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Bevacizumab for Retinal Vein Occlusion: Outcomes in Smec Eye Hospital Medan

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ABSTRACT

***Introduction**: Central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) cause sudden visual decrease that most often treatable. This paper aims to describe clinical characteristics and outcomes using bevacizumab for macular edema caused by retinal vein occlusion in real-life practice.*

***Methods**: This retrospective study conducted in SMEC Eye Hospital Medan (from June 2017 until January 2019), included 91 treatment-naïve eyes with macular edema due to CRVO (55 eyes) and BRVO (36 eyes), who were treated with intravitreal bevacizumab (IVB) in pro re nata (PRN) regimen. Best corrected visual acuity (BCVA) and central macular thickness (CMT) before and after treatment were evaluated.*

***Result**: The mean age of patients was 60.3 ± 11.2 years for CRVO and 55.7 ± 8.2 years for BRVO. The mean baseline BCVA in the CRVO group was 1.41 ± 0.55 logMAR. There was statistically significant improvement in BCVA after intravitreal bevacizumab compared to baseline ($p < 0.001$) in CRVO and BRVO group. Twenty six (47.3%) eyes with CRVO had BCVA ≥ 1.0 logMAR (Snellen 20/200) at the last follow-up. In the BRVO group, the mean baseline BCVA was 0.93 ± 0.48 logMAR. At the end of the follow up, 19 eyes (52.8%) with BRVO had BCVA ≥ 0.3 logMAR (Snellen 20/40). There was also statistically significant improvement in CMT between all time points and baseline ($p < 0.001$) in both groups. At the end of the follow up, 26 (47.3%) eyes with CRVO and 25 eyes (69.4%) in BRVO group presented resolution of macular edema (CMT ≤ 300).*

***Conclusion**: Intravitreal bevacizumab resulted in significant anatomical and functional improvement in macular edema associated with CRVO and BRVO.*

Keywords: Branch retinal vein occlusion, central retinal vein occlusion, macular edema, intravitreal anti vegf, bevacizumab

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INTRODUCTION

Retinal vein occlusions (RVO) are the second most frequent retinal vasculopathy after diabetic retinopathy. Its prevalence is 0.5% in individuals over 40 years[1,2] It is even higher in Asian population, reaching over 0.7% in individuals over 40 years according to Singapore Malay Eye Study (SiMES) and the Singapore Epidemiology of Eye Disease Study (SEEDS).[3,4] It is estimated that 16,4 million adults are affected by RVO worldwide, corresponding to 13,9 million with Branch RVO (BRVO) and 2.5 million with Central RVO (CRVO).[2]

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The exact pathogenesis of RVO is not fully understood. Blockage of retinal vein leads to impaired retinal blood flow, increased intraluminal retinal capillary pressure and ischemic damage to the retina.[2]

This ischemic damage results in photoreceptors cell death including in the macula. It also stimulates increased production of many inflammatory cytokines, such as interleukin-8, interleukin-6, placenta growth factor and vascular endothelial growth factor (VEGF). Elevated levels of VEGF result in increased vascular permeability and leakage causing significant macular edema, neovascularization in the anterior/posterior chamber, traction retinal detachment and neovascular glaucoma (NVG).[1,2]

Macular edema (ME) in RVO is the most frequent cause of visual loss in RVO.[5] Randomized controlled trials (RCTs) which showed efficacy and safety of ranibizumab for BRVO (BRAVO) and CRVO (CRUISE), also aflibercept for CRVO (Galileo and Copernicus) and BRVO (Vibrant), made them approved by FDA (Food and Drug Administration) and EMA (European Medicine Agency) for treating macular edema related to RVO.[6-10] However, these approved anti-VEGFs are expensive and protocol trials require intensive treatment of monthly injections for the first six months. Frequent intravitreal injections can be burdensome for patients or healthcare provider, therefore some institution choose to administer bevacizumab (off-label) on as needed or pro re nata (PRN) basis after the first injection to minimize cost.[11]

In actual clinical practice, the most frequently used anti-VEGF drug is bevacizumab.[11,12] Since the first report on the efficacy of intravitreal bevacizumab in a patient with ME secondary to CRVO in 2005, several studies have been conducted to evaluate its efficacy and safety.[14] Clinical trials comparing six monthly injections of bevacizumab and ranibizumab in the treatment of macular edema due to retinal vein occlusion (CRAVE) and bevacizumab versus aflibercept (SCORE2) for CRVO showed non inferiority of bevacizumab to other anti-VEGFs.[14,15] Another randomized trial (MARVEL) showed that even with PRN regimen, bevacizumab and ranibizumab had similar effects on improving visual acuity and reducing macular thickness in BRVO.[16] There was evidence that in real life clinical setting, anti-VEGF injections are administered less frequently than in the large registration studies, due to strain in healthcare provider/insurance or doctors' discretion.[11,12] The purpose of this study was to evaluate the efficacy and safety of bevacizumab as used in clinical practice for the treatment of RVO-associated ME.

PATIENTS AND METHODS

The study was a retrospective study conducted in SMEC Eye Hospital Medan. Medical records of patients with ME due to RVO from June 2017 to January 2019, were retrospectively reviewed.

Branch RVO was defined as a retinal vein occlusion involving one of the following: 1) vein draining single retinal quadrant, 2) macular draining vein, or 3) vein draining hemiretinal quadrant (hemi RVO/HRVO). Central RVO was defined as intraretinal flame-shaped hemorrhages and dilated tortuous retinal veins in all four quadrants. Macular edema was defined as an increased mean central macular thickness (CMT) more than 300 µm in the central subfield diagnosed by spectral-domain optical coherence tomography/OCT (Nidek RS-3000).

Inclusion criteria were 1) patients older than 18 years old, 2) had CRVO or BRVO and ME, and 3) onset to presentation less than 90 days. Exclusion criteria were 1) presence of ME due to other retinal disease (diabetic retinopathy, epiretinal membrane, vitreomacular traction, vasculitis/uveitis and age-related macular degeneration),

2) evidence of anterior or posterior neovascularization, 3) history of intravitreal anti-VEGF or retinal/macular laser, 4) prior ocular surgery (except for uneventful cataract surgery), 5) history of prior ocular trauma and 6) history of cerebral vascular accident or myocardial infarction.

Baseline best-corrected visual acuity (BCVA) in Snellen chart (converted to logMAR for statistical comparison), intraocular pressure using non contact tonometer, biomicroscope of anterior segment and indirect ophthalmoscopy were examined in all patients. Macular OCT was performed in all patients. Once the patient was diagnosed with ME secondary to RVO, intravitreal bevacizumab was administered within one week.

After detailed explanation of risks, benefits and off-label use of the medication, all the participants signed the informed consent before the intravitreal injections. Intravitreal bevacizumab (IVB) injection was performed using sterile technique. Topical 0.5% tetracaine was applied to the ocular surface followed by preparation of the eyelid and conjunctiva with 5% povidone iodine. An eyelid speculum was used and injection of 1.25 mg of bevacizumab in 0.05 mL given 3.5-4 mm posterior to the surgical limbus using a 30-gauge needle.

All the patients were followed up monthly with anterior segment and fundus examination and BCVA, CMT and intraocular pressure measurement. Retreatment was based on findings of CMT more than 300 μm or reccurent/persistant submacular cysts/fluids that affected the visual acuity. Patients were assessed for adverse events including elevated intraocular pressure, presence of iris/angle neovascularization, cataract progression, retinal detachment, postinjection inflammation, endophthalmitis, and systemic conditions (stroke or myocardial infarction).

The primary outcome measure in this study is improvement of BCVA, recorded as the best-refracted vision or the pinhole vision if refraction was not performed and mean change in CMT compared to baseline. Secondary outcome measures included mean frequency of anti-VEGF injection and predictive factors for final visual outcome.

For the description of patients' characteristics at baseline, mean $\pm$ SD was used for continuous variables and counts with percentages for categorical variables. For the longitudinal comparisons of BCVA and CMT between baseline and each time follow-up, the Wilcoxon signed t-test was used, with the level of statistical significance was 0.005. For the assessment of factors that may determine the visual acuity, linear regression analysis was performed. Visual acuity was the dependent variable. Factors that were assessed as potential predictors for visual acuity were age, gender, hypertension, diabetes mellitus, glaucoma and the CMT. Statistical analysis was performed using SPSS version 20.0. A P value <0.05 was considered statistically significant.

RESULTS

A total of 91 eyes with ME secondary to RVO were included in this study. There were 55 (60.4%) eyes with CRVO and 36 (39.6%) eyes with BRVO.

Study population and baseline values

Baseline demographics and clinical characteristics are shown in Table 1. There was no significant differences between the studied variables when comparing patients with BRVO or CRVO. There was no differences between groups concerning age or baseline BCVA.

Table 1. **Demographic and Clinical Characteristics at Baseline**

	CRVO (n=55)	BRVO (n=36)	p value
Age (years)	60.3 ± 11.2	55.7 ± 8.2	0.08
Gender			
Male	24 (43.6)	18 (50.0)	0.66
Female	31 (56.4)	18 (50.0)	
Baseline BCVA (LogMAR)	1.41 ± 0.55	0.93 ± 0.48	0.007
CMT (µm)	472.1 ± 119.7	498.8 ± 118.1	0.22
Hypertension	34 (61.8)	21 (66.6)	0.30
Diabetes	11 (20)	2 (5.5)	0.09
Open angle glaucoma	5 (9,1)	0 (0.0)	0.08

Best-corrected visual acuity after treatment according to type of RVO

The mean baseline BCVA in the CRVO group was 1.41 ± 0.55 logMAR. Figure 1 shows the evolution of BCVA over time, depicting that there was statistically significant improvement in mean BCVA between all time points and baseline (Wilcoxon t test, $p < 0.001$). At the end of the follow up, mean BCVA was 0.74 ± 0.37 logMAR, and 26 eyes (47.3%) had BCVA ≥ 1.0 logMAR (Snellen 20/200). Only 2 (3.6%) eyes had final BCVA more than 0.3 logMAR (Snellen 20/40).

In the BRVO group, the mean baseline BCVA was 0.93 ± 0.48 logMAR. Figure 1 shows the evolution of BCVA over time, illustrating that there was statistically significant improvement in BCVA at all time points and baseline (Wilcoxon t test, $p < 0.001$). At the end of the follow up, mean BCVA was 0.25 ± 0.11 logMAR, and 19 eyes (52.8%) with BRVO had BCVA ≥ 0.3 logMAR.

CMT reduction after treatment according to type of RVO

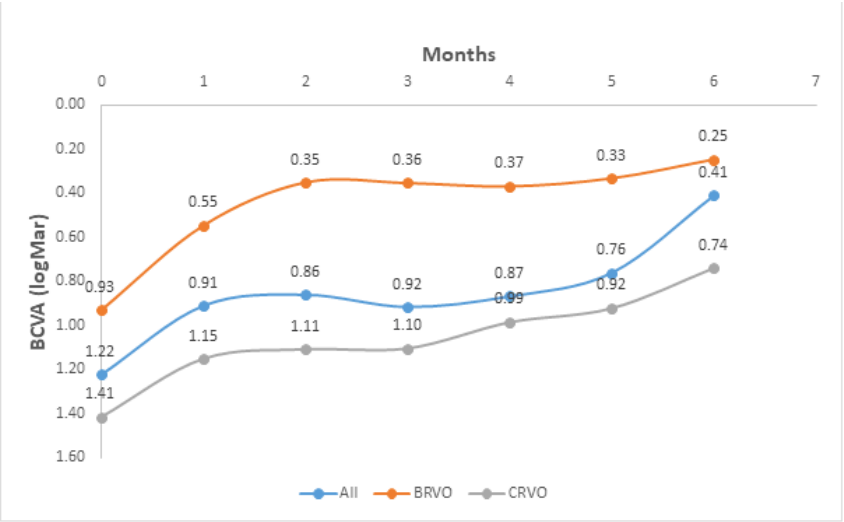
Figure 2 shows the evolution of CMT over time. In the CRVO group, the mean CMT was 472.1 ± 119.5 µm at baseline. There was statistically significant improvement in CMT between all time points and baseline (Wilcoxon t test, $p < 0.001$). At the end of follow-up, the mean CMT was significantly decreased by 165,1 µm compared with baseline. In BRVO group, the mean baseline CMT was 498.8 ± 107.2 µm. There was statistically significant improvement in CMT between all time points and baseline (Wilcoxon t test, $p < 0.001$). The mean CMT was decreased by 218,1 µm compared with baseline. At the end of the follow up, 26 (47.3%) eyes with CRVO and 25 eyes (69.4%) in BRVO group showed resolution of ME (CMT ≤ 300). In the CRVO group there was about 52.7% did not achieve CMT ≤ 300 µm at their last follow-up.

There were 23 (63.9%) eyes in the BRVO group that had resolution of ME after only 1 injection of IVB, out of which, 5 eyes had recurrence of ME during week 8 – 12 and needed retreatment. In the CRVO group, there were 17 (30.9%) eyes that had resolution of ME after only 1 injection of IVB, out of which, 6 eyes had recurrence of macular edema during week 8 – 20 and needed retreatment.

Number of injections during follow-up

The mean number of injection was 2.05 ± 1.29 (range, 1 – 7) in the CRVO group during follow-up time 5.13 ± 3.98 (range 1 – 15) months. In the BRVO group, the mean number of injection was 1.66 ± 1.17 (range 1-5) during follow-up time 4.08 ± 3.01 (range 1 – 12) months.

* Values are represented as mean ± SD or n (%)



Parameter		Baseline	1 month	2months	3 months	4 months	5 months	6 months
Visual Acuity	BRVO	0.93 ± 0.48	0.55 ± 0.45	0.35 ± 0.25	0.36 ± 0.30	0.37 ± 0.09	0.33 ± 0.06	0.25 ± 0.11
	CRVO	1.41 ± 0.55	1.15 ± 0.52	1.11 ± 0.57	1.10 ± 0.49	0.99 ± 0.42	0.92 ± 0.51	0.74 ± 0.37

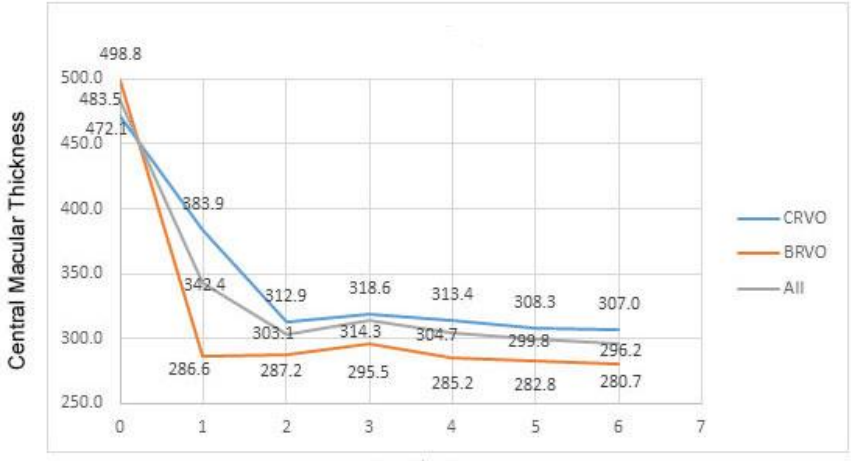
Figure 1. **Evolution of visual acuity in patients with CRVO and BRVO over time.**

Complication and safety

There was no complication such as endophthalmitis, retinal detachment, stroke or myocardial infarction. There were 4 (7.2%) eyes ended up having neovascular glaucoma in the CRVO group. As many as 25 (45.5%) eyes in the CRVO group received panretinal photocoagulation during the follow up, as well as 16 (44.4%) eyes in the BRVO group received sectoral laser photocoagulation. Moreover, one eyes in CRVO group developed vitreous hemorrhage in Month 11 which was unable to resolve and was treated with pars plana vitrectomy.

Regression analysis

Results of the logistic regression analysis, examining the factors associated with final visual acuity are presented in Table 2. In this study, we did not find any predictors for better final BCVA in CRVO and BRVO. Older age (≥ 60 years), hypertension, glaucoma and CMT > 500 µm are factors associated with poor improvement in BCVA however, they are not statistically significant.



Parameter		Baseline	1 month	2months	3 months	4 months	5 months	6 months
CMT	BRVO	498.8 ± 107.2	286.6 ± 95.3*	287.2 ± 63.5*	295.5 ± 79.6*	285.2 ± 91.5*	282.8 ± 94.7*	280.7 ± 91.3*
	CRVO	472.1 ± 119.5	383.8 ± 146.7*	312.9 ± 96.4*	318.6 ± 133.5*	313.4 ± 122.3*	308.3 ± 99.4*	307 ± 98.2*

* Wilcoxon t-test, $p < 0.001$

Figure 2. **Evolution of CMT in patients with CRVO and BRVO over time.**

Table 2. **Results of Logistic Regression Analysis, Examining the Factors Associated With Outcome of BCVA**

Variable	Category	CRVO		BRVO	
		Coefficient (95%CI)	p value	Coefficient (95%CI)	p value
Age	≥ 60 years vs < 60 years	-3,0 (-1,28 - +11,4)	0.1	-1.9 (-3.5 - +13.2)	0.5
Gender	Male vs Female	+1.7 (-2 - +5.9)	0.38	2.9 (-2.5 - +21.0)	0.27
Hypertension	Yes vs No	-1.42 (-5 - +2.7)	0.71	-10 (-100 - +1.45)	0.09
Diabetes	Yes vs No	-3.3 (-14.2 – +1.5)	0.16	-10 (-14.2 - +1.3)	0.99
Glaucoma	Yes vs No	-2 (-14.2 - +4.2)	0.56	-2.5 (-12.5 - +4.4)	0.51
CMT (μm)	≥ 500 vs < 500	-2 (-10 - +1.9)	0.34	-2.6 (-20 - +2.5)	0.31

DISCUSSION

Our results showed that mean BCVA and CMT improved in both CRVO and BRVO group at all time points compared to baseline. However, there are some demographic data at baseline that did not match the findings in some RCT/prospective studies. First, we had more CRVO than BRVO patients with younger age (mean age 60 years in CRVO and 55 years in BRVO) compared to previous RCT studies (approximately 66-70 years and older for previous studies).[6-9,15,17] Second, mean baseline BCVA in this study (1.41 logMAR in CRVO and 0.93 logMAR in BRVO) was lower compared to other studies. In our institution, we treated both types of RVO (ischemic and non ischemic) with the range of severity from finger counting until nearly normal visual acuity at baseline. This study found that as needed (PRN) intravitreal bevacizumab might be beneficial in improving vision in RVO patients even in those with poor visual acuity, and this finding is consistent with existing studies.[12,18-21]

Poor baseline vision may be indicative of macular ischemia.[20] It is believed that macular ischemia is one of the most significant causes of severe and permanent vision loss in ischemic CRVO.[20,21] We could not evaluate macular ischemia in this study because we did not perform fluorescein angiography to our patient. Nevertheless, a study about bevacizumab in ischemic CRVO was carried by Tam et al, in which baseline BCVA was 1.42 logMAR (20/520), after treatment with bevacizumab BCVA improved to 0.64 logMAR (20/87).[20] This is almost similar to our study, in which the mean final BCVA in CRVO group was 0.74 logMAR. Another bevacizumab retrospective real-world study by Kornhauser that included eyes with severe baseline visual acuity showed that BCVA outcome in CRVO group was poorer especially in patients with low (<1.25 LogMAR) baseline BCVA.[21] The Rubeosis Anti-VEGF (RAVE) trial for ischemic central retinal vein occlusion study demonstrated that ischemic CRVO is still a very important entity to treat; with early and aggressive treatment, these eyes may not only have the potential to do significantly better if recanalization of ischemic vessels can be achieved but also have the potential to prevent severe consequences such as intractable NVG.[22]

Although baseline BCVA in BRVO group is worse than other studies, the final BCVA outcome in BRVO (0.25 $\pm$ 0.11 logMAR equivalent to Snellen 20/40) is comparable to other literatures, even with PRN regime and low frequency of injection.[16-19] This is probably because BRVO had more benign nature of the disease and also younger age compared to CRVO.

In terms of CMT reduction, eventhough we found statistically significant reduction of CMT compared to baseline, there were about 52.7% patients in CRVO group and 30,6% in BRVO group that did not achieve CMT $\leq$ 300 μm at their last follow-up. This is probably not only due to the less amount of injection in both groups or the differences in ischemic status,

but some patients might be non-responder to bevacizumab.

When considering the number of injections, it was seen that patients received a mean of one to two injection for treatment during the six month follow-up period (2.05 in CRVO group and 1.66 in BRVO group). This study's results were similar to those from other non-interventional studies, which reported that the number of anti-VEGF injections in real-life conditions was considerably lower than in the RCTs.[12,18,23,24]

This could be due to other possible potential factors that were not accounted for in this study such as frequency of follow-up visits; prolonged duration of eye symptoms; not realizing the importance of treatment after receiving a good baseline VA; declining motivation to receive treatment after some consecutive doses; poor access to services and hospital facilities; and non-affordable travel expenses.[12] However, even with lower number of injection, intravitreal bevacizumab improves visual acuity and reduce ME related to RVO.[12,18,23,24]

Adverse events were infrequent, highlighting the well-established safety profile of bevacizumab in this population.[25] Four patients (7.2%) in CRVO group had neovascular glaucoma after commencing on bevacizumab therapy. In our institution, as soon as ME resolved, we performed laser photocoagulation in RVO patients. The reason for this early laser is to reduce the possibility of reccuring ME and neovascularization that probably undetected especially in patients with poor compliance to regular follow up.[26]

In common with real-world studies, the major limitations of this study were the retrospective study design, lack of protocol refraction and visual acuity measurements using research standard logMAR visual acuity charts, lack of control group and small sample size. Although we used a standard method of converting Snellen visual acuity to logMAR units, there is a known tendency to overestimate visual acuity using the Snellen chart at lower levels of acuity, and this may have occurred in our study. We also did not examine the macula perfusion status. Since retinal vein occlusion is a chronic disease, the follow-up period in this study may not have captured the long-term effect, efficacy or effectiveness of bevacizumab in RVO. The long-term outcomes such as more than 1-year monitoring and evaluation are still needed to confirm the effectiveness of this intervention to better ascertain the best longterm management strategies for patients with ME secondary to RVO.

CONCLUSION

In summary, intravitreal bevacizumab is effective for ME secondary to RVO. Through this report, we have described our approach to bevacizumab therapy for RVO and also reported our outcomes. Such evidence from real-world experience may be useful as a pragmatic benchmark in future audits on outcomes of RVO therapy using either bevacizumab or other anti-VEGF agents.

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