ORIGINAL ARTICLE

BEVACIZUMAB VS RANIBIZUMAB IN MACULAR EDEMA DUE TO RETINAL VEIN OCCLUSION: SHORT-TERM OUTCOMES

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ABSTRACT

Introduction: *Bevacizumab or Ranibizumab was widely used as therapy for macular edema (ME) in retinal vein occlusion (RVO) and diabetic retinopathy. The purpose of this study was to comparing short-term outcomes for patients who received intravitreal Bevacizumab (IVB) injection or Ranibizumab (IVR) for ME due to RVO*
Methods: *This was observational, cross sectional study comparing patients received IVB or IVR. Primary outcomes data (visual acuity and central macular thickness/CMT) and secondary outcomes data (number injection and intra ocular pressure/IOP) were collected at baseline and 3 months after injection*
Discussion: *There were 4 eyes in each group. There were no significant difference in mean change of visual acuity (-0.275±0.25 vs -0.15±0.5 logMAR; p=0.676) and CMT (-171.50 ±129.08 vs -98.25±37.67 um; p=0.345) in IVB vs IVR groups. There were also no significant difference in mean change of IOP (2±2.16 vs 2±4.69 mmHg; p=1) and number of injection (2.25±0.50 vs 1.75±0.9; p=0.401) in both groups.*
Conclusion: *In short-term both IVB and IVB have relative similar outcomes on increasing visual acuity and decreasing CMT in ME due to RVO*

Keywords: *vein occlusion, macular edema, macular thickness, visual acuity*

INTRODUCTION

Retinal vein occlusion is the second most prevalent retinal vascular disease, after diabetic retinopathy, affecting an estimated 16 million people worldwide.[1] Branch retinal vein occlusion (BRVO) is the most prevalent type compared to central retinal vein occlusion (CRVO) which is 0.44% vs 0.08%.[1,2] CRVO is caused due to thrombosis in the central retinal vein as it passes through the lamina cribrosa, whereas BRVO is caused due to venous thrombosis in the artery venosus crossing where arteries and veins have the same vascular membrane.[3,4]

The development of ME is the most important cause of visual impairment in all forms of RVO. Retinal ischemia resulting from circulatory stasis because of venous obstruction promotes the production of VEGF-A, leading to increased vascular permeability and, finally edema.[5,6]

Intravitreal injections for anti-VEGF therapy are the standard care for ME occurring after RVO. Ranibizumab (Patizra) [0.5 mg/0.05 mL] and bevacizumab (Avastin) [1.25 mg/0.05 mL] are anti-vascular endothelial growth factor inhibitors given by a repeated intravitreal injection to treat MO due to RVO. Bevacizumab, a humanized fulllength antibody,

currently available off-label for this indication; while ranibizumab, a humanized high-affinity antibody fragment that targets all isoforms of VEGF-A, has the clearence for ME cases.[7,8] Several study demonstrated that intravitreal injection of Bevacizumab or Ranibizumab resulted in significant functional and anatomical improvements in patients with RVO.[9-11] There are two points of ME therapy in RVO which are improving visual acuity and reducing macular thickness. The purpose of anti-VEGF therapy is to decreasing the levels of VEGF resulting decreasing the macular edema and consequently improving visual function.

Whereas other study comparing Bevacizumab and Ranibizumab for ME in RVO in long term outcome,[13-15] our study focusing on short-term outcome, particularly in 3 moths after first intravitreal injection of anti VEGF.

METHODS

This was a retrospective study of macular edema patients due to RVO treated with intravitreal bevacizumab or ranibizumab injection. The data collected from 2021 until 2022 at Santosa Hospital and Karisma Cimareme Hospital.

The inclusion criteria for this study were foveal-involved macular edema due to RVO, onset of symptoms not more than 6 months duration, and at least 30 years old. Exclution criteria were injection of any other intravitreal drug during study period, history of intraocular surgery in the study eye during the study period, prior anti VEGF or corticosteroid intravitreal use in the study eye within 3 months, presence of any other macular pathology (diabetic retinopathy, myopic choroidal neovascularization, age-related macular degeneration), senile cataract that resulted in poor image quality, coexisting ocular disease (i.e., epiretinal membrane or glaucoma)

Patients were divided into 2 groups, bevacizumab and ranibizumab injection therapy. Patients were follow up for a period of 3 months. All patients received a complete ocular examination, including visual acuity, intraocular pressure (IOP) examination, slit lamp biomicroscopy examination, indirect funduscopy, and CMT measurements by spectral-domain optical coherence tomography (SD-OCT) (Zeiss Cirrus). BCVA was measured with a standard Snellen chart at 6 m and converted to logMAR visual acuity for statistical analysis.

The primary outcomes after 3 months folow up were the mean change from baseline of visual acuity and CST assessed by SD-OCT from both groups. The secondary outcomes were the difference of mean number injections and the difference of mean change from baseline of IOP from 2 groups.

Statistical analyses performed using R Statistical Software (version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria).

There was no statistical difference between Bevacizumab group and ranibizumab group in baseline data, including age, gender, duration of symptoms, diabetes, hypertension, hypercholesterol, smoking habits, lens, diagnosis, additional laser retina and number of injection. There was also no statistical difference in baseline of visual acuity, intraocular pressure and central macular thickness between two groups. (Table 1)

Table 1. Patients demographics and characteristics

	Bevacizumab Group (N=4)[1]	**Ranibizumab Group (N=4)[1]**	***p* value [2]**
Age, years	50 (8.16)	43.25 (9.03)	0.310
Sex,			1
Male	3 (75%)	2 (50%)	
Female	1 (25%)	2 (50%)	
Duration of symptoms, week	3.50 (1)	2 (1.41)	0.139
Diabetes	0 (0%)	0 (0%)	1
Hypertention	4 (100%)	4 (100%)	1
Systolic	164 (15.17)	158.75 (14.68)	0.637
Diastolic	101.75 (7.27)	96.75 (9.07)	0.424
Hypercholesterol	0 (0%)	1 (25%)	1
Smoking	3 (76%)	1 (25%)	0.486
Lens			1
Phakic	3 (75%)	4 (100%)	
Pseudophakic	1 (25%)	0 (0%)	
Diagnosis			1
BRVO	2 (50%)	3 (75%)	
CRVO	2 (50%)	1 (25%)	
Additional Laser Retina	1 (25%)	0 (0%)	1
Visual acuity baseline, logMAR	0.73 (0.33)	0.70 (0.23)	0.906
IOP Baseline, mmHg	14.25 (1.26)	14.75 (1.50)	0.628
CMT baseline, *u*m	430.50 (137.01)	395.25 (46.93)	0.654
Number of injection	2.25 (0.50)	1.75 (0.96)	0.401

[1]Mean (SD); n/N (%); [2]Calculated using t-test for continous variable and Fisher-test for categorical variable; [3]Hypertension if systolic ≥140 mmHg and diastolic ≥90 mmHg;
[4]CMT=central macular thickness

Mean visual acuity at baseline and month 3 in IVB group was 0.73±0.33 LogMAR (range: 1.2-0.5 LogMAR) and 0.45 ±0.24 LogMAR (range: 0.7-0.2 LogMAR) repectively. Mean visual acuity at baseline and month 3 in IVR group was 0.70±0.23 LogMAR (range:

0.9-0.5 LogMAR) and 0.55±0.41 LogMAR (range: 0.9-0.1 LogMAR) respectively. There was no statistical significant difference change in visual acuity between 2 groups. (Table 2)

Although there was a decrease in CMT in the 3rd month, there was no significant difference in the change in CMT between 2 groups (-171.50±129.08 um vs -98.25±37.67 um). (Table 2) Mean CMT at baseline and month 3 in IVB group was 430.50±137.01 um (range: 336-632 um) and 259±18.30 um (range: 240-280 um) respectively. Mean CMT at baseline and month 3 in IVR group was 395±46.93 um (range: 336-445 um) and 297±59.12 um (range: 248-325 um) respectively.

Table 2. Clinical Outcome

	Bevacizumab Group (N=4)[1]	**Ranibizumab (N=4)[1]**	***p* value[2]**
Change in visual acuity, (logMAR)	-0.275 (0.25)	-0.15 (0.5)	0.676
Change in CMT, (um)	-171.50 (129.08)	-98.25 (37.67)	0.345
Change in IOP, (mmHg)	2 (2.16)	2 (4.69)	1

[1]Mean (SD); [2]calculated using t-test

The same thing happen with change in IOP between 2 groups. There was only 2 mmHg increase in IOP in IVB or IVR groups (Table 2) without significant difference among 2 groups.

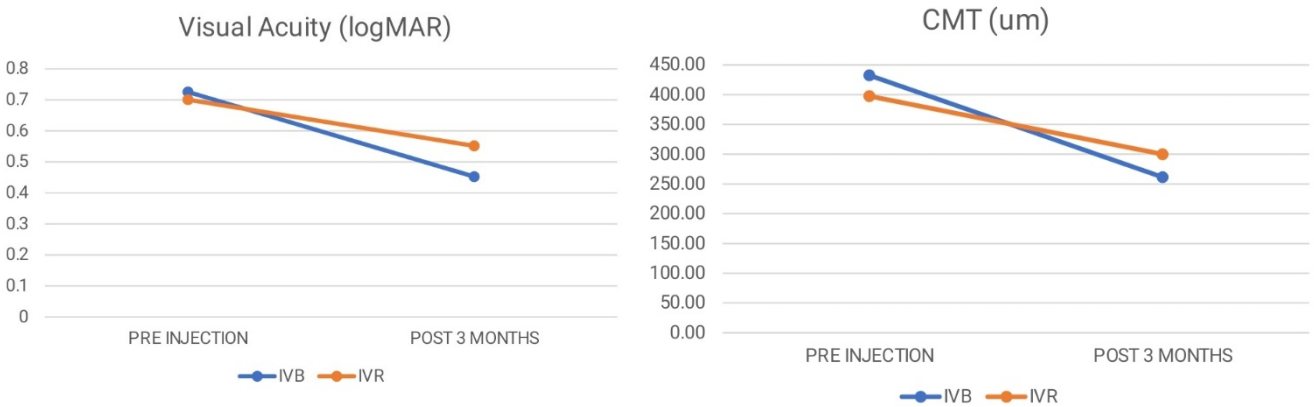

Figure 1. Graphs of mean changes in visual acuity and mean change in CMT from baseline to 3 months from IVB and IVR groups

DISCUSSION

Although the prevalence of RVO is more prevalent at the age of more than 65 years, in this study a younger age was obtained.[16] The Beijing Eye Study conclude that patients under 45 years old can also develop an RVO.[17] RVO is also more common in males and BRVO is 4-6 times more common than CRVO in other study the BRVO. Both condition were seen in this study.

There are several systemic diseases as risk factors for RVO such as hypertension, diabetes, and hypercholesterolemia.[18] In this study it appears that hypertension and hypercholesterolemia are risk factors for RVO. Cigarete smoking increases risk of RVO and most of the participants in this study were active smooker.[18,19]

There were 3 Randomized Controlled Trial (RCT) study comparing bevacizumab and ranibizumab in macular edema due to RVO, BRVO or CRVO or both. The final results of all of the study were 6 months (change in visual acuity and change in CMT in 6 months of therapy).[20-22] Our study concluded the final result in just 3 months after intravitreal injection. IVB is noninferior to IVR for patients with DME resulting from RVO after 6 months treatment in The Bevacizumab to Ranibizumab in Retinal Vein Occlusions (BRVO) sudy. The VA improved for IVB and IVR were 15.3±13 letters and 15.5±13.3 respectively. Change in CMT were 287±231.3 $\boldsymbol{u}$m and 300.8±224.8 $\boldsymbol{um}$ respectively.[20]

Similar conclusion from the Bevacizumab versus Ranibizumab in Branch Retinal Vein Occlusion (MARVEL) study and the Bevacizumab versus Ranibizumab in Treatment of Macular Edema From Vein Occlusion (CRAVE) study.[21-22] Both study found a similar effect on improving visual acuity after 6 months therapy. Mean CMT reduction between IVB and IVR in CRAVE study were 212.6 $\boldsymbol{u}$m and 243.8 $\boldsymbol{u}$m respectively while in MARVEL study were 201.7±166.2 $\boldsymbol{u}$m and 177.1±122.3 $\boldsymbol{u}$m respectively. In CRAVE study the VA gain were 0.33 logMAR for IVB and 0.34 logMAR for IVR, while in MARVEL study the mean gain BCVA were +15.6 letters for IVB and +18.1 letters for IVR.[21-22]

Increase in ocular volume or pharmacologic drug properties of anti VEGF injection could elevate the IOP wheither acute or sustained rise in IOP. Although the incidence of this ocular hipertension is low after a single or multiple IVB and/or IVR, clinician must aware cause it could end up as glaucoma or impair retinal blood flow.[23-25] In this study there was no significant changes in IOP between IVB and IVR eventhough we didn't check the effect on the mean ocular perfusion pressure (MOPP).

In BRAVO and CRUISE study, IVR was given monthly for 6 months then given as needed for 1 year which were 2.8 addittional injection and 3.6 additional injection for BRAVO and CRUISE respectively.[26-28] In real-world study, anti-vegf wheither bevacizumab or ranibizumab or aflbercept was administered 5-7 times yearly.[29] Our research cut-off point was the first 3 months after the first anti-VEGF injection. In those 3 months it was found that only about 2 anti-VEGF injections were given both in IVB and IVR. The next injection will still be given according to the development of macular edema.

This study, although both showed a decrease in CMT for the IVB and IVR groups, showed a lower decrease in CMT compared to the other three studies. This is reasonable because the CMT measurement was carried out only within 3 months after the injection. The same result of this study also occurred in the measurement of visual acuity after 3 months after the IVB or IVR injection. There was an increase in visual acuity but not as dramatic as the other three studies above.

Major limitation of this study included the small sample size. To overcome this problem, future studies should include more subjects in each group or conduct the RCT studies.

CONCLUSION

As the conclusion from this study that in the initial 3 months after injection, IVB and IVR gave the same results in terms of increasing visual acuity and decreasing CMT in patients with macular edema due to RVO.

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