CENTRAL RETINAL VEIN OCCLUSION: CAUSES AND OUTCOMES, A RETROSPECTIVE CASE-CONTROL STUDY

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DECLARATION

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ABSTRACT

Purpose: To identify the causes and outcomes of Central Retinal Vein Occlusion (CRVO).

Study design: A retrospective case-control study

Methods: Patients diagnosed with CRVO from January 2010 to December 2015 were compared to age and gender-matched controls. The risk factors were evaluated between the two groups, and the visual and structural outcomes were analysed in the study group.

Results: A total of 57 patients were enrolled in the study, 27 cases and 30 controls. The mean age in the CRVO group was 64years (SD 9 years), there were 17 females (62.9%) and 10 males (37.0%). There was no statistical difference between the two groups for hypertension (P = 0.579), glaucoma (P=0.411) diabetes (P = 0.379) by univariate analysis. The unaided visual acuity at presentation was CF in 62.9% of patients with CRVO. The final unaided visual acuity was 6/60 in 22.2%, and NLP in 18.5% of patients. The most common complication was cystoid macular edema (59%), vitreous haemorrhage (4%) and neovascular glaucoma (4%).

Conclusion: There was no statistical significance between our cases and controls for hypertension, glaucoma, and diabetes for the development of CRVO. The initial visual acuity was not predictive of the final visual outcome. Cystoid macula edema is the most common complication of CRVO. The mean age of patients with CRVO was lower than what is reported in the literature. We had more females with CRVO compared to males, contrary to other studies.

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LIST OF ABBREVIATIONS

BCVA- Best Corrected Visual Acuity

CME- Cystoid Macula Edema

CRT- Central Retinal Thickness

CRVO- Central Retinal Vein Occlusion

CVOS- Central Vein Occlusion Study

DM- Diabetes Mellitus

FA- Fluorescein Angiogram

HLD- Hyperlipidaemia

HTN- Hypertension

INV- Iris neovascularisation

IOP- Intraocular pressure

ME- Macula Edema

NICE- National Institute for Clinical Excellence

NV- Neovascularisation

NVI- Neovascularisation of Iris

NVG- Neovascular Glaucoma

OCT- Optical Coherence Tomography

OR- Odds Ratio

PPV- Pars Plana Vitrectomy

PRP- Pan Retinal Photocoagulation

POAG- Primary Open Angle Glaucoma

RAPD- Relative Afferent Pupillary Defect

RON- Radial Optic Neurotomy

ROVO- Radial Optic neurotomy for Vein Occlusion

RVO- Retinal Vein Occlusion

SCORE- Standard Care vs Corticosteroid for Retinal Vein Occlusion

TRD- Tractional Retinal Detachment

VA- Visual Acuity

VEGF- Vascular Endothelial Growth Factor

VH- Vitreous haemorrhage

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1. INTRODUCTION

1.1 Background

Blockage of blood flow in the retinal vein is the second most common retinal disease of the retinal vasculature following diabetic retinopathy[1-6]. Blockage of the central retinal vein often leads to a severe loss of visual acuity with devastating consequences to quality of life. The most recent research summarising the prevalence of retinal vein occlusion (RVO) as reported in research from various continents such as the United States of America, Europe, Australia as well as Asia has shown an age-matched and gender-matched prevalence of 5.20 per 1000[1-3, 7] .The major risk factors are age and hypertension [1-3]. The prognosis of CRVO depends upon the re-establishment of patency of the venous system by recanalisation, dilution of the clot, or optociliary shunt formation. The most common complications are cystoid macula edema (CME) and neovascularisation (NV).

1.2 Literature review

1.2.1 Pathophysiology

Central retinal vein occlusion (CRVO) was first described by appearance as apoplexy of the retina in 1854 and was later described in 1877 as haemorrhagic retinitis[5]. Blockage of venous blood flow in the optic nerve head is now implicated as the cause of CRVO[5, 6].

The pathophysiology is thought to involve a triad for thrombogenesis: sluggish venous blood flow, blood vessel wall changes, and hypercoagulability of blood[2, 4]. Blockage of blood flow in the central retinal vein causes decreased blood flow in the retinal venous system leading to ischemia of the retina. At the arterio-venous crossing which lies posterior to the lamina cribosa, is a common adventitial sheath shared by the two retinal vessels. Compression of the vein by an arteriosclerotic vessel then results in occlusion of the vein[1]. The rheological

properties of the vein change due to compression by the artery thus contributing to venous flow stagnation, thrombosis and finally causing occlusion. The pathophysiology of different types of retinal vein blockage is multifactorial. There are predisposing as well as precipitating factors which cause occlusion of the retinal vein[5, 6].

1.2.2 Risk factors

Data have recently been published on risk factors connected to CRVO among a diverse group of patients. The age of the patient and the presence of systemic vascular disorders are associated with the risk of developing central retinal vein blockage[1-3]. Patients with a history of hypertension (HTN), diabetes mellitus (DM), cardiovascular disease, or open-angle glaucoma are at increased risk of blockage of the retinal vein[4, 6-8]. A large number of people with CRVO have two or more components of the metabolic syndrome e.g. co-existing hypertension, diabetes mellitus, and hyperlipidaemia (HLD). The risk of developing a blockage of the central retinal vein is increased by up to 58% compared to those who do not have the conditions[2].

CRVO is very strongly increased in subjects with a proven hypercoagulable state[2]. However, the use of anticoagulants does not decrease the development of CRVO[4].

The most important risk factor for CRVO is age. More than 90% of cases of CRVO occur in subjects older than the age of 55 years[2]. The mean age is 69 years[6, 8]. A major systemic vascular risk for development CRVO is hypertension. Hypertension increases the risk of blockage of the central retinal vein by 66% [3]. Subjects with non-complicated HTN have a 36% increased risk of developing CRVO[2]. Moreover, subjects with advanced HTN which is associated with end-organ damage have 92% higher risk of CRVO[2].

Diabetes is also a risk for RVO in 5% of patients[1]. Subjects with no end-organ damage caused by DM are not at increased risk for CRVO but those with advanced disease resulting in end-organ damage have an increased risk[2]. Hyperlipidaemia has been studied as a risk factor of CRVO, defined as a total cholesterol > 6.5mmol/L. Blockage of the central retinal vein is found in 20% of subjects with hyperlipidaemia. There was no higher risk of CRVO in those with hyperlipidaemia alone as opposed to those with other components of the metabolic syndrome(co-existing HTN, HLD and DM)[6]. Risk factors for arteriosclerosis such as systemic hypertension, hyperlipidaemia, and less so diabetes are common causes of CRVO [4].

Glaucoma is a very important risk factor for CRVO[1, 2, 4, 8, 9]. Blockage of the central retinal vein is found in up to 4.5% of patients with primary open-angle glaucoma *(*POAG*)* and POAG or ocular hypertension (OHT) in 4- 43% of patients with CRVO[8]. It remains unclear how an elevated IOP results in central retinal vein occlusion. It is thought that compression of the central retinal vein due to increased intraocular pressure caused by turbulent flow leads to thrombus formation[4, 5, 10].

Males are more likely to develop blockage of the central retinal vein compared to females[6, 11]. Racial differences have not been found in patients with CRVO.

1.2.3 Classification

CRVO is divided into 2 clinical types, ischaemic (non-perfused) and non-ischaemic (perfused), each of which has implications for prognosis and treatment[1, 3, 5]. Patients may also present with a variable and intermediate clinical course.

Non-ischaemic CRVO is the more common of the two, it occurs in about 81% of cases of central retinal vein occlusion. Patients often present with a history of acute, unilateral blurring

of vision with mild to moderate loss of vision. Some patients with mild disease are asymptomatic and recover with no sequelae. There may or may not be a relative afferent pupillary defect. Fundoscopy shows scattered retinal haemorrhages, few cotton spots, and good perfusion to the retina[5].

Ischaemic retinal vein occlusion is marked by rapid venous blockage resulting in decreased blood flow to the retina, capillary shutdown and hypoxia. This is a severe form of CRVO in which patients present sudden, painless visual loss. Clinical features include widespread retinal haemorrhages and cotton-wool spots, presence of relative afferent pupillary defect (RAPD), severe optic nerve swelling and hyperaemia[1, 3]. In addition, this may result in neovascular glaucoma and a painful blind eye. The initial presentation could be ischaemic in nature or progress from non-ischaemic occlusion, commonly within 6-12 months[4].

It is not always easy to differentiate these two clinical types in the early acute phases of the illness, the one reliable clinical feature is the presence of more extensive retinal haemorrhage in the ischaemic type[5, 12]. An RAPD is an important and reliable functional test which helps to distinguish an ischaemic from a non-ischaemic CRVO, where it has a high specificity and sensitivity for detecting an ischaemic vein occlusion[12].

There is a less recognised subtype known as partial central retinal vein occlusion. It is an ill-defined condition where patients may have mild, transient blurring of vision or they may not have any symptoms. Fundus examination shows mild dilatation and tortuosity of the veins with widely distributed flame-like haemorrhages in the retina.

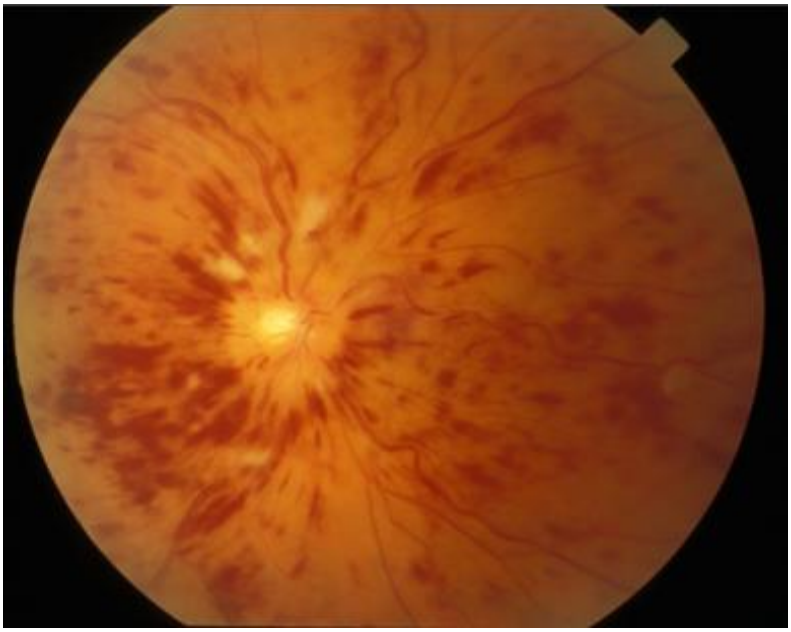


Figure 1: Central retinal vein occlusion[13]

1.2.4 Investigations

The following investigations for vascular risks factors are required in all patients with a retinal vein occlusion:

- Blood pressure
- Random blood glucose or Hba1c in patients known to have diabetes
- Total cholesterol

Additional investigations for patients without systemic risk factors include:

- Kidney function test to rule out renal damage
- Erythrocyte sedimentation rate and other inflammatory markers
- Clotting profile
- Carotid duplex imaging

Fundus Autofluorescence can detect perivenular hypo-autofluorescence with a fern-like appearance in patients with recent-onset vein occlusion, caused by coverage of normal autofluorescence by ischaemic edema[1, 5].

A CRVO may be classified on Fluorescein angiography (*FA*)as perfused when the area of no retinal capillary perfusion is fewer than 10 disc areas, as non-perfused when the area of non-perfusion is 10 or more disc areas, or as indeterminate if intraretinal haemorrhage prevents the evaluation of retinal capillary detail on FA[1, 8]. Areas of non-perfused retinal capillaries are seen in between 22% and 36% and has been shown to predict the development of rubeosis[5]. Up to one-third of FAs are insufficiently assessed because of factors such as haemorrhages on the retina and in the vitreous. Cystoid macular edema develops in cases where there is marked venous leakage[5]. The retinal circulation time may be mildly increased in impending CRVO.

In the non-ischaemic type, a prominent delay is seen in the flow of the dye from the arterial to the venous retinal circulation, with a duration which is longer than 20 seconds. A distinct feature of moderate or severe obstruction is late staining in the retinal vein. Widespread areas of absent capillary perfusion are characteristic of ischaemic occlusion. The principal factor influencing the development of NV in CRVO seems to be the severity and extent of retinal ischaemia[10, 14].

Optical Coherence Tomography (OCT)is very useful in evaluating, monitoring and treating macula edema which the most common complication of CRVO[5].

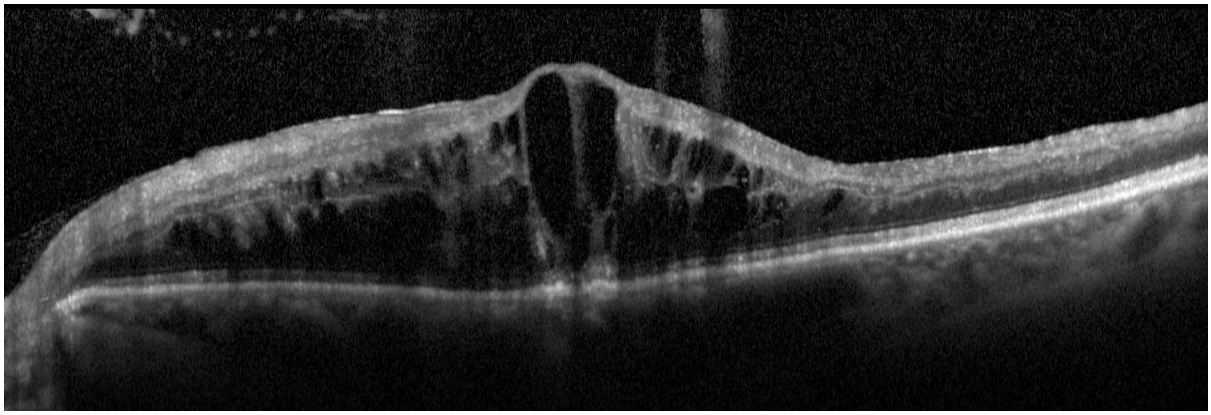


Figure 2: CME secondary to CRVO[13]

The first large series on Electroretinography (ERG) in CRVO was provided in 1953[5]. A number of researchers have since discovered that ERG is a useful test for detecting ischaemia. A common abnormality is a decrease in the b wave or b/a ratio.

Colour Doppler imaging is a new modality which has recently been used to evaluate the onset neovascularization of the iris. It can be used to assess patients before 3 months when FA assessment is not recommended[5].

1.2.5 Management

CRVO is associated with vision-threatening consequences including cystoid macula edema, ischaemic maculopathy as a result of non-perfusion of capillaries, formation of new vessels in the anterior or posterior segments of the eye, and NVG[1]. It is known that treatment does not significantly improve loss of vision, therefore treatment measures are considered palliative. Preventing further loss of vision from complications is the main focus of treatment. Follow-up is planned to fit the different types as well as to prevent complications.

Treatment of pre-existing systemic conditions helps to prevent worsening or complete blockage of the vein in patients with impending CRVO.

For subjects with non-ischaemic type, monitoring every 12 weeks for signs of progression into ischaemic blockage is recommended[7]. Further review depends largely on examination findings. Patients are usually discharged between 18 to 24 months where there is full recovery without sequelae.

In ischaemic retinal vein occlusion, monthly assessments for a period of 6 months for the detection of new vessels on the iris (NVI) is required, which can result in neovascular glaucoma, usually occurring after 3 months following a CRVO (90-day glaucoma) [1, 3, 8]. A follow up period of 24 months is recommended to monitor and detect significant macula edema and ischaemia[10].

The Central Vein Occlusion Study (CVOS) failed to show benefit from grid laser photocoagulation for ME[15-17]. Combining macular grid laser with intravitreal anti-VEGF or intravitreal steroids for treatment of ME due to blockage of the central retinal vein has not been proved beneficial. The use of prophylactic xenon pan-retinal photocoagulation (PRP) has been shown to reduce the incidence of (NV) and CME but had no impact on visual acuity[5, 7]. Recently, the CRVO study group suggested frequent follow up of patients at risk and application of laser when NV develops because there was no benefit of prophylactic therapy over therapy when complications occur[5].

Iris neovascularization (INV) can occur at any point but occurs commonly from 6 months (71% of cases) although it can develop as late as 24 months from presentation[5]. Neovascular glaucoma (NVG) develops in 8% of CRVO overall, 67-82% of ischaemic CRVO, and as little as 1% of who have non-ischaemic disease[5]. When untreated, NVG results in blindness in 76% and causes phthisis bulbi or enucleation for pain in 26% [5].

Intravitreal triamcinolone is beneficial in treating macula edema from CRVO[18]. The *SCORE study*[18]: A total of 271 patients with CRVO participated in the SCORE study (Standard Care Versus Corticosteroid for Retinal Vein Occlusion) in November 2004 and February 2008 which was designed to compare 1mg and 4mg injection of triamcinolone into the vitreous with those who were observed for loss of visual acuity associated with ME secondary to blockage of the retinal vein. As a primary result, a gain of 15 or more letters in the visual acuity chart was 6.8% for the observation group, 26.5%, for the 1mg group, and 25% for the 4mg group. The thickness of the retina did not change at 12months. Measurement the central retinal thickness (CRT) was performed using OCT, which was decreased in all three groups. The 4mg triamcinolone group had higher reports of adverse events.

Ozurdex GENEVA study group[19]: A total of 1267 patients took part in the period from November 2004 to February 2008. The average initial visual acuity was estimated to be 20/80 in all groups while the average central retinal thickness was about 550um. Patients who were treated with a dexamethasone implant amounting to 0.7 or 0.35mg were able to read 15 or more letters in best-corrected visual acuity which was quicker than the sham group. In addition to a better visual acuity, a marked lowering of the central retinal thickness was observed in the dexamethasone group over those in the sham group.

Ranibizumab for The Treatment of Macular oedema After Central Retinal Vein Occlusion Study (CRUISE) [18-21.] In total, 392 patients with a diagnosis of CRVO seen between July and December 2008 were divided randomly into 3 groups consisting of intravitreal sham injection group and 0.3mg or 0.5mg intravitreal ranibizumab group. Patients were given monthly injections for a period of 6 months. The average best-corrected visual acuity was 20/100 with a central retinal thickness average of 685.2um At 6 months, the primary result was a 12.7 average letter

improvement in the 0.3mg group, 14.9 average improvement in the 0.5mg group, while only 0.8 letter improvement in best-corrected visual acuity was observed for the sham group. Secondary results revealed that 46.2% of eyes in the 0.3mg group improved by 15 or more letters, 47% for the 0.5mg ranibizumab group had achieved the same result in best-corrected visual acuity in comparison to 16.9% eyes in the sham group. Ranibizumab therapy was also associated with a fast reduction in central foveal thickness. During the 6 month period, no complications were reported from the use of ranibizumab.

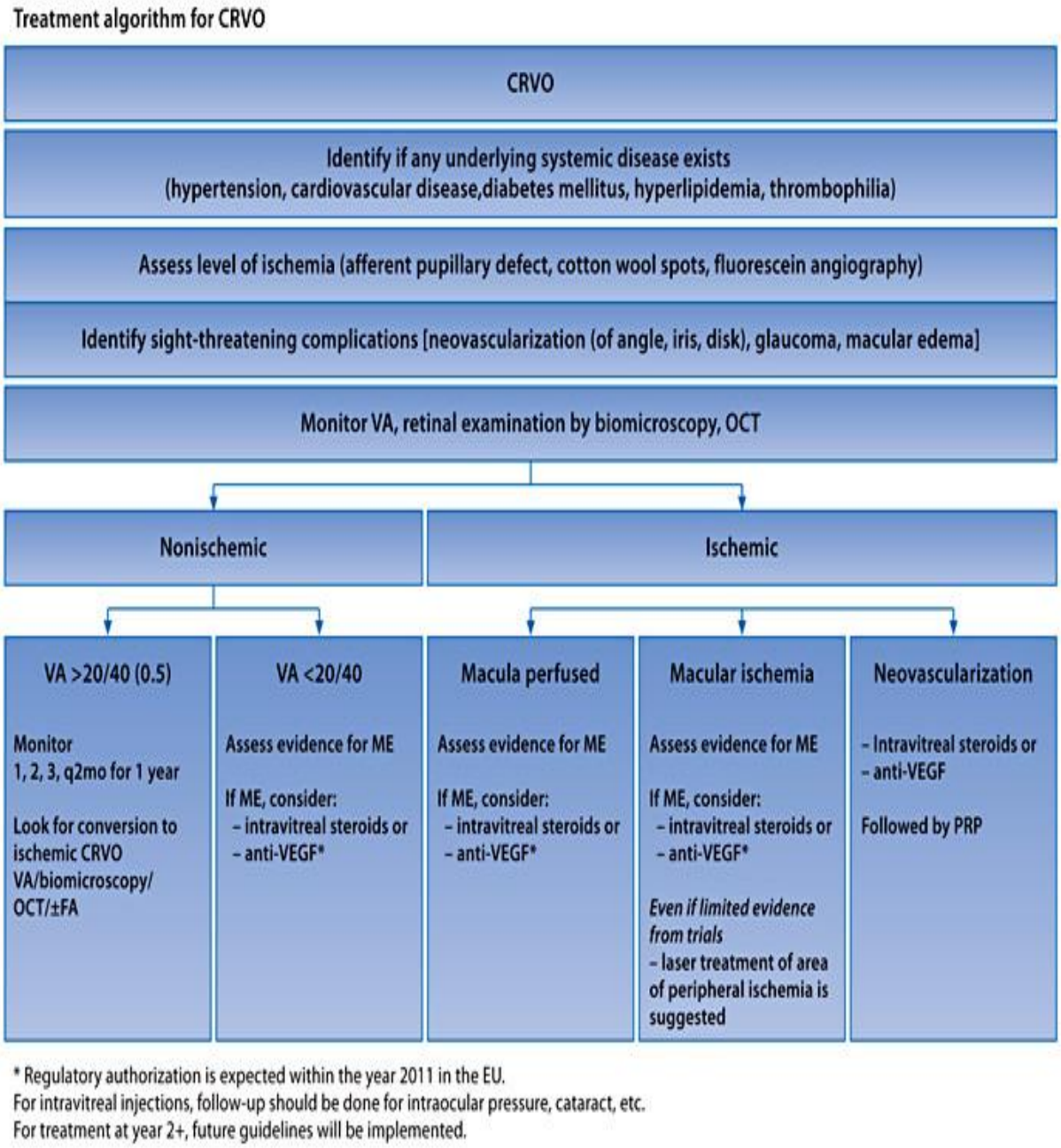
(COPERNICUS) [19, 21] Controlled Phase 3 Evaluation of Repeated Intravitreal Administration of VEGF Trap-Eye in Central Retinal Vein Occlusion: Utility and Safety. 56.1% of patients who were treated with 2mg of VEGF Trap-Eye every month improved by a minimum of 15 letters of vision from compared to 12.3% patients in the sham injection group.

GALILEO study[19, 21]: the primary result showed that 62% of eyes treated every month with 2mg vascular endothelial growth factor (VEGF) Trap-Eye improved their vision by a minimum of 15 letters while the sham group achieved an improvement of 22.1%. As a secondary outcome, there was an improvement of 18 letters in visual acuity in patients treated with 2mg anti-VEGF-trap in contrast to an average improvement of 3.3 letters in the sham group. At week 10 after intravitreal injection of VEGF Trap, it was concluded that its biological activity was the same as that of Ranibizumab at one month.

Vitreous haemorrhage is a known complication of CRVO, it causes sudden visual loss and results in media opacification which blocks the view of the retina. Pars plana vitrectomy (PPV) in conjunction with intraoperative pan-retinal photocoagulation (PRP) is indicated in patients with non-resolving vitreous haemorrhage[1, 5]. Vitrectomy has been found to increase the availability of oxygen to the retina for many months, thereby relieving ischaemia and

preventing the development of neovascular glaucoma and macula traction[22]. Anti- VEGF has been used to theoretically to reverse the formation of abnormal blood vessels in response to ischaemia by reducing VEGF drive in the eye[22].

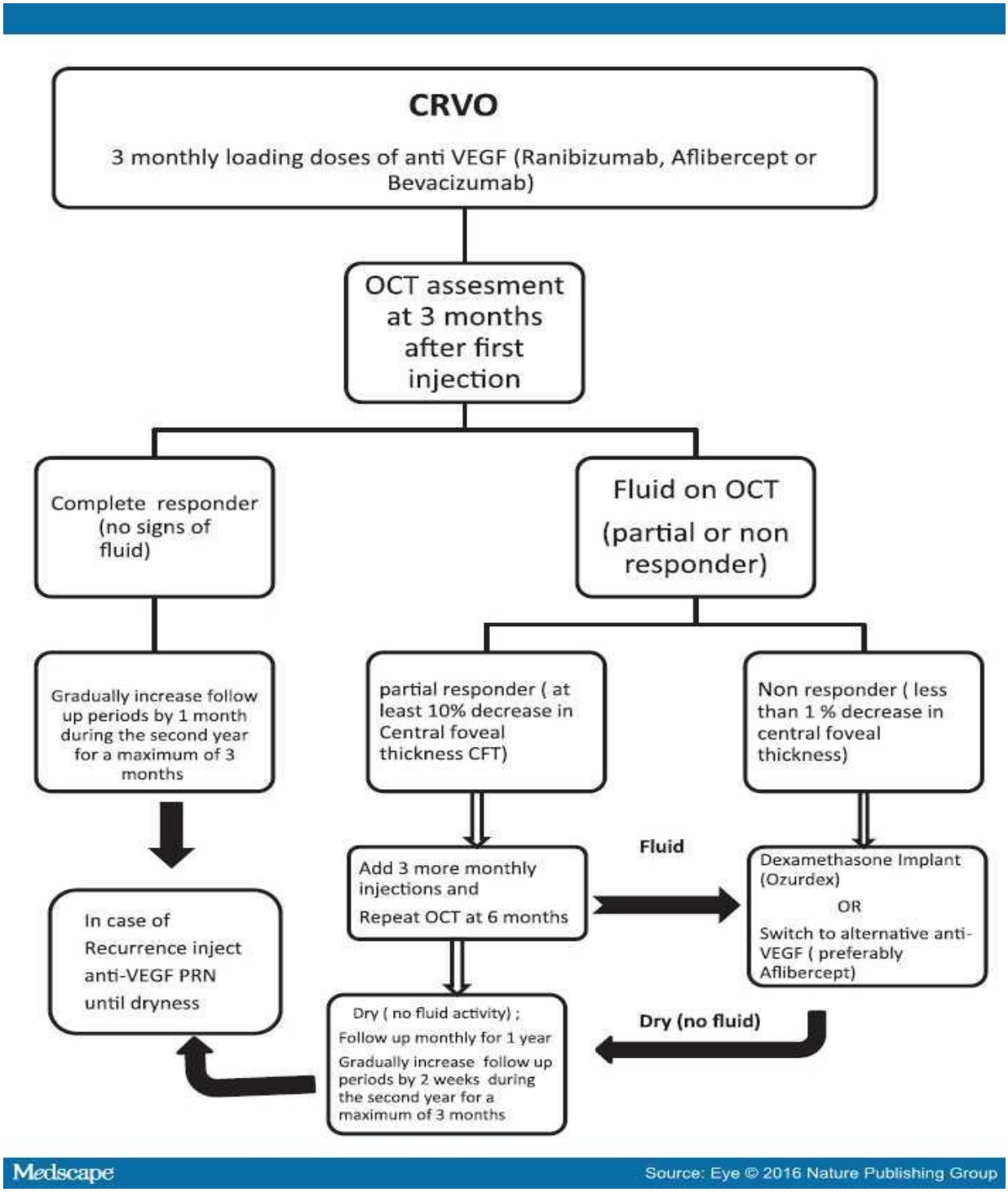
Table 1: CRVO treatment algorithm[23]



Newer treatment algorithms have been developed, specifically looking at anti-VEGF treatment with OCT guidance for the treatment of CME. All three commonly used anti-VEGF

treatments i.e. ranibizumab, aflibercept, and bevacizumab have been studied in the management of CME due to CRVO.

Table 2: Anti-VEGF Treatment algorithm for CRVO[24]



Other treatment modalities:

- Haemodilution

  Patients need to be carefully selected. Several studies have suggested that isovolaemic haemodilution could be effective[3].

- Antithrombotic agents

  Antiplatelet drugs (i.e. aspirin) are commonly prescribed to patients with comorbid conditions such as hypertension, atherosclerosis or diabetes even though there is no proven ocular benefit[3].

- Thrombolytics

  The use of recombinant tissue plasminogen activator (rt-PA) intravitreally in order to reduce risks from systemic administration has been studied. The results have been varied[3, 5].

- Chorioretinal venous anastomosis

  Creating an anastomosis between the retinal vein and the choroidal circulation to bypass the occluded central vein has been assessed, with the use of both laser and incisional techniques, showing varied visual results[3, 5].

  Chorioretinal anastomosis using laser may result in complications such as choroidal haemorrhage, subretinal haemorrhage, vitreous haemorrhage, CNV, TRD, and distal retinal ischaemia.

- Vitrectomy with radial optic nerve neurotomy (RON)

  No evidence has been published to prove that this procedure is of benefit. The procedure is invasive, therefore its role needs to be well defined through further research[3]. However, the ROVO (Radial optic neurotomy for central vein occlusion)

study group found an improvement in visual acuity in the RON group compared to the placebo or those who received a single intravitreal dose of triamcinolone

- Optic nerve sheath decompression

  Due to limited data available and owing to its invasiveness, optic nerve sheath decompression is seldom used as a treatment modality in CRVO[3].

1.2.6 Outcomes

Chronic macula oedema is the main cause for poor vision, which may result in secondary retinal pigment epithelium (RPE) changes[2, 3, 5]. The final visual outcome is determined by the visual acuity at presentation[1, 3, 10, 20, 21].

Non-ischaemic CRVO has better visual acuity at baseline whereas the prognosis for the recovery of vision in ischaemic cases is poor. Non-perfusion of the retina and the visual acuity at presentation strongly predict the probability of developing new vessels on the iris or angle of the anterior chamber[5, 10]. It is crucial to classify patients into non-ischaemic or ischaemic occlusion because this will be a good indicator of possible complications and visual outcome[25]. In a prospective study, 87% of the ischaemic group had a final visual acuity of 3/60 whereas 80% of the non-ischaemic group had 6/18 vision or better. In a retrospective study, a final visual acuity of less than 6/60 in 93% of ischaemic eyes in contrast with 50% of non-ischaemic eyes was reported[5]. In another study, visual acuity at presentation was a strong indicator of the final visual outcome because 57% of patients did not change[5].

Conversion of non-ischaemic into ischaemic has been observed in 10-33% of primary non-ischaemic cases[3]. The risk of development of CRVO in the fellow eye was reported to be 1% (CVOS)[16].

Further follow-up for all patients is dependent on treatment and complications arising within the earlier period. A good indicator of a favourable outcome is the formation of collateral vessels and or the resolution of the central retinal vein blockage, which should lead to discharge from clinical observation[25].

1.3 Rationale and hypothesis

CRVO is a common cause of visual loss with severe complications and poor visual outcomes. This condition has not been studied in our South African setting and will be a useful analysis of our population and in the management of our patients.

We hypothesise that patients with CRVO have identifiable risk factors in our South African setting which might be amenable to intervention and some might be unique to our patients e.g. HIV related CRVO.

1.4 Study objectives

The primary objective was to identify the risk factors of central retinal vein occlusion in patients seen at two academic hospitals in Johannesburg, Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and St John Eye Hospital (SJEH). The risk factors we studied were age and gender, hypertension, diabetes, and glaucoma which have been found to be common risk factors in the literature.

The secondary objectives were to describe the visual and anatomical outcome of CRVO in these patients. The outcome measures were:

- Change (decline or improvement) in visual acuity from baseline to 3 months using the Snellen visual acuity chart

- Change in macula retinal thickness from baseline to 3 months using Optical Coherence Tomography (OCT).

2. METHODS AND MATERIALS

2.1 Study design

This was a retrospective case-control study of 57 patients seen between January 2010 and December 2015. There were 27 study patients with CRVO and 30 patients in the control group. The study patients with CRVO were from retina specialist clinic and the patients without CRVO were those who came to the eye clinic for routine cataract pre-op assessment.

2.2 Ethics approval

The study protocol was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Ref M160818). The study adheres to the principles set out in the Declaration of Helsinki. To ensure confidentiality, all patient records were allocated a study number in lieu of a patient name. The investigator has no financial or conflicting interests to declare.

2.3 Site of Data Collection

Data were obtained from medical records of patients diagnosed with CRVO and from patient files who were seen for routine pre-op cataract surgery at Charlotte Maxeke Johannesburg Academic Hospital and St John Eye Hospital, Johannesburg, South Africa.

2.4 Data collection

Records of patients who met the inclusion criteria were collected by the primary researcher.

Demographic information for both groups was recorded as follows:

- Age-matched to up to 10 years

- Gender-matched
- Race – Black, White, Indian, Coloured

For both groups, the past medical history was recorded together with recorded BP and HGT. Hypertension and Diabetes were defined according to the American Heart Association as follows[20]:

- Hypertension – a patient currently receiving antihypertensive medication, or demonstrating a diastolic blood pressure greater than 90mmHg or systolic blood pressure greater than 140mmHg
- Diabetes – a patient being treated by diet, oral hypoglycaemic, or insulin, or with a fasting glucose level greater than 11mmol/L.

In the ocular history of the study group, we recorded the following:

- Glaucoma – patients with the diagnosis of Primary Open Angle Glaucoma (POAG) or other types of glaucoma.
- Intraocular pressure.

Additional important information was also collected in the study group:

- Affected eye (Right or Left)
- Initial and last recorded visual acuity using the Snellen visual acuity chart
- OCT CFT at baseline and 3 months
- Complications e.g., CME, VH, NVG
- Type and duration of treatment e.g. IVT Anti-VEGF treatment, PPV, Glaucoma treatment.

2.4.1 Inclusion criteria

- Cases

- All patients with a diagnosis of CRVO seen at CMJAH and SJEH between January 2010 and December 2015.
- Patient records available from presentation (baseline) to 3 months follow up.

- Controls

  Consist of patients without CRVO seen in the eye clinic for routine cataract pre-operation assessment, meeting the following criteria:

  - Patients who are age-matched to within 10 years of study patients.
  - Patients gender-matched to study patients.
  - Patients with documented BP and HGT in their records.

2.4.3 Exclusion criteria

- Cases

- Incomplete records - due to loss or poor legibility.

- Controls

- Patients who did not have their blood pressure and blood sugar (HGT) checked when examined in the eye clinic at the time of pre-op assessment.

According to the records, patients underwent complete ophthalmic examination, including a routine slit-lamp examination and fundus examination.

Optical Coherence Tomography (OCT) was the commonly performed investigation for CME in patients at presentation and at 3 months follow-up. Patients with CME were treated with

Anti-VEGF intravitreal injections monthly for 3 months. Fluorescein angiography was not performed on our patients.

2.5 Statistical analysis

Data were captured on an Excel spreadsheet (Microsoft). New variables and categories were created in order to analyse the data. For the descriptive analysis, we calculated the means, medians and interquartile ranges on Excel. Conditional logistic regression models (STATA statistical analysis software) were used to model risk factors and adjust for mutual confounding between covariates by analysing the association of all variables together. Logistic regression will model the chance of an outcome based on individual characteristics. For all tests, a P value less than 0.05 was considered to be significant. The Chi-square test was used for categorical analysis to determine the odds ratios (OR). All results were then converted into tables and graphs to aid analysis and discussion.

3. RESULTS

A total of 57 patients were enrolled in the study, 27 cases and 30 controls. The mean age of the CRVO group was 64 years (standard deviation, (SD), 9 years) ranging from 45 to 79 years. The mean age of the control group was 67 years (SD 9.2 years, range 50 to 81 years). There was no statistical significance between the two groups ($P< 0.222$). The means were calculated using the two-sample t-test with equal variances.

There were 23 males (40%) and 34 females (60%) in the study. The male to female ratio in the study group was 3/5, it was 4/5 in the control group as shown in table 3.

Out of the 57 patients, 46 (79%) were black patients (including 4 Indians (5%) and 1 coloured (2%), and 12 white patients (22%). Table 3.

Table 3: Demographic data analysis

Demographics	Cases (n=27)	Controls (n=30)
Age:		
Subjects younger than 60 years	5(19%)	8 (27%)
Subjects 60 years and older	22(81%)	22(73%)
Gender		
Male: n (%)	10(37%)	13(43%)
Females: n (%)	17(63%)	17(57%)
Race		
Blacks: n (%)	18(67%)	23(77%)
Coloureds: n (%)	1(4%)	0(0%)
Indians: n (%)	3(11%)	0(0%)
Whites: n (%)	5(18%)	7(23%)

There were 20 patients diagnosed with hypertension (74%), 9 with diabetes (33%), 6 with hyperlipidaemia (22%), and 2 known glaucoma patients (7%) who developed CRVO (Table 4).

Table 4: Ocular and systemic risk factor analysis

Risk Factors	Study Group (n=27)	Control Group (n=30)
Glaucoma	2 (7%)	1(3%)
Hypertension	20 (74%)	24 (80%)
Diabetes	9(33%)	9 (30%)
Cholesterol	6(22%)	0 (0%)

Of the eyes affected by CRVO, 20 involved the right eye (74%), 7 involved the left eye (26%), and 1 patient had a bilateral CRVO (3%).

The risk factors were analysed by univariate analysis using conditional logistic regression model (Table 5). There was no statistical significance between the two groups for hypertension (P=0.579), diabetes (P=0.379), and glaucoma (P=0.411). Multivariate analysis was therefore not indicated because there was no statistical difference by univariate analysis. We used the Chi-square test to calculate the odds ratio for each variable. A positive association was found in patients with diabetes (Odds ratio {OR} 1.21) and glaucoma (OR 2.86). Black patients were at increased risk of CRVO (OR 1.26) compared to white patients (OR 0.8), although it was not statistically significant. The median follow-up period was 16 months with an interquartile range of 12-22 months.

Table 5. Univariate risk factor analysis

Characteristics	Cases (n27)	Controls (n30)	Unadjusted OR	95% Confidence interval	P-value
Age /mean (SD)	64 (9)	67 (9.2)	0,96	0.91-1.02	0,222
Black	22	23	1,26	0.35-4.57	0,723
Hypertension	20	24	0,71	0.21-2.41	0,579
Diabetes	9	9	1,21	0.40-3.67	0,739
Hyperlipidaemia	6	0			
Glaucoma	2	1	2,86	0.23-35.03	0,411

Table 6 shows the breakdown of the initial and final visual acuity in the study group. The unaided visual acuity at presentation was poor and ranged from 6/60 to NLP. The majority of patients had CF vision (63%) at presentation. The final unaided visual acuity showed gains of

6/60 or better in 12/27(44%) of patients compared to 3/27(11%) who had the same level of vision at the time of presentation. Those who progressed from 6/60 to NLP vision were complicated by vitreous haemorrhage and neovascular glaucoma. The absence of FFA made it difficult to determine which type of CRVO our patients had. We found that an RAPD was present at the time of presentation in all but one the patients who ended up with NLP vision. Therefore we infer that these patients most likely had the ischaemic type of CRVO.

Table 6. Initial and final visual acuity

Visual acuity	Initial	Final
6/24	-	1
6/36	-	5
6/60	3	6
CF	17	2
HM	2	4
LP	4	4
NLP	1	5
Grand Total	**27**	**27**

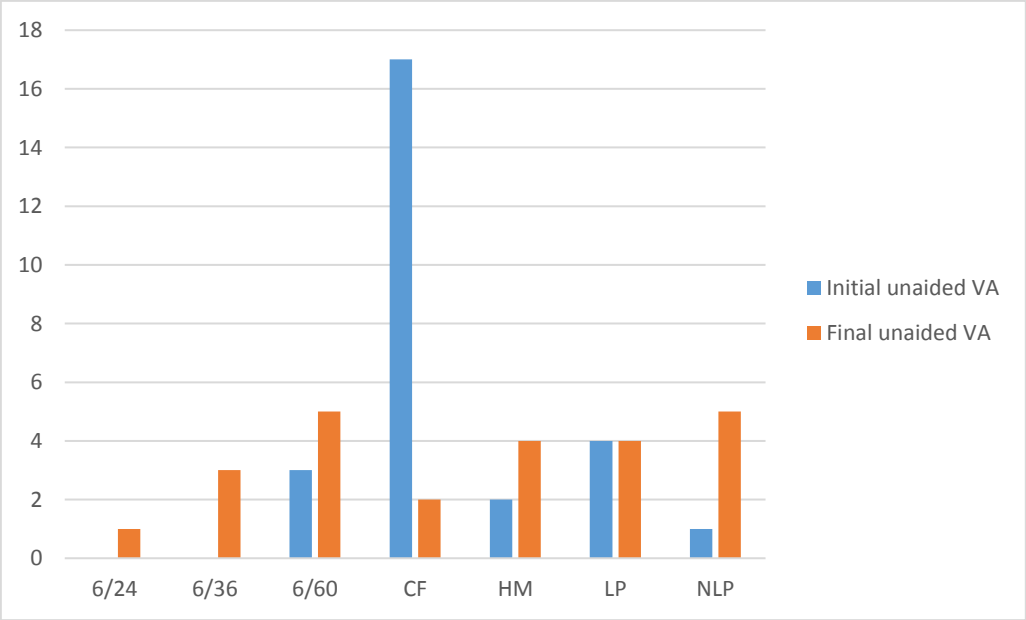


Figure 3: Initial and final visual acuity

Figure 3 shows the graphical picture of the visual findings at presentation and the last recorded visual acuities. The mean intraocular pressure in the study group was 17mmHg {SD 8} (Figure 4). 4 patients had highly elevated IOP at the time of diagnosis with CRVO. Of those, 2 were known with glaucoma prior to the development of CRVO and other 2 were presumably undiagnosed. NVG was managed with topical glaucoma medication, 1 patient underwent trabeculectomy for neovascular glaucoma.

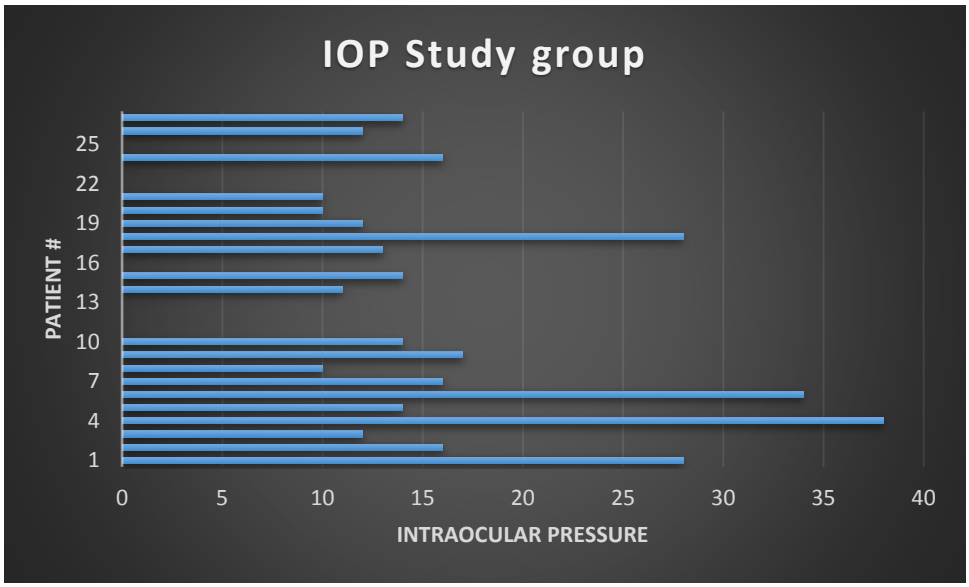


Figure 4: Intraocular Pressure analysis

OCT was performed in 16/27(59%) patients with CRVO. The initial Central Foveal Thickness (CFT) ranged from 280 µm to 1000µm, at 3 months the CFT was between 254µm and 1072 µm as shown in Figure 5.

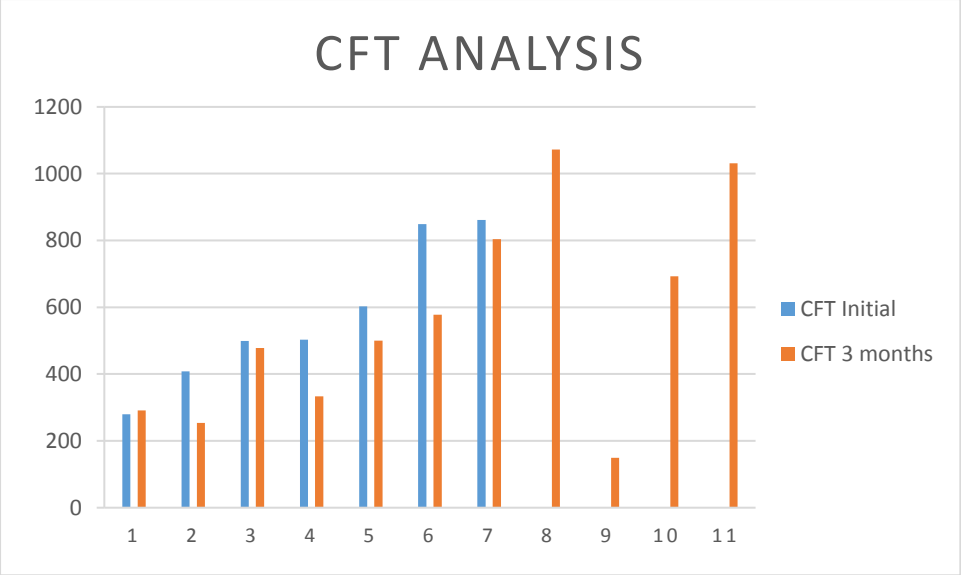


Figure 5: Central Foveal Thickness results

The most common complication of CRVO in this study was CME which occurred in 21 out of 27 cases (59%), shown in figure 6. We had 5 of our patients (4%) were complicated by vitreous haemorrhage (VH), and another 5(4%) developed neovascular glaucoma. 19/27 (70.4%) of patients with CME alone were treated with Anti-VEGF. 2/27 patients underwent PPV and treated with Anti-VEGF, and 1/27 patients received anti-VEGF as well as Pan Retinal Photocoagulation (PRP). Another 1 of the 27 patients was treated with PRP alone for NV (Table 7).

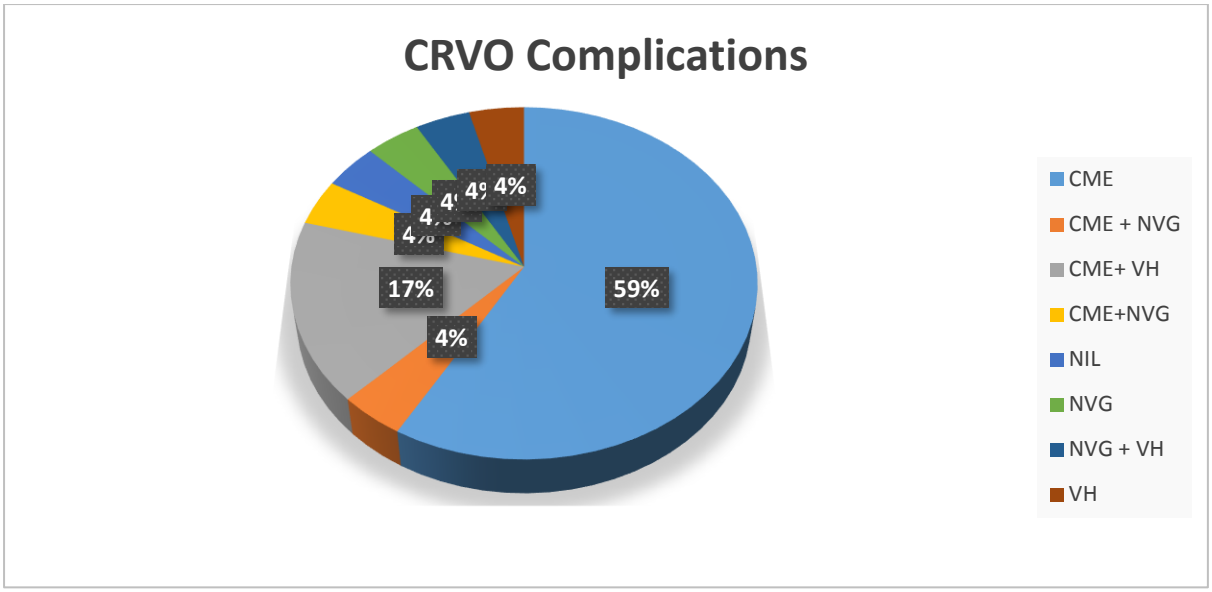


Figure 6: Study group complications

Table 7: Study group treatments

Treatment	Patients treated
IVT anti-VEGF	19
No treatment	3
IVT anti-VEGF + PPV	2
IVT anti-VEGF + PRP	1
Glaucoma medication	1
PRP	1
Grand Total	**27**

We set out to identify the risk factors and outcomes of CRVO by conducting a retrospective case-control study conducted between two academic hospitals over a five year period. In the risk factor analysis, we looked at demographical data, vascular risk factors such as hypertension, diabetes, and hyperlipidaemia. We also looked at glaucoma as the major ocular risk factor.

Advancing age is a major risk factor for the development of CRVO [2,3,4,6]. The mean age of patients with CRVO in our study was 64 years which was slightly younger than what has been

reported [9, 10]. About 19% of our subjects were younger than 60 years while 74% were over the age of 60 years (Table 3). This shows that our patients were of similar age to what is published.

We found a preponderance to females diagnosed with CRVO compared to males (63% vs. 37%), with female to male ratio of 5/3. It has been previously reported that CRVO occurred slightly more frequently in males than in females[6]. There were more females than males in the control group as well with the F: M ratio of 5/4. This might represent a selection bias where more females present to hospitals compared to males.

Racial preference has not been found in patients with CRVO. In our demographical data, 68% of patients with CRVO were black and 77% in the control group were black patients (Table 3). This could be due to the profile of patients seeking medical care in the public sector so could represent a selection bias. Kolar, in the analysis of socioeconomic factors for CRVO, reported an increased risk of 58% in American blacks compared with non-Hispanic whites 3. There are no studies to support this association in our population.

The literature emphasises the significance of hypertension as a major risk factor for CRVO followed by glaucoma, hyperlipidaemia, and diabetes. In this study, there was no statistical significance between the two groups for hypertension, glaucoma, and diabetes by univariate analysis (Table 5). However, there was a positive association with glaucoma and diabetes to the development of CRVO with the Odds ratio of 2.86 {CI 0.23- 3.05} and 1.21{CI 0.30-3.67} respectively.

In our study, 20/27 (74%) of the patients with vein occlusion and 24/30 (80%) of the controls were already on treatment for hypertension. There was no statistical difference between the two groups. This finding infers to the prevalence of hypertension in our population. The degree of control of hypertension in both of our groups was not documented. Also, 11/27(41%) patients did not have a recorded BP reading at the time of diagnosis with CRVO. Out of those who had a BP taken, 3 had elevated blood pressure. None of the controls had an elevated BP, however, these patients were seen for pre-op assessment for routine cataract surgery which requires patients to have good control of BP and diabetes. It is published in the literature that patients with non-complicated hypertension have a 36% increased risk of developing CRVO and that 92% of patients with advanced hypertension (end-organ damage) had increased risk of CRVO[3].

We had a similar number of patients with diabetes in both the study and control groups. None of the study patients had an elevated HGT at the time of diagnosis, although not all patients were tested for this at presentation. The current incidence of diabetes in the population seems to be as common as in the reported cases of vein occlusion, meaning that diabetes is as common in patients with retinal vein occlusion as the general population. In a meta-analysis of risks for CRVO, diabetes was a risk factor in 5% of patients[1]. It is of great value to test for diabetes, hypertension, and hyperlipidaemia in all patients with a retinal vein occlusion[6]. These vascular conditions cause arteriosclerosis of the blood vessel wall which affects blood flow in the adjacent retinal vein, leading to venous stasis and the resultant occlusion of the vein. Our results show that diabetes probably does not play a big role as an independent risk factor in the development of CRVO.

Glaucoma has been identified as a major ocular risk factor for CRVO, 4 - 4.5% of eyes with POAG develop retinal vein occlusion. On the other hand, POAG or Ocular Hypertension is found in 4% to 43% of patients with CRVO [8]. We found no statistical significance between the two groups for glaucoma for the development of CRVO. However, there was a positive association with an Odds Ratio of 2.86 {CI 0.23- 3.05}, although there was no statistical significance. In our results, the mean intraocular pressure was 17mmHg {SD 8} in eyes with CRVO. We had 2 patients who were diagnosed with glaucoma (1 POAG and 1 Pseudo exfoliation glaucoma) prior to developing CRVO. In these patients, the intraocular pressure was highly elevated at the time of diagnosis. There were 2 undiagnosed glaucoma patients who had an elevated IOP at the time of diagnosis with CRVO. This finding of elevated or uncontrolled IOP speaks to the theory of raised intraocular pressure causing external pressure on the central retinal vein, resulting in turbulent blood flow distal to the constriction and subsequent thrombus formation. However, it remains unclear how these two interact to result in blockage of the central retinal vein. We also had 1 patient in the control group with POAG. This patient did not have CRVO according to the exclusion criteria. We did not include IOP in the control group as part of data collection, and in retrospect would have given rise to more discussion to the unclear connection between raised IOP and CRVO. It has been published also that patients may have low intraocular pressure following a vein occlusio[26]. Although not clearly understood, it is postulated that retinal hypoxia following a CRVO results in a drop in IOP, followed by normalisation after some time to equal levels to that of the normal eye[26]. This could be a consideration in our patients in whom the mean IOP was in the normal range.

In our secondary outcomes, we found important and relevant findings regarding visual outcomes and complications of CRVO. For visual outcomes we looked at visual acuity using

the Snellen visual acuity chart at diagnosis and last visual acuity, essentially analysing the natural history of CRVO in the study group. The presenting visual acuity at baseline is said to be a strong predictor of final visual acuity[1, 5, 27]. Figure 3 and Table 6 outline the unaided visual acuity at the beginning and at last recorded visit, showing improvements at last visit. This is evidenced by 4/27 of patients presenting with VA of 6/60, and 12/27 ending up with 6/60 vision or better. There was a substantial improvement from 17 (63%) of the 27 CRVO eyes presenting with profound vision loss of CF to only 2 (7.5%) ended up with the same CF vision. Improvements in vision are attributed to the management of the complications resulting in visual gains in the era of Anti-VEGF.

The results also show a visual decline of 5 patients ending up with NLP, including 1 patient who presented with NLP vision. It is interesting to note that 4 of the 5 patients with NLP vision had an RAPD at first visit which is a common finding in ischaemic vein occlusions[12]. The presence of RAPD at presentation is a crude way of inferring an ischaemic type of CRVO. The ischemic subtype of CRVO accounts for about 20% of cases and is associated with worse initial presenting visual acuity and poor visual prognosis even after resolution of edema[28]. Fluorescein angiography was not done in all our cases. It is highly likely that these 5 eyes fell into this subtype. All 5 NLP eyes were complicated by CME, 2 were complicated by NVG, and 1 with vitreous haemorrhage. Fluorescein angiography is not a reliable morphological test in the early stages of the disease [12]. However, it is useful in the later stages of the disease to detect ischaemia.

A CRVO may be associated with vision-threatening sequelae including CME, ischaemic maculopathy from capillary non-perfusion, posterior segment neovascularization, vitreous haemorrhage, anterior segment neovascularization (Iris or angle), and NVG [1].

The main cause for poor vision is CME, which may lead to RPE changes [3, 8, 5]. We found the commonest complication of CRVO to be CME (59%), VH (4%) and NVG (4%) as depicted in Figure 6. The rest of the patients had a mixed picture of complications at different stages of follow up. 23/27 (85%) of our patients were treated with anti-VEGF (Bevacizumab) for CME intravitreally, monthly for 3 months. Treatment was continued in patients with partial or no response. None of our patients developed endophthalmitis, a serious sight-threatening complication of intravitreal anti – VEGF treatment.

Ranibizumab and Aflibercept are FDA and EMA approved as well as being recommended by NICE (NICE TA and NICE TA 305) for the treatment of visual impairment due to macula edema secondary to CRVO. Bevacizumab is unlicensed for intravitreal injections and is considered as a first-line drug if Ranibizumab or Aflibercept is unavailable or due to economic considerations. This was the case for our patients for whom Bevacizumab was the 1st line and only anti-VEGF treatment available. There were no second-line treatment options in the form of another anti-VEGF or intravitreal steroids.

At 3 months patients should be assessed for fluid on OCT[24]. The response can be variable amongst patients and defining this response is crucial to tailoring a patient-centric treatment regimen. A simple definition could be the one that categorises patients with a CFT >250 µm after three injections as late or partial/ non-responders and those with a CFT of <250 µm as early or good responders[24]. In our CFT results analysis, our patients fell into the group of the former based on the OCT at 3 months where most patients' CFTs were >250µm (Figure 5).

OCT measured CFT is a useful tool for detecting and monitoring of CME in CRVO, but cannot be a reliable substitute for visual acuity measurement[29]. Therefore our visual outcomes and anatomical outcomes cannot be reliably compared.

Very few of our patients received PRP during the course of treatment and follow-up. One of the patients received both anti-VEGF and PRP. Early intravitreal Bevacizumab followed by pan-retinal and macular grid laser may provide visually and anatomically favourable results in a case of CRVO[30]. In the RELATE trial, they found that scatter PRP does not reduce CME or treatment burden in patients with CRVO[31].

None of our patients were treated with intravitreal steroids. This was most likely due to the unavailability of the drug in our state hospitals at the time of treatment. Steroids can be used as a second-line drug in resistant cases. Because there are minimal differences in visual outcomes as well as the higher complications with steroids, anti-VEGFs are the preferred agents for 1st line treatment.

A retrospective study by Sharareh et al looked at 18 patients categorized as complete or partial responders to Bevacizumab that were given Dexamethasone implants. The study showed that both subgroups responded with an improvement in both central macular thickness(average 147 µm) and visual acuity[24].

4.1 Conclusion

Our study of CRVO in the South African setting shows that age and vascular risk factors are important factors in patients with CRVO. We also found good visual outcomes following treatment with Avastin. Anti-VEGF drugs have revolutionised how we manage patients with complications following a CRVO, mainly CME and NV. We did see improvements in anatomical outcomes based on the OCT findings. Our complications are similar to those noted in the literature, CME being a major cause of vision loss. Our patients showed response to the anti-VEGF treatment we have available in our state hospitals (bevacizumab). However, there was no second-line treatment in the two hospitals for patients who were partial or non-

responders, leaving the patients with chronic CME. The literature has shown that changing to another anti-VEGF agent in partial or non-responders is beneficial[22]. The benefit of switching to another anti- VEGF or changing to intravitreal steroids in our state hospitals could further improve our outcomes of this sight-threatening condition with devastating consequences for vision and quality of life. The unavailability of fluorescein angiography resulted in an inability to classify our patients into non- ischaemic or ischaemic types of CRVO which might have better predicted our outcomes and directed management. However, it has been shown that functional tests such as visual acuity, RAPD, visual fields and ERG in patients with vein occlusion, are more reliable than morphological tests e.g. Fluorescein angiography and clinical appearance in the acute stages of the disease[12].

The limitations of this study were mainly related to its retrospective nature. The biggest limitation was the small sample size, a larger sample size was needed in order to substantiate the results. Lack of electronic record keeping, loss of records and illegible records were reasons for this. Larger numbers are needed to confirm these findings, and ideally in a prospective manner. Also, some of the needed variables were not in the records which resulted in missing information.

The control group was not entirely representative of the general population. This is because the controls were required to have well-controlled hypertension and diabetes for their pre-op visits, so there was a selection (hospital) bias. Some risk factors were not measured in the control group e.g. IOP. Finally, the reviewer of the records was not blind to the etiologic relation being studied or the hypothesis being tested. Larger numbers are needed to confirm these findings, and ideally in a prospective manner.

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