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MANAGEMENT OF RETINAL VEIN OCCLUSION IN AN AFRICAN POPULATION-ANALYTICAL COMPARATIVE RETROSPECTIVE STUDY

Francis Kwasi Obeng[1],Vipan Kumar Vig[2], Mani Alagar[3],Keziah Obeng[4], Michael Asare[5], Samuel Obeng[6], Preetam Singh[7], Rajbir Singh[8], Juhisudha Manivannan[9], Baaba Dennis[10]

[1]Eye Department, 37 Military Teaching Hospital, Accra, Ghana (Bay University School of Medicine, USA)
[2]Amritsar Eye Hospital, Amritsar 143001, Punjab State, India
[3]Bay University School of Medicine, USA
[4]Department of Public Health, Korle-Bu Teaching Hospital, Accra, Ghana
[5]Department of Anaesthesia, 37 Military Teaching Hospital
[6]University of the People, 595 E, Colorado Boulevard, Suite 623, Pasadena, CA 91101, USA
[7]Dr. Sohan Singh Eye Hospital, Shivala Bhaiyan, Batala Road, Amritsar, Punjab State, India
[8]Sardar Bahadur Dr. Sohan Singh Eye Hospital, Amritsar, Punjab State, India
[9]Bay University School of Medicine, USA
[10]Department of Biostatistics, 37 Military Teaching Hospital, Accra, Ghana

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Corresponding Author
Francis Kwasi
Eye Department, 37 Military Teaching Hospital, Accra, Ghana (Bay University School of Medicine, USA)

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ABS TRAC T

Introduction: *Introduction* Retinal Vein Occlusion (RVO) is a severe ophthalmic disease capable of causing blindness and morbidityif not properlymanaged.Interventional options include management of systemic and ocular risk factors with intravitreal anti-vascular endothelial growth factors (IVAVEGF), steroids (IS), gene therapy (GT), peptide-based agents (PBA) and small molecule inhibitors (SMI).

Aim: To assess visual prognosis, most common etiology and type of occlusion inlarge series ofpatients after being diagnosed with RVO.

Materials and Methods: Records of patients who had been managed for RVO were reviewed retrospectively for safety, complication, visual outcome and prognosis. Patients' demographic data, indications of treatment and length of follow up were collected and analysed using Welch Two Sample t-test.

Results: Eighty-four eyes of 80 patients (44 females and 36 males) were identified. Mean age at diagnosis was 57.19 ±7 (range 30-70 years) with minimum follow up of 7 years (range 7 – 10). Visual acuities improved in 74 (88.09%), worsened in 4 (4.76%) and remained unchanged in 6 (7.14%) eyes managed withIVAVEGF, observation and steroids respectively. The most common etiologies were hypertension 42 (50%), glaucoma 16 (19.04%) and diabetes 10 (11.90%). Four Yeyes had complications the most common of whichwas neovascular glaucoma (NVG) 2 (50.00%). Seventy-four (88.09%) had non ischemic whilst 4 eyes (4.76%) had ischemic occlusions.

Conclusion: Visual prognosis of RVO is generally good with IVAVEGF. IS are useful when IVAVEGF fails in visual recovery. Novel treatment like GT, PBA and SMI are promising. Management of underlying systemic and ocular diseases and risk factors is equally fundamental.

Keywords: Vein occlusion, anti-VEGF, retinal vein, neovascular glaucoma, macular oedema, gene therapy, peptide-based agents, small molecule inhibitors.

INTRODUCTION

Globally, 28 million people are estimated to have RVO with a 10-year cumulative incidence of 1.63% [1]. RVO is the second most common cause of retinal vascular diseases after diabetic retinopathy [2], with a uniform sex distribution globally [3].In Europe, 0.7% of persons aged 55 years and olderhave RVO [4].In United States of America, there is a 15-year incidence of 500 new cases of central retinal vein occlusion (CRVO) per 100,000 population and 1800 branch retinal vein occlusion (BRVO) cases per 100,000 population [5].Australian data suggests that the prevalence of RVO

is 0.7% for people younger than 60 years, 1.2% for those 60-69 years, 2.1% for those 70-79 years and it increases to 4.6% in individuals aged 80 years and above [1].
RVO is classified into central, hemispheric and branchas well as RVO with any retinal artery occlusion[6].

The pathogenesis of CRVO (fig 1) is as highlighted. An obstruction occurs at central retinal vein at the optic nerve head leading to remarkable reduction or complete blockage of blood flow. Usually there is a thrombus in the central retinal vein at the level of or posterior to the lamina cribrosa [7].Ocular risk factors for development of CRVO areocular hypertension, glaucoma and hypermetropia. These entities can cause obstruction and compromise venous outflow at the level of the lamina cribrosa. Systemic risk factors associated with CRVO include but not limited to hypertension, diabetes and hyperlipidemia [8].

The mechanisms involved in the pathophysiology of BRVO (fig 2) is characterized by Virchow triad: hemodynamic changes, vascular endothelial damage, and a hypercoagulable state [9]. At arteriovenous crossing sites the retinal artery and vein share a common adventitial sheath. The artery is usually anterior whilst the vein is posterior. The thickened rigid arterial wall mechanically compresses and narrows the thinned wall venous lumen inducing hemodynamic changes and occlusion. Accordingly, atherosclerosis andother vasculopathies like diabetes mellitus,arterial hypertension, hyperlipidemia and smoking which are etiologies of arteriolar sclerosis are common risk factors in patients with BRVO [6].

BRVO occurs at arteriovenous crossing and is classified into 3 main groups according to the site occluded: major, hemispheric and macular [10].Major BRVO is classified into nonischemic and ischemic subtypes, which can be found in one-third and two-thirds of cases, respectively. In BRVO, ocular neovascularisation is less frequent than in CRVO and can develop only in ischemic major BRVO.

In hemispheric RVO (fig 3) there is occlusion involving one hemiretina due to an arteriovenous crossing at or in the proximity of the optic disc [11]. Although discussed separately, it shares the same pathogenesis and clinical features of major BRVO.Its ischemic and nonischemic subtypes as well as its neovascular complications are similar to those found in major BRVO.

Macular BRVO is characterized by an occlusion of a small venous vessel draining a specific sector of the macula. Its diagnosis requires careful fundus biomicroscopic and angiographic examinations to detect subtle clinical changes.

Although all the combinations may be possible, majority of scientific studies focus on CRVO combined with central retinal artery occlusion and commonly associated with systemic comorbidities, hypercoagulability status [2,12], drug-induced retinal toxicity, and recently coronavirus disease 2019 [13].

Anticardiolipin antibodies, protein *C* or *S* deficiency, prothrombin gene mutation, factor V Leiden mutation and hyperhomocysteinemia have all been individually identified to be risk factors for RVO [6].

Macular Optical Coherence Tomography (MOCT) test (fig 4) is done to detect how much oedema there is precisely at the macula apart from serving as a baseline reference comparative test to monitor treatment pattern or change from one management plan to another. It can also help in making a choice of IVAVEGF or changing from IVAVEGF to steroids. Treatment modalities include but not limited to appropriate management of the underlying diseases, making changes to all modifiable risk factors, use of IVAVEGF, intravitreal steroids (IS), gene therapy (GT), peptide-based agents (PBA) and small molecule inhibitors (SMI).

To date a few publications have shown several types of management modalities with variable visual outcomes and prognosis of the affected eye in management of RVO. To the best of our knowledge, this is the first time a study is being published to ascertain visual prognosis, most common etiologyand type of occlusion of cross section of Africans who had RVO.

The purpose of the study was to analyse visual prognosis, most common etiology and type of occlusion of patients in Sub-Sahara Africa who underwent different types of treatment after being diagnosed with RVO.

Materials and Methods
This is an analytical comparative retrospective study carried out from October 2022 to review medical records of 80 patients (84 eyes) who underwent various types of management from September 2013 to September 2023 after being diagnosed with RVO (fig 1, 2 and 3) in the study hospital.

Fig 1 CRVO

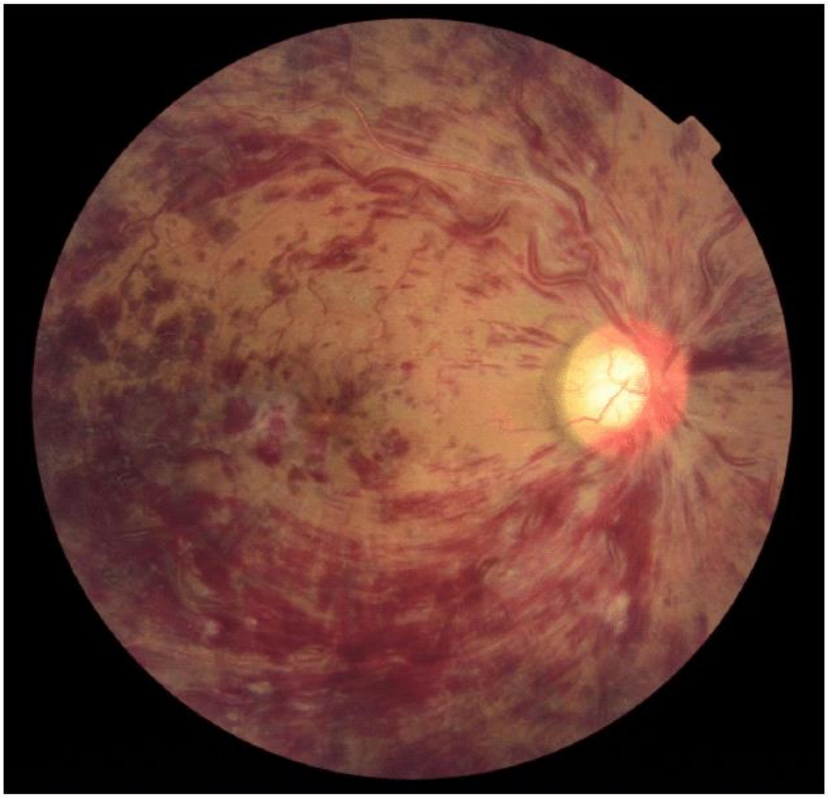


Fig 2Supero-temporal BRVO

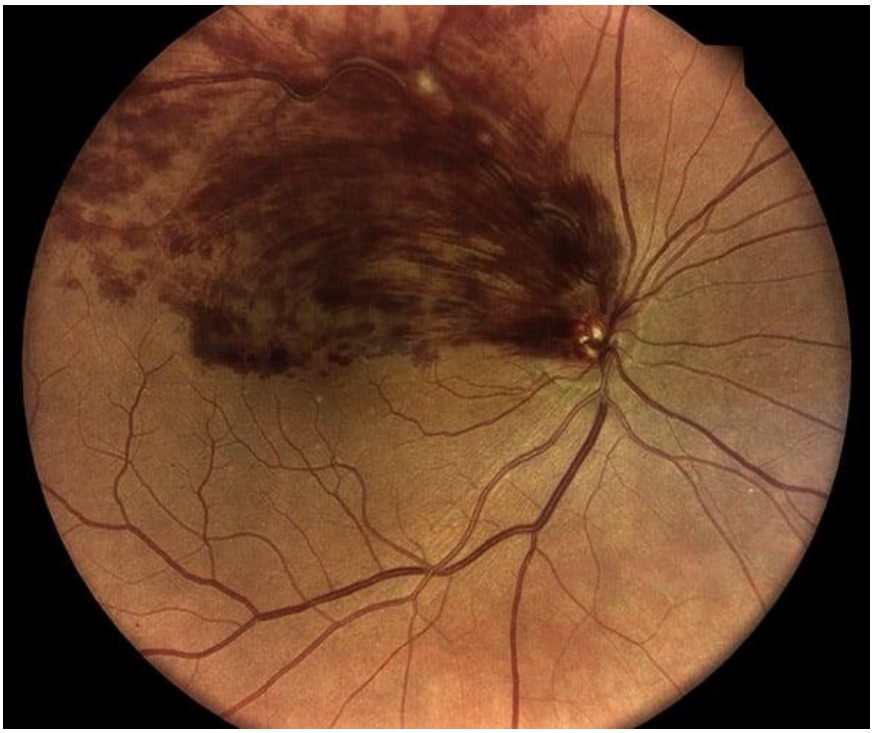


Fig 3 Superior Hemispheric Vein Occlusion

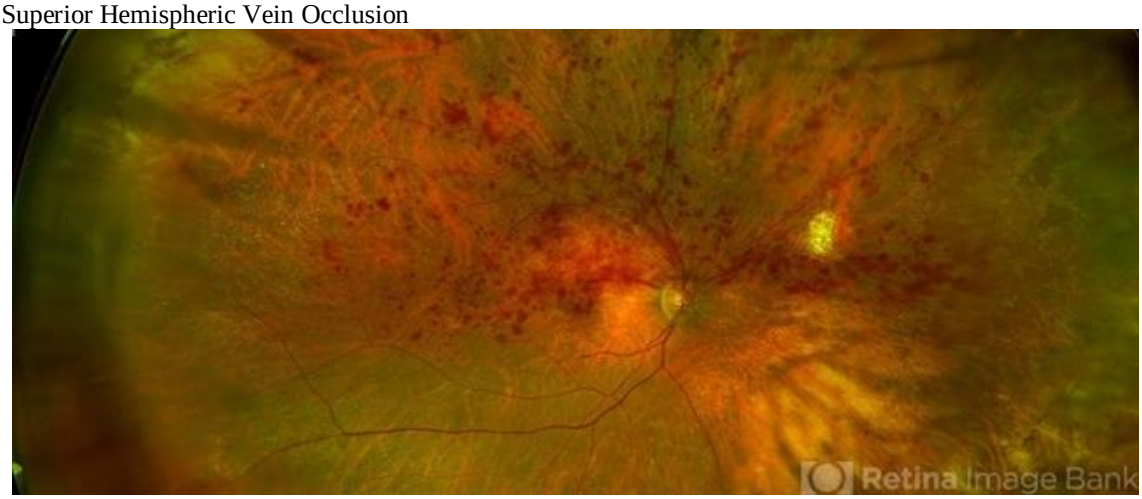
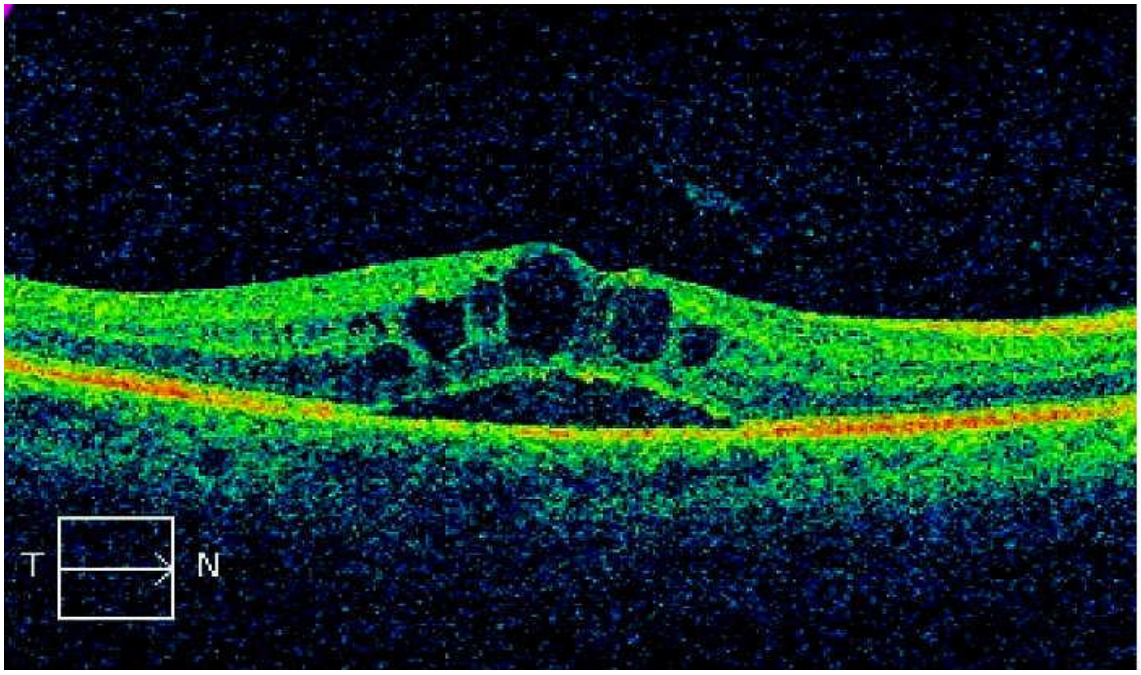


Fig 4 MOCT of RVO with macular oedema



These patients had a minimum follow up of 7 years. One experienced Professor Vitreoretinal and Ophthalmic Surgeon (FKO) performed all the procedures and followed up the patients on regular basis. Institutional ethical approval was acquired for this research and tenets of Declaration of Helsinki, applied.

Inclusion criteria - Patients in the study were those who were examined and diagnosed at the retina clinic of 37 Military Hospital in Accra, Ghana. Exclusion criteria were other co-morbidities in the affected eye: age related macular degeneration, macular hole, end stage glaucoma, retinitis pigmentosa, history of retinal detachment surgery and trauma. Out of 100 patients whose medical records were reviewed, 20 were excluded from the study because they were either followed up for less than 7 years or lost to follow up.

Some of the patients had been referred from other Sub-Saharan African countries. In addition to general demographic data, information on underlying systemic diseases, visual acuity, indication for procedures, complication rate and latest Best Corrected Visual Acuity (BCVA) was collected and analyzed.

One Professor Vitreoretinal and Ophthalmic Surgeon (FKO) did comprehensive eye examinations at the Out-Patient Department to diagnose RVO (fig 1, 2 and 3). Those whose intra-ocular pressures were high (more than 21mmHg)

were given selective alpha-2 adrenergic receptor agonist (alphagan-P bd) and or other intra-ocular pressure reducing medications (beta adrenergic receptor antagonist (gutt timolol bd) and carbonic anhydrase inhibitors (diamox 250 mg od). Other staff assisted in checking the patients's blood pressures, fasting or random blood sugar, fasting lipid profile and weight with the aim to identifying systemic risk factors. All patients were referred to the Medical Department Emergency Unit (MDEU) for further assessment, detection and management of systemic risk factors.

Physician specialists at MDEU, on the other hand, referred patients with underlying systemic diseases to the retina clinic for further evaluation especially if the latter complained of visual impairment. Those with hypercholesterolaemia were managed with oral atorvastatin (VIATRIS LIPITOR10-80mg daily). Patients who had diabetes were on metformin (oral glucophage 1g to 3g daily). Other diabetic patients were on insulin for management. All clients who had hypertension were put on oral captopril (US brand capoten 25-450mg daily), systemic beta-adrenergic receptor antagonists or calcium channel blockers.

IVAVEGF was administered by 1 retina specialist (FKO) under sterile and aseptic conditions in an operation theatre using same procedures in all patients. Ten percent povidone iodine was used to clean skin around the eyelids with gauze. Topical anaesthetic drops were administered, the injection site washed with 5% povidone iodine, a lid speculum used, a 30-gauge needle inserted through pars plana and bevacizumab (Avastin, 1.25 mg in 0.05 mL) injected into the vitreous. Other IVAVEGFs (ranibizumab and aflibercept) were used when bevacizumab became scarce. A cotton-tipped applicator was used to apply mild pressure for 15 seconds at the site of injection immediately after needle withdrawal. The eye was then patched after instillation of one drop of 5% povidone iodine onto the ocular surface. Patches were removed 2 hours after the procedure and patients, reviewed 1 day and 1 week after injection. A treat and extend approach was used in all patients with total number of injections in an eye ranging from 6 to 10 depending on severity of RVO on first examination and most currentMOCT(fig 4) results. Intravitreal steroid (Ozurdex or Kenalog) was used if there was poor response from IVAVEGF. Poor response was defined as non-resolving macular oedema (MO) and or non-improvement in visual acuity 4 weeks after administration of IVAVEGF. Poor response to steroid was defined as non-resolving macular oedema and or non-improvement of visual acuity 90 days after the procedure.

Snellen best corrected visual acuity (BCVA) was converted into logarithm of minimum angle of resolution (logMAR) units in order to get better statistical analysis. Patients whose visual acuities were hand movement were assigned equivalence of 1.7 logMAR units.

Statistical Analysis

The Welch Two Sample t-test was conducted to compare the means of pre-treatment and post-treatment groups as summarized in table 1 below. The results show a test statisticswith degrees of freedom = 90.127.All tests were considered statistically significant if p-value was 0.05 or less. The p-value (2.2e-16)was extremely small indicating strong evidence to reject the null hypothesis, which states that there is no difference between the means of the two groups. The 95% confidence interval for the difference in means is between -0.7827 and -0.6580, which does not include 0, confirming the statistical significance of the difference. The mean for the pre-treatment group is 0.1767, while the mean for the post-treatment group is 0.8971. These results indicate that the mean value for the post-treatment group is significantly higher than the mean for the pre-treatment group. In conclusion, the analysis demonstrates that the treatment had a significant effect, as evidenced by the notable increase in the mean value from the pre-treatment to the posttreatment group.

Results

Eighty-four eyes of 80 patients (44 females and 36 males) were identified. Mean age at diagnosis was 57.19 $\pm$ 7 (range 30-70 years) with minimum follow up of 7 years (range 7 – 10). Mean pre-treatment BCVA was 0.8$\pm$ 0.4logMAR units which depended on stage and severity of disease. The mean difference between final post- and pre-treatment visual acuity was 0.1 ± 0.2 log MAR units which was statistically significant ($p < 0.005$).

In all 84 eyes were managed for RVO with the most common aetiologies being hypertension 42 (50.00%), glaucoma 16 (19.04%) and diabetes 10 (11.90%) as shown below[table-2]. Four eyes had complications the most common of which was neovascular glaucoma (NVG) 2 (50%) as shown in table 3.

Table 1

TREATMENT	T-TEST	DF	P-VALUE	MEAN DIFF.	C.I LOWER (95%)	C.I UPPER (95%)
PRE	-22.9513	90	2.2e-16	0.17679	-0.78271	-0.65800
POST	-22.9513	90	2.2e-16	0.89714	-0.78271	-0.65800

Table 2 Most Common Etiologies of RVO

Serial	Underlying Disease	Number of affected Eyes (%)	Type of occlusion
1	Arterial Hypertension	42 (50.00%)	CRVO
2	Glaucoma/Ocular hypertension	16 (19.04%)	Superior Hemispheric
3	Diabetes	10 (11.90%)	CRVO
4	Hypercholesterolaemia	10 (11.90%)	Macular VO
5	Obesity	5 (5.95%)	Superotemporal BRVO
6	Sickle Cells	1 (1.19%)	SuperotemporalBRVO

Table 3 Most Comon Complications of RVO

Serial	Complication	Number of affected eyes (%)	Management
1	Neovascular Glaucoma	2 (50%)	ARC+AGM
2	Vitreous Haemorrhage	1 (25%)	IVAVEGF+PPV+EL+ARC
3	TRD	1 (25%)	PPV+MS+MD+FAE+EL+ARC+SOI

TRD – Tractional Retinal Detachment ; ARC – Anterior Retinal Cryotherapy; AGM – Anti Glaucoma Medications
PPV – Pars Plana Vitrectomy; EL – Endo Laser ; MS - Membrane Segmentation; MD – Membrane Delamination
FAE – Fluid Air Exchange ; SOI – Silicone Oil Injection

Discussion

Wong et al established in their study that the risk for BRVO and CRVO increases with age and concurrent cardiovascular conditions such as arterial hypertension, atherosclerosis, and diabetes [14]. Similarly, in the current study, it was detected that the most common risk factor was age (57.19 $\pm$ 7 years) and the most common etiology wasarterial hypertensionas shown in table 2.

A study published by Hayreh et al revealed that macular oedema (MO) is the cause of vision loss in all types of RVO. It leads to retinal pigment epithelium degeneration, serous macular detachments and irreversible ischemic damage to macular ganglion cells if therapeutic interventions are not initiated early[15]. Similarly, Yamaguchi et al detected in their study that 90% of major BRVO and 97% of macular BRVO get declined visual acuity from MO [16]. In the present study, 80out of 84 eyes (95%) which were managed had decline in visual acuity due to MO at presentation.According to Rogers et al, each MO must have some form of therapy because only 41% of MO from BRVO resolved spontaneously in their study [17]. The remaining 59% had complications. In the present study, 95% of eyes with MO were managed with conventional therapy. The remaining 5 % had to get management according to the complications they presented with as shown in table 3.

According to Ageno et al, the use of anticoagulation or antiplatelets drugs has no advantages in the management of RVO [18]. In the study hospital, 2 patients who had been enrolled into the study because of CRVO also had deep vein thrombosis on account of which they were put on warfarin. Their visual acuities did not change whilst on warfarin but became better when IVAVEGF was started. This finding supports what other researchers found [18].

Russo et al researched and found out that intravitreal bevacizumab performed better than macular grid laser in their publication in management of MO associated with RVO [19]. A real-world study of 135 eyes reported visual improvement of 14 letters at 2 years with a median of 7 injections using bevacizumab [20]. In the study hospital 80% of the participants were managed with bevacizumab gaining 15 letters with an average of 8 injections in an eye within 3 years.

The BRAVO study revealed that ranibizumab-treated eyes gained an average of 17 letters compared with 7.3 letters of

the sham group in 6 months [21]. In the study hospital, 15% of patients were managed with ranibizumab and after 1 year, they had gained an average of 20 letters. Campochiaro et al published a study in which the use of intravitreal aflibercept in patients with BRVO with MO helped in gaining 17 letters in 52 weeks. [22]. In the current study, aflibercept was used to manage MO in 5% of the participants gaining 19 letters on the average within 60 weeks.

The LEAVO study compared the effectiveness of bevacizumab, ranibizumab, and aflibercept in the management of MO secondary to CRVO. Results were inconclusive with regards to which product was most effective [23]. In the current research, there was also the use of faricimab in addition to the aforementioned IVAVEGFs. Oneproduct was not superior to another because they equally performed well. However, maximum resolution of MO was achieved when each ofthe 4 took turns in their use in a patient.

A real-world study of 221 eyes showed good long-term outcomes of eyes managed with IVAVEGFs with an improvement in vision sustained for 8 years [24].In the study hospital, the improvement in visual acuity with use of IVAVEGF was maintained for at least 7 years.

The use of intravitreal triamcinolone acetonide is recommended in management of RVO when IVAVEGFs are not effective enough to treat the MO [25]. An implant containing dexamethasone (ozurdex) was evaluated in the GENEVA studyfor MO due to CRVO and BRVO. The study found that the Ozurdex implant group had a higher percentage of patients with CRVO and BRVO gaining more than15 letters at the 90-day period compared with the sham group and a lower percentage of patients losing more than15 letters [26]. Steroids are not the first choice because of how theyeasily cause cataract and increased intraocular pressure. They are therefore used if IVAVEGF therapy fails. In the current study, intravitreal steroids were used in 6 (7.14%) eyes which had not responded well to IVAVEGF therapy. Four eyes were managed with triamcinolone acetonide and the remaining 2 were treated with dexamethasone implant. The 2 arms of treatment (dexamethasone and triamcinolone acetonide) gave similar outcomes becausevisual acuities did not change due to the fact that complications had already set in before the patients reported. There was ocular hypertension in both arms of treatment but this was managed with anti-glaucoma medications.

Ocular neovascularization (NV) is one of the most serious complications of RVO. In a large prospective series on ischemic CRVO, anterior segment was more common than posterior segment NV and the cumulative probability within 6 months from the onset was 49% for the iris, 37% for the angle, 9% for the retina and 6% for the discNV [27].In the case of BRVO, however, the reverse is true. Scott et al detected that in BRVO, posterior was more common than anterior segment NV [2]. This fact was substantiated by the Branch Retinal Vein Occlusion Study Group which found an incidence of retinal or optic disc NV of 41% [28]. In the study hospital, 2 patients did not honour their review appointments after initial diagnosis of ischaemic CRVO. One of them came back 3 months after the initial visit complaining of severe pains in the affected eye. The second patient was forced to come back for eye examination because of drastic decline in visual acuity. In both cases, neovascular glaucoma (NVG)had already developed making 50% ofall complications.

Several researchers have shownNVG can be managed using IVAVEGF, anti-glaucoma medications or Ahmed glaucoma valve implantation and pan-retinal photocoagulation if the ocular medium is clear [29, 30, 31]. In the current study, patients with NVG were managed with anti-glaucoma medications and anterior retinal cryotherapy because the involved patients also had associated vitreous haemorrhage (VH).

Some researchers have realized10% of eyes with untreated ischaemic CRVO will develop VHin 9 months, an incidence which increases to 13% in 10 years [32,33]. VH is the second cause of poor visual acuity after MOin BRVO and was found to occur in 61%–73% of patients with untreated ischemic BRVO and posterior segment NV [32,33]. The current research, which took place over a period of 10 years, revealed VH as the second most common cause of poor visual acuity and second most common complication (25%) in untreatedischaemic CRVO. In the study hospital, VH was managed as shown in table 3.

A systematic review revealed bilateral BRVO is found in 4.5%–6.5% of patients at presentation, whereas the risk of developing BRVO in the contralateral eyeif unaffected initially increases to 7%–10% [17]. In the current study, 5% of participants had BRVO bilaterality at presentation. There was no contralateral eye disease in the course of the study period.

The future is bright with regards to RVO management. Gene therapy (GT) techniques aim to modulate at molecular level the expression of vascular endothelial growth factors(VEGF), a critical player in BRVO pathogenesis. Strategies include using gene transfer to deliver VEGF inhibitors directly to the retina [34]. The purpose of GT is to correct genetic mutations which contribute to retinal diseases in order to get new avenues for treating BRVO [35]. Many studies are underway to evaluate its safety and efficacy. Early results reveal itcan provide long-lasting effects by reducing the need

for repeated injections [36]. Despite its potential, GT faces challenges including delivery methods, potential immune responses, and the need for long-term safety data [37].

Peptide-based agents (PBA) are designed to target specific proteins or signaling pathways involved in retinal inflammation and angiogenesis. By interfering with these pathways, these agents aim to reduce retinal edema and improve visual outcomes [38]. Some PBA act as anti-inflammatory agents, targeting cytokines and other inflammatory mediators which contribute to BRVO pathology [39]. Peptides can also inhibit angiogenic factors which promote abnormal blood vessel growth, which is a key feature in BRVO. By blocking these factors, PBA prevent the progression of the disease and improve visual acuity [40]. The development of peptide-based therapies faces challenges such as efficient delivery, potential immunogenicity, and the need for extensive clinical validation [41].

Small Molecule Inhibitors (SMI)work by blocking the downstream effects of VEGF signaling [42]. Certain small molecules specifically target inflammatory pathways, thereby reducing the production of cytokines and other inflammatory mediators which contribute to retinal damage and edema [43]. However, the development of SMI presents several challenges. Key issues include ensuring effective delivery to the retina, minimizing off-target effects, and establishing long-term safety and efficacy through comprehensive clinical trials [44].

As different modalities of treatment are being analysed, it is also important to take into consideration prognostic factors such as central macular thickness, hyper-reflective foci, foveal intraretinal hemorrhage, disruption of the ellipsoid zone, integrity of the inner retinal layers and vitreomacular adhesion [45,46,47,48].

There was no use of any of the new therapies in the study hospital because they are all still in the process of clinical trials.

Limitation
Limitations of this study include its retrospective nature, single-centre focus, variable follow up lengths and the fact that only one retina specialist performed all the procedures.

Conclusion
To date, there is no treatment which safely and reliably reverses the actual occlusion in RVO. The affected patient is managed from general and ophthalmic points of view.

The general point of view encompasses managing systemic and ocular causes and risk factors of RVO. This cannot be achieved without inter-disciplinary co-operation.

The ophthalmic therapies aim at preventing or treating the previously discussed vision-threatening complications of RVO using IVAVEGF, IS or surgery depending on the presentation. The RVOs which are difficult to treat can be managed with GT, PBAor SMI in future. Future research should focus on how to change poor to become good prognostic factors at molecular level in the management of RVO.

Declaration of Conflicting Interests
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