

Fibrinolytic and Surgical Treatment Approaches for Retinal Vein Occlusion

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ABSTRACT

Retinal vein occlusion (RVO) is the second most common vascular disease after diabetic retinopathy. Although its high frequency, mechanisms underlying RVO and optimal treatment strategies are still controversial. There are various treatment modalities for retinal vein occlusion including observation, systemic treatments, intravitreal agents, laser photocoagulation, fibrinolytic treatment and surgical approaches. Despite most of the treatment strategies are directed at secondary complications of RVO that affect vision including macular edema and retinal neovascularization, some treatment options also have the ability to create a bypass around the obstructed retinal vein and to decrease the raised venous hydrostatic pressure. The aim of this review is to describe the outcomes of fibrinolytic and surgical treatment modalities for RVO.

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Key words: Branched Retinal Vein Occlusion; Central Retinal Vein Occlusion; Fibrinolytic Treatment; Surgical Treatment

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INTRODUCTION

Retinal vein occlusion (RVO) is a common cause of unilateral visual loss and the second most common vascular disease after diabetic retinopathy^[1]. RVO can be evaluated as two primary categories depending on the site of the occlusion: branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO); the first one is more common ranging from 3 to 10 times^[2]. The pathogenesis of RVO is still unclear and may be due to a combination of three main mechanisms which known as Virchow's triad: hemodynamic changes (venous stasis-compression of the vein), degenerative changes of the vessel wall, and blood hypercoagulability^[3]. Due to its complicated and multifactorial nature, treatment strategies of RVO are still controversial. There are four main goals to treatment of RVO: first, to limit retinal damage during the acute phase of RVO; second, to find out and modify and/or remove the risk factors; third one, to treat following ocular complications including macular edema and retinal neovascularization and the lastly to prevent recurrent events^[4]. To date, no proven effective treatment has been shown in large randomized studies. There are various treatment modalities for retinal vein occlusion including systemic treatments such as hemodilution, anticoagulation therapy and fibrinolysis; intravitreal agents such as steroids, anti-vascular endothelial growth factor agents (VEGF), and dexamethasone implant; laser photocoagulation treatment, fibrinolytic treatment modalities such as intravitreal administration of t-PA, direct injection of tissue plasminogen activator (t-PA) into the lumen of a retinal vein via retinal vein cannulation, super selective ophthalmic artery catheterisation, and surgical approaches such as pars plana vitrectomy (PPV), arteriovenous sheathotomy, radial optic neurotomy (RON), chorioretinal venous anastomosis^[5-11]. The aim of this review is to describe the outcomes of fibrinolytic and surgical treatment modalities for RVO.

FIBRINOLYTIC TREATMENT MODALITIES

Since the mid of the last century, systemic and intravitreal fibrinolytic treatment modalities have been studied for the

management of RVO. Fibrinolytic treatment of RVO based on the thrombotic pathogenesis of the disease and administration of fibrinolytic agent may the recanalize the obstructed vein by lysing the thrombus^[12]. Some studies showed that despite systemic thrombolytic agents have beneficial effects on the blood flow of the obstructed retinal vein and improvement in visual acuity, these systemic agents associated with some side effects as massive subretinal haemorrhage, vitreous haemorrhage, gastrointestinal haemorrhage, cerebral haemorrhage even death^[9,13-15]. Because of the serious side effects, systemic fibrinolytic agents are not preferred for RVO anymore. To reduce the side effects, investigators tested these agents locally within the eye and two techniques were developed. These are intravitreal administration and direct injection into the retinal vein. Firstly, Lahey *et al.*^[16] reported on the intravitreal administration of t-PA for CRVO. Their study included 23 patients with CRVO with recent onset of visual symptoms (less than or equal to 21 days) and were given an intravitreal injection of 65-110 microgram of t-PA. They reported that 8 of 23 patients (34.8%) achieved vision greater than or equal to 20/40 at 6 months after administration. In addition, one patient developed small vitreous hemorrhage and two patients developed an increase size of macular hemorrhage in their series. The justification for intravitreal administration of t-PA is that it can diffuse across the internal limiting membrane and enters the retinal circulation through capillaries damaged by breakdown of the blood-retina barrier following RVO. The t-PA would then be transported by residual venous flow towards the lamina cribrosa, the presumed site of thrombus, to cause thrombus lysis^[6]. Also, Glacet-Bernard *et al.*^[17] investigated the effect of intravitreal t-PA in the patients with recent onset CRVO. At the end follow-up, visual acuity had improved 20/30 or better in 5 of 15 patients (36%) and no complication of t-PA was observed. However, subsequent some studies revealed that intravitreal administration of t-PA did not have a beneficial effect on the management of RVO even worsened visual acuity was observed in some patients^[18,19]. In addition, intravitreal injection of t-PA had some complications such as vitreous haemorrhage and increase in macular edema. Because of these unsuccessful results, different ways were searched to administration of t-PA into the obstructed retinal vein and in the year of 2001 Weiss and Bynoe described a surgical procedure that allowed direct injection of t-PA into the obstructed vein^[20]. This surgical procedure included PPV with peeling of posterior hyaloid followed by cannulation of a peripapillary retinal vein branch and injection of a bolus 200µg/mL t-PA towards the optic nerve head (ONH). This study included 28 patients with CRVO whose average duration was 4.9 months and visual acuity were 20/63 or worse before intervention. At the final follow-up visit, 22 of 28 patients who underwent the procedure experienced at least one line of visual improvement. However significant side effects were reported in this study, 7 patients had postoperative vitreous hemorrhage and 1 patient had a retinal detachment. This technique works by several different mechanisms: firstly, pars plana vitrectomy with removal of posterior hyaloid provides high oxygen levels to retina, relieves macular traction and contributes to resolution of macular edema; secondly, direct injection of t-PA causes lyses of thrombus by providing high local concentration and thirdly, bolus of t-PA may flush out the thrombus with its high flow velocity^[21]. Similarly, Bynoe *et al.*^[22] revealed favorable results with retinal endovascular surgery. The study included 25 patients with CRVO; 18 patients (72%) recovered more or equal 3 lines and 9 patients (36%) recovered more or equal 8 lines of visual acuity. On the other hand, Feltgen *et al.*^[23] observed a disappointing visual outcome and high complication rates with this surgical technique. In the study which was a prospective

case series of 13 patients with ischemic CRVO, while only 3 patients (23%) recovered more or equal 2 lines, visual acuity worsened more or equal 2 lines in 6 patients (46%). In addition, 6 eyes developed neovascular glaucoma, of which 2 had to be enucleated; retinal detachment was found in 3 eyes and cataract in 4. It was suggested that these disappointing results were due to a long interval before intervention and inexperience of the surgeons. Considering the results of these previous reports, a recent study showed that three main factors appear to be important to affect results: first is the time between intervention with RVO; second is experience of the surgeon and third is RVO subtype, ischemic or non-ischemic^[24].

In summary, direct administration of t-PA via retinal vein cannulation during vitreoretinal surgery is a feasible technique and has been shown to be effective in patients with CRVO; but currently there are no studies on its effectiveness in BRVO. However, direct injection of t-PA has serious ocular complications including vitreous haemorrhage, retinal detachment, increase in macular edema, endophthalmitis and even phthisis bulbi. Therefore, its application is limited and needs experience.

Another way for direct injection of t-PA into the obstructed retinal vessels is super selective ophthalmic artery catheterisation. Recent progress in interventional neuroradiology has made possible the selective catheterisation of small vessels as ophthalmic artery and infuse a fibrinolytic agent close to the obstructed vessel. In this way, this technique aims to maximise the concentration of fibrinolytic agent close to obstruction site and reduce the side effects of systemic fibrinolysis complications. There are some studies which use this technique in the patients with CRVO^[25-27]. In these studies, the technique was performed by interventional neuroradiologists in the angiography room with the patient under neuroleptanalgesia. A catheter was inserted into the internal carotid artery via the femoral artery. Then, an initial carotid cerebral arteriogram was used to fashion the tip of the microcatheter in accordance with the geometry of the carotid arterial siphon and ophthalmic arterial ostium. Urokinase was then infused over 1 hour. After, to inhibit coagulation on the thrombus and to limit clot extension and to prevent recurrence, all patients were given intravenous heparin for 48 hours followed by subcutaneous low molecular weight heparin for 1 month and to modify risk factors for atherosclerosis and prevent further thrombosis oral aspirin for 3 months. Paques *et al.*^[25] reported that selective ophthalmic artery infusion of urokinase was followed by improvement in visual acuity in 6 out of 26 cases of CRVO and eyes with combined central retinal arterial occlusion (CRAO) and CRVO with recent visual loss appeared to be the most responsive. In addition, Vallée *et al.*^[26] performed this technique to 13 patients who had recent severe non-ischemic CRVO for which no alternative therapy was available. 5 of the 13 patients treated experienced visual improvement and retinal perfusion within 24-48 hours. Vision returned to normal within 24-48 hours in 3 patients, within 1 week in 1 patient, and within 1 month in 1 patient. These five patients exhibited progressive lesion regression within 2-4 weeks at funduscopy. Their clinical course prior to treatment resembled combined CRAO and CRVO, which typically has a poor visual outcome. It seems, therefore, the short period between fibrinolysis and substantial visual improvement, combined with marked retinal perfusion improvement, suggests that fibrinolysis is beneficial for CRVO, especially for recent CRAO and CRVO. Since patients with combined CRAO and CRVO were found to respond well to thrombolysis another prospective study was undertaken with this group patients^[27]. 11 consecutive patients with visual loss of less than 72 hours were treated with during a 6 year period. Significant

improvement in visual acuity and retinal perfusion was noted in 7 of the 11 patients treated. Mean vision improvement was significant within 24-48 hours after fibrinolysis, increased until 1 month after then remained stable throughout the follow-up period. Also, one patient had intravitreal hemorrhage shortly after fibrinolysis.

As a result, in the light of these studies, super selective ophthalmic artery catheterization technique looks a suitable treatment for RVO, especially in cases with combination of CRAO and CRVO. In addition, the technique seems appropriate to administer treatment before the thrombus becomes organised and has some complications such as vitreous hemorrhage and increase in macular edema.

SURGICAL TREATMENT MODALITIES

Common surgical treatment modalities for RVO can be summarized as follows: vitrectomy with or without internal limiting membrane (ILM) peeling, arteriovenous sheathotomy, radial optic neurotomy (RON), and chorioretinal venous anastomosis.

Vitrectomy with or without Internal Limiting Membrane (ILM) Peeling

There are different non-surgical treatment options for macular edema which is a major complication of RVO, including observation for spontaneous resolution, intravitreal and periocular application of steroids, intravitreal injection of VEGF inhibitors and laser photocoagulation treatments. On the other hand, it generally takes several months to resolve of the macular edema with these treatment modalities. Macular edema can be persistent despite these options and persistent macular edema may cause irreversible visual loss as a result of apoptosis of the photoreceptors, therefore rapid resolution of macular edema is needed^[28]. Although, the mechanisms are not clear, PPV has been suggested as beneficial effects for the rapid resolution of macular edema and retinal damage in patients with RVO. It is shown that the absence of posterior vitreous detachment can contribute to the occurrence or the persistence of macular edema in CRVO^[29,30]. The adherence of the vitreous cortex on the macular region can produce tractional forces. Some studies showed that PPV with ILM peeling rapidly reduced the macular edema caused by CRVO or BRVO, with improvement in visual acuity^[31,32]. Mandelcorn *et al*^[33] reported that this surgical procedure provides significant improvement in visual acuity and decrease in retinal thickness in the patients with CRVO and BRVO. Baharivand *et al*^[34] showed similar result by performing PPV with ILM peeling. In their study, intraretinal blood and retinal thickening diminished within 2 months of surgery in all patients. The decrease in macular thickness was statistically significant, on the contrary improvement in visual acuity was not. In addition, Park *et al*^[35] revealed that these favorable effects persisted up to 5 years. In these studies mentioned above hypothesized that vitrectomy with ILM would peeling allow the congested, hemorrhagic retina to decompress by facilitating the release of extracellular fluid and blood into the vitreous, which would, in turn, restore normal retinal thickness and intraretinal tissue pressure, reduce opacities within the retina that could interfere with light transmission to photoreceptors, remove tractions and scaffold for proliferating astrocytes and reduce intraretinal pressure around adjacent retinal venules and capillaries that would allow these blood vessels to reopen where possible. Also, Furino *et al*^[36] showed that peeling of ILM which is formed by Muller cell foot plates is thought to induce gliotic response, which helps to release the extracellular fluid into the vitreous cavity by contracting the retinal layers and decreasing extracellular spaces. On the other hand,

Radetzky *et al*^[37] reported contrary results after PPV with ILM peeling in the longterm. To evaluate the efficiency of the PPV with ILM peeling in persistent macular edema with different diagnosis, they retrospectively analysed 23 patients who underwent PPV and ILM peeling for persistent macular edema. In the study, the main diagnoses were uveitis, CRVO, diabetic retinopathy, vitreoretinal traction syndrome, and Irvine-Gass syndrome. In the CRVO group, they reported that an initial positive response to PPV with ILM peeling, but a less beneficial effect in the longterm. Therefore, they proposed that vitrectomy and ILM peeling might be beneficial in the reduction of intraretinal edema, but failed to identify the underlying the pathophysiological mechanisms such as growth factor expression or altered fluid dynamics.

Moreover, comparatively successful results have also been reported for vitrectomy without ILM peeling. Some studies reported that vitrectomy with gas/air tamponade appears effective and provides significant improvement in visual acuity in the patients with BRVO^[38,39]. Vitrectomy without ILM peeling may provide resolution of macular edema by mechanically removing VEGF and other cytokines such as IL-6 from the vitreous cavity and by enhancing oxygen transport to the hypoxic retina^[40,41]. Tachi *et al*^[42] suggested that early vitrectomy may be recommended for retinal vein occlusion associated with macular edema in the patients with BRVO and CRVO. In the study, they showed statistically significant visual improvement by performing PPV. Similarly, Sekiryu *et al*^[43] performed PPV in 5 cases affected by CRVO and observed a reduction of the retinal thickness in all the cases by evaluating optical coherence tomography. In opposition to reports in favour of vitrectomy, Hvarfner & Larsson^[44] did not confirm its benefits in longterm. They retrospectively evaluated the efficiency of PPV in 8 eyes with non-ischaeamic macular edema secondary to CRVO and hemi-retinal vein occlusion and reported that PPV showed an initial positive effect for the reduction in retinal thickness and improvement in visual acuity in the early postoperative phase but no beneficial effect in the longterm.

In conclusion, vitrectomy with or without ILM peeling seems to be able to contribute considerably to a reduction in macular edema in RVO by providing relief of the tractional forces on the macula, removing VEGF and other cytokines such as IL-6 within the vitreous cavity and enhancing oxygen transport to the hypoxic retina.

Arteriovenous Sheathotomy

Branch retinal vein occlusion (BRVO) usually occurs at arteriovenous (A-V) crossing points where arterioles and venules share a common adventitial sheath^[45-47]. An artery which is affected by hypertensive and atherosclerotic changes leads to compression, venous turbulence, endothelial damage, and secondary thrombosis. Arteriovenous adventitial sheathotomy has been proposed as a direct approach to release compressive vein force and to restore venous flow. Venous compression in BRVO may be relieved by dissection of common adventitial sheath. The procedure which is named as arteriovenous sheathotomy or adventitial sheathotomy requires vitrectomy, followed by an incision of the adventitial sheath adjacent to the arteriovenous crossing and separation of the adhesions. This procedure was performed for the first time by Osterloh and Charles in 1988^[48]. After standard pars plana vitrectomy, surgical separation of the posterior cortical vitreous from optic nerve and posterior retina was performed. The responsible arteriovenous (AV) crossing site was identified and a microvitreoretinal (MVR) blade was used to separate the overlying artery from vein. An inner retinal incision was started between 100-500 µm proximal to the AV crossing and continued until it reached

the common AV crossing sheath. Blade were used to incise through the arteriovenous sheath and to separate the arteriole from underlying venule. Finally, arteriole elevated from the underlying venule^[49]. Opremcak and Bruce^[50] reported postoperative visual acuity improved in 10 of 15 patients, but vision did not improve in three patients despite surgical success and resolution of fundus changes. This was attributed by the authors, to rising of the postoperative intraocular pressure. In another study which includes 43 patients with BRVO were treated with A-V decompression while 25 patients who rejected surgery were accepted as control group^[51]. In the study, 26 patients (60%) gained at least two lines of vision and 12 patients (28%) gained at least four lines of vision. Macular edema and retinal haemorrhages had resolved after 6 weeks' follow up and also patients with the highest gain also showed angiographic improvements in venous perfusion, Despite visual improvement, capillary reperfusion was only detected in four eyes. Overall, the functional outcome were significantly better in patients with A-V decompression than controls. Also, Cahill *et al*^[52] reported a complete resolution of cystoid macular edema and postoperative vision improvement in one third of the patients after A-V sheathotomy. However, Yamamoto *et al*^[53] retrospectively studied 16 eyes that underwent PPV with sheathotomy and 16 eyes that underwent only PPV for macular edema secondary to BRVO. They reported that there was no significant difference in the improvement of macular function between the two groups at any postoperative period and also there were no differences in the functional and morphologic improvements between patients with and without sheathotomy. Moreover in some studies, complications were reported including cataract, nerve fibre layer defects, haemorrhage, retinal tear, postoperative gliosis, and retinal detachment.

With regard to optimum surgical timing, an association between early intervention and better visual outcomes has previously been described. Mason *et al*^[54] showed the relation between the improved visual outcomes and early intervention. Mester and Dillinger^[51] reported that best functional improvement was observed in eyes with a shorter duration of symptoms. Similarly, Yamane *et al*^[55] reported that earlier treatment might have resulted in better visual outcomes.

In conclusion, despite some investigators reported early arteriovenous sheathotomy may result in better visual outcomes for the patients with BRVO, others suggested that PPV provides this beneficial effect, additional arteriovenous sheathotomy did not lead to a significant functional benefit. Further investigations are required to show a significant improvement in outcomes of BRVO that would justify the risks of the arteriovenous sheathotomy procedure.

Radial Optic Neurotomy

Although the pathogenesis of RVO is not clear, one of the main theories behind the formation of RVO involves central retinal vein (CRV) thrombosis at the level of lamina cribrosa. Another theory about CRVO suggests a compartment-like syndrome caused by increased pressure around the optic nerve head (ONH). Based on this knowledge, Opremcak *et al*^[56] treated CRVO patients by performing a novel surgical method which was described as radial optic neurotomy (RON). They hypothesized that the anatomy of the ONH and scleral outlet which is defined as the space confined by the scleral ring containing the lamina cribrosa, central retinal artery (CRA), CRV and optic nerve might play a role in the pathogenesis of CRVO. Moreover, RON was thought to induce the post-operative development of optociliary venous anastomosis or retinochoroidal shunts, leading to increased retinal venous outflow. In accordance with the hypothesis, after a standard three port vitrectomy, a radial incision on the nasal side of the optic disc is performed by using

a MVR blade to relax nonelastic scleral outlet and to improve venous outflow. The excision was done radial to the nerve, parallel to the nerve fiber layer and on the nasal side of the disc to protect papillomacular bundle and major vessels. In this way, lamina cribrosa, scleral rim and neighboring sclera were incised with RON. Their retrospective non-randomised pilot study included 11 patients with severe, hemorrhagic CRVO patients whose visual acuities were 20/400 or worse. After the radial surgical relaxation of the scleral outlet, all patients showed clinical improvement with dramatic and rapid clearing of intraretinal haemorrhages and increased retinal blood flow. The surgery was reported to be safe and 8 of 11 patients (73%) had rapid improvement of visual acuity with an average gain of 5 lines of vision with RON. There were no operative complications reported^[56]. On the contrary, these results were challenged by Hayreh *et al*^[57] who suggested that RON was not a safe procedure given the close proximity of the incision site to the CRA, and thus, this surgical procedure carries a potential risk of cutting off the blood supply to the ONH, resulting in acute ischaemia of the ONH and visual loss. They also emphasized that surgical relaxation of the vein could not be achieved by performing RON while the lamina cribrosa is a compact rigid band of collagen tissue, and is not simply an elastic envelope. Thus, a radial incision cannot be effective in decompressing the obstructed retinal vein. Also, in the majority of cases the occlusion takes place in the optic nerve at a variable distance posterior to the lamina cribrosa, and not at the lamina cribrosa. Moreover, they suggested that it was unlikely to recanalize the CRV, which was completely obliterated by an organized thrombus. The controversial opinions about the RON necessitated further investigations with larger patient populations. Accordingly, Opremcak *et al*^[58] evaluated the effectiveness of RON in 117 patients with severe CRVO. They reported anatomic resolution in 95% of patients, and snellen visual acuity improved by an average of 2.5 lines (range, 1-12 lines) in 71% of patients within 3 months postoperatively. Based on these favorable outcomes, they suggested that RON might be a technically feasible and safe procedure. In another study, 107 patients were treated with RON for CRVO at five collaborating ophthalmologic centers^[59]. In the study, visual improvement of equal or more 2 lines was detected in 48.5% of all patients within 1 year postoperatively. However, only the non-ischaemic eyes achieved a statistically significant increase in visual acuity compared with baseline values. Similarly, Binder *et al*^[60] reported that patients with nonischemic CRVO may respond more favorably than patients with ischemic CRVO after performing RON. Moreover, while improvements in visual acuity after RON have been confirmed by several other reports^[61-64], some studies found a resolution of macular edema that was not accompanied by an improvement in visual acuity in all eyes following RON^[65,66]. On the other hand, some studies revealed that RON induce the development of retinochoroidal shunt vessels in 46.7– 83.3% of patients and this may represent the mechanism of any beneficial effect this surgical procedure^[67-71]. In addition, several authors suggested that the creation of RON involves a PPV and the beneficial effects of RON are due to this alone^[72,73]. Nomoto *et al*^[68] treated 15 eyes with CRVO by performing RON to evaluate the effects of RON on retinal circulation in patients with CRVO by indocyanine green (ICG) videoangiography and a computer-assisted image analysis. Retinal circulation times were calculated before and after the surgery. They observed that retinal circulation times (RCT) decreased after the surgery in 7 of the eyes which developed chorioretinal anastomosis (CRA). In contrast, RCT decreased postoperatively in only one of the 8 eyes without CRA. These results suggested that CRA seems to be the major factor influencing postoperative visual acuity. CRA may

contribute to visual improvement by draining retinal circulation to the choroid and accelerating the resolution of retinal edema after RON. However, opposing the increased retinal perfusion after RON, Horio and Horiguchi^[174] detected a reduction in retinal blood flow following RON in a series of seven eyes with CRVO and reduction occurred although chorioretinal anastomoses were found in all seven eyes. The authors suggested that the development of severe gliosis and edema at the neurotomy site or intravascular thrombus formation may be possible reasons for the reduction.

Although RON has been proposed as safe by most authors, complications of the procedure should not be overlooked. Complications of RON include vitreous haemorrhage, retinal detachment, various visual field defects, choroidal neovascularization at the neurotomy site, central retinal artery occlusion, globe perforation and anterior segment neovascularization^[56,62,66,75-77].

In summary, RON may be effective as a result of these possible pathophysiological mechanisms: relaxing the confined scleral outlet, inducing the formation of chorioretinal shunt vessels and the additive positive effects of PPV. Consequently, RON seems to be controversial and its efficacy may be proved in comprehensive prospective randomised clinical studies.

Chorioretinal Venous Anastomosis

Chorioretinal venous anastomosis (CRA), in which a shunt is performed between a retinal vein and the choroids, aims to bypass the occluded vein via an alternative route, to improve retinal outflow and relieve the venous obstruction. Firstly in 1948, Verhoeff^[78] described chorioretinal anastomosis which allows blood to bypass the occluded vein into the choroidal circulation. It is hypothesized that visual acuity is improved by a reduction in macular edema and in progress to an ischemic status. CRA may be induced either by laser or surgery and has been applied to both BRVO and CRVO.

Firstly, McAllister and Constable^[79] performed laser induced chorioretinal anastomosis as a treatment options for the patients with non-ischaemic CRVO. They reported that a successful CRA was created in 8 of 24 patients (33%) with improvement in visual acuity. Some studies revealed similar successful rates with this technique^[80,81]. The effect of laser induced CRA depends on the type of RVO, chorioretinal venous anastomosis in ischaemic eyes is very difficult to achieve, perhaps because of the presence of endothelial cell damage^[82]. Furthermore, this treatment was frequently associated with some serious complications including choroidal or vitreous haemorrhages, choroidal neovascularization, segmental retinal ischaemia, pre-retinal fibrosis and retinal detachment^[81,83-85]. Because of the high complication rates and limited successful rates of the laser induced CRA, surgical methods are being evaluated. Surgically induced CRA has been described several surgeons who used some different approaches to perform the anastomosis^[86-90]. Fekrat and de Juan^[86] described transvitreal venipuncture technique to develop chorioretinal anastomoses in a case of ischaemic CRVO. In the same year, Peyman *et al.*^[87] described a new surgical technique to induce chorioretinal venous anastomosis in 5 patients with ischaemic CRVO. In this technique, following PPV, the posterior hyaloid was removed, and slit-like incisions were made with a MVR blade adjacent to a major retinal vein in each quadrant. Small pieces of 5/0 mersilene sutures were positioned over the vein and inserted into these incisions sites to promote the formation of collaterals and then endolaser was performed around the incision site followed by panretinal photocoagulation. Final visual acuity was better in 3 of 5 patients after the surgery. Quiroz-Mercado *et al.*^[88] performed another surgical technique in two eyes with ischaemic CRVO. This

technique included a standart PPV and posterior hyaloid detachment and the creation of chorioretinal venous anastomosis by using an erbium:YAG laser. In their study, visual improvement was observed with successful creation of chorioretinal anastomosis and without any complications in both cases. Mirshahi *et al.*^[89] subsequently described a modified surgical technique in 10 patients with ischaemic CRVO. Their technique consisted of PPV with incisions into the choroids adjacent to the partially cut major retinal veins in each quadrant. After then, mersilene sutures were inserted into the incised sites to induce a chorioretinal venous shunt and mild endolaser was applied. Although, visual improvement was reported in 8 of the patients, 3 patients experienced complications including retinal detachment, vitreous hemorrhage and cataract with this surgical technique. On the other hand, Koizumi *et al.*^[90] treated 7 patients with CRVO by cutting off the affected retinal vein by means of vitrectomy and making a small incision at both sides of the vein interruption through the full thickness of the retina, retinal pigment epithelium and Bruch's membrane. In 5 of 7 patients, successful chorioretinal venous anastomosis was observed and all five patients showed an improvement of two or more lines in visual acuity 6 months postoperatively. They proposed that surgical interruption of the affected vein allowed it to connect to another venous route more easily.

As a result, there are several different approaches to perform surgically induced CRA which do not lead to reperfusion of the areas with capillary nonperfusion. These different techniques may reduce the ischaemia of parafoveal and perifoveal areas and improve visual acuity by improving venous outflow and reducing macular edema. However, potential complications of these procedures should not be overlooked.

In conclusion, none of the treatment procedures have been found to effectively prevent or retrieve visual loss after RVO. The results of the studies to date are limited, more comprehensive and extensive randomised studies are required. Differences in initial treatment times, follow-up periods, duration of RVOs, and ischaemic or non-ischaemic status prevent accurate comparisons between studies and make it difficult to reach a final decision.

CONFLICT OF INTERESTS

The authors declare that they do not have conflict of interests.

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