a retrospective case-control study observed no significant differences were noted between cases

and controls in the mean serum total cholesterol levels, use of lipid lowering agents, prevalence of diabetes, ischaemic heart disease, previous transient ischaemic attack, or stroke. Di Crecchio L et al[21] in 2014, noted that atherosclerosis (age, hypertension) and not Hcy may be the main culprit for RVO.

Recent studies evaluating Hypertension as a risk factor:

Year	Study	Retinal venous occlusion	Significance
2015	Prakhar et al[19]	RVO	Significant
2014	Di Crecchio L et al[21]	RVO	Significant
2014	Lam HD et al[22]	BRVO	Significant

Recent studies evaluating Diabetes Mellitus as a risk factor:

Year	Study	Retinal venous occlusion	Significance
2015	Johnston RL et al[23]	BRVO	Not significant
2013	Swart J et al[24]	RVO	Significant
2014	Lam HD et al[22]	CRVO	Significant

Recent studies evaluating Dyslipidemia as a risk factor:

Year	Study	Retinal venous occlusion	Significance
2014	Lam HD et al[22]	RVO	Significant
2012	Salomon O et al[25]	BRVO	Significant

Elevated Hcy is both an independent risk factor for atherosclerotic vascular disease and interacts with other risk factors such as smoking and hypertension to increase cardiovascular disease risk.[26,27] Hcy levels are determined by both genetic and nutritional factors and possible mechanisms of action of Homocysteine on vascular endothelium include promotion of platelet activation, enhanced coagulability, and smooth muscle proliferation.

Year	Study	Retinal venous occlusion	Age group	S
2014	Di Crecchio L et al[21]	RVO	-	NS
2016	Lahiri KD et al[28]	RVO	Below 40	S
2015	Chua B et al [29]	CRVO	Below 50	S
2015	Di Crecchio L et al[21]	BRVO	Below 40	S
S - Significant; NS - Not significant				

Ocular Perfusion pressure is inversely proportional to Diastolic Blood Pressure and Intraocular Pressure.POAG is known to cause CRVO by reducing Ocular Perfusion Pressure and by causing a mechanical stretch on Lamina cribrosa. POAG is six times more likely to cause CRVO than BRVO.

Year	Study	Retinal venous occlusion	Significance
2010	Cahill MT et al[30]	CRVO	Significant
2012	Appiah AP et al[31]	CRVO	Significant
2012	Appiah AP et al[31]	BRVO	Not Significant

CONCLUSION

Age above 65 years, is a significant risk factor There is a statistically significant difference between Known cases and Newly Diagnosed cases of RVOs, showing that there is a higher risk of developing RVOs in patients who are known cases of above mentioned risk factors. Serum Homocysteine is a significant risk factor below 40 years of age and its level are higher in the age group of patients below 40years. Hypertension, more specifically Diastolic Hypertension is a significant risk factor. Known case of POAG more than 5 years duration is a significant risk factor for development of CRVO. The intraocular pressure values are significantly higher in CRVO group than in BRVO group. Presence of Multiple risk factors carries a significantly higher risk of developing RVOs.

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