Original Article

Intravitreal Bevacizumab for Macular Edema Secondary to Retinal Vein Occlusion

Anil Parajuli[1], Purushottam Joshi[1], Prabha Subedi[1], Chandni Pradhan[1]
[1]Mechi Eye Hospital, Birtamod, Jhapa, Nepal

Abstract

Introduction: The most common cause of vision loss in cases of Retinal vein occlusion (RVO) is due to macular edema. This study was conducted to examine the effect of intravitreal bevacizumab (IVB) in the treatment of macular edema secondary to RVO.
Materials and methods: The authors conducted a retrospective study of 94 eyes (N) of 92 patients with macular edema associated with decreased visual acuity secondary to RVO who were treated with IVB. Patients received IVB at baseline, 1 month and 2 months. At each follow up patients were evaluated and re-injected if necessary.
Results: The mean age of the patients was 56.6 ±11.51 years. The average number of injections per eye was 2.1 ± 0.87. The baseline median central macular thickness (CMT) and best-corrected visual acuity (BCVA) in LogMAR was 465.00µm (Min 254µm, Max 1218µm) and 1.00 (Min 0.30, Max 2.28), respectively. The median CMT at one month following first, second and third dose of IVB was 258µm (N=94, Z= -7.64, p <0.001), 261µm (N=63, Z= -0.17, p=0.86), and 292µm (N=41, Z= -0.21, p= 0.83), respectively. The median LogMAR BCVA at one month following first, second and third dose of IVB was 0.60 (N=94, Z= -5.70, p < 0.001), 0.60 (N=63, Z= -1.69, p=0.09), and 0.60 (N=41, Z= -0.03, p=0.97), respectively. Pre-operative BCVA was the best predictor of the final visual outcome after IVB in cases of RVO. None of the patients developed any serious ocular or systemic complications due to IVB.
Conclusion: IVB is an effective and safe treatment for macular edema associated with decreased visual acuity secondary to RVO. The most beneficial effect of IVB is seen at one month after the first dose. The efficacy of subsequent doses could not be established in this study.

Key words: Anti-VEGF, Avastin, Bevacizumab, Macular edema, Retinal vein occlusion.

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Corresponding author
Anil Parajuli
Mechi Eye Hospital
Birtamod, Jhapa, Nepal
E-mail: anil.parajuli861@gmail.com
Contact: +9779841282642

Introduction

Retinal vein occlusion (RVO) is second only to diabetic retinopathy as the most common retinal vascular disease and is an important cause of vision loss (Parodi and Bandello, 2009). The prognosis and outcome of RVO depends upon the site of occlusion (Wong and Scott, 2010).

The prevalence of RVO is 1% to 2% in persons older than 40 years of age (Mitchell et al, 1996; Klein et al, 2000). Branch retinal vein occlusion (BRVO) is found to be four times more common than central retinal vein occlusion (CRVO) (Rogers et al, 2010). The strongest risk factor for BRVO is hypertension (Rath et al, 1992; Hayreh et al, 2001; Elman et al, 1990; Wong et al, 2005); however other risk factors include diabetes mellitus (Hayreh et al, 2001; Elman et al, 1990; Wong et al, 2005), dyslipidemia (Wong et al, 2005) and cigarette smoking (Mitchell et al, 1996). Glaucoma and elevated intraocular pressure comprise additional risk factors for CRVO (Mitchell et al, 1996).

Macular edema is the most common cause of vision loss from RVO (Yau et al, 2008). If left untreated, patients with BRVO generally do not achieve full recovery owing to persistent macular edema and gain on average only 0.23 lines on the Early Treatment of Diabetic Retinopathy Study (ETDRS) scale after 3 years, to an average level of 20/70 (The Branch Vein Occlusion Study, 1984). The prognosis of patients with macular edema secondary to CRVO if left untreated is usually worse (McIntosh et al, 2010).

RVO is found to be associated with varying amounts of retinal ischemia. Consequently, there is an increased concentration of vascular endothelial growth factor (VEGF) (Hayreh, 1983; Aiello et al, 1994). Since the approval of pegaptanib and ranibizumab by the Food and Drug Administration (FDA) for age-related maculopathy in 2004 and 2006, respectively, the use of anti-VEGF has been gaining popularity in treatment of various retinal diseases. Studies to see their efficacy on management of macular edema secondary to RVO are still widely going on. Bevacizumab is a recombinant humanized monoclonal antibody directed against VEGF and available for cancer therapy (Michels et al, 2005). The off-label use of IVB as a potential therapy for macular edema secondary to CRVO was first reported in 2005 and presently, it is the most studied anti-VEGF in regard to RVO (Rosenfeld et al, 2005). There are various studies showing reduction of macular edema and improvement of vision in patients with RVO after intravitreal bevacizumab (Spandau et al, 2006; Pai et al, 2007). This study will provide some key information regarding the effect of bevacizumab in eyes affected by RVO in the Indian subcontinent.

Materials and methods

We conducted a retrospective review of 94 eyes of 92 patients with macular edema secondary to retinal vein occlusion that were treated with off-label intravitreal bevacizumab (Avastin®, Genentech, South San Francisco, CA, USA). Among the 94 eyes, 31 eyes received single dose, 22 received two doses and 41 received three doses of IVB. Informed written consent was obtained from all patients before the procedure. The study was approved by the Local Ethical Committee Board of Mechi Eye Hospital. The study was conducted according to the tenets of the Declaration of Helsinki. Medical records were reviewed for all patients with RVO. Only those patients who had CMT $\geq$ 250 μm and decreased BCVA ($\leq$ 20/40) (log MAR 0.301) were included in the study. CMT was recorded using spectral domain OCT (Cirrus OCT, Carl Zeiss Meditec, Dublin, CA, USA). Patients who received at least one injection of intravitreal bevacizumab (1.25 mg) at the Mechi Eye Hospital, between January 2014 and December 2016, with at least one follow up at one month of injection were included in the study. The eyes that received other treatments prior to IVB or during the study; like, laser treatments, other drug injections and vitrectomy were excluded from the study. Likewise, patients with other comorbid conditions such as: age-related macular degeneration, diabetic retinopathy, or central serous chorioretinopathy, which affected the macula, were also excluded from the study.

All intravitreal injections were performed according to the standard protocol of Mechi Eye Hospital. Topical anesthetic was applied followed by povidone-iodine (5%) scrub of the eyelids and lashes. A 4 mL vial containing 100 mg bevacizumab was used to prepare a sterile 1-mL insulin syringe containing 0.05 mL (1.25 mg) bevacizumab. It was then injected through the pars plana into the vitreous cavity. Superotemporal and superonasal quadrants were the most preferred sites by the surgeons. After the injection, a combination of antibiotic and steroid (ciprofloxacin 0.3% + dexamethasone 0.1%) (Zoxan-D®, FDC limited, Mumbai, India) was prescribed four times daily for 7 days. The patients were also given tablet acetazolamide 250mg, (Acetamide-250®, Micro Labs Limited, Nashik, Maharashtra, India) one tablet stat after the injection. Follow-up evaluations were scheduled one month apart. Criteria for repeat injection of IVB was either persistent CMT ≥ 250 μm and/or decreased BCVA (≤ 20/40) (log MAR 0.30).

The following data were collected: (1) ophthalmic and medical history; (2) duration of symptoms; (3) previous treatments; (4) BCVA; (5) intraocular pressure (IOP); (6) blood pressure and random blood sugar before injection; and (7) CMT. None of the patients underwent fundus fluorescence angiography to define macular ischemia or capillary nonperfusion.

IBM SPSS Statistics for Macintosh, Version 20.0. Armonk, NY: IBM Corp. was used for statistical analysis. The visual acuity was converted to logMAR before analysis. The changes in BCVA and CMT from baseline to the various follow-up endpoints were assessed by the Wilcoxon signed ranks test. Spearman Rank correlation coefficient (ρ) was used to measure the linear correlation between two variables. A probability value of 0.05 or less was considered statistically significant.

Results

Table 1 shows the demographic features of the patients enrolled in the study.

First Dose Outcomes ***(Figure 1)***

Records at 1 month of first injection were available for all the eyes. The median BCVA improved to LogMAR 0.60 (Min 0.17, Max 1.98) from baseline value of LogMAR 1.00 (Min 0.30, Max 2.28)(Z= -5.70, p < 0.001). The median post-treatment CMT improved to 258.00μm (Min 64μm, Max 790μm) from the baseline median CMT of 465.00μm (254μm -1218μm) (Z= -7.64, p <0.001).

Second Dose Outcomes ***(Figure 1)***

Among the 94 eyes, records after one month following the second dose were available for 63 eyes (67.02%). At one month following second dose, the median BCVA was LogMAR 0.60 (Min 0.17, Max 1.98) which improved from pre-operative median BCVA of LogMAR 1.00 (Min 0.30, Max 2.28) (Z= -4.97, p<0.001) and but failed to improve from the median BCVA after 1 month of first dose, LogMAR 0.60 (Min 0.17, Max 1.98) (Z= -1.69, p=0.09). The median CMT at one month following second dose was 261.00μm (Min 134μm, Max 763μm), which improved from pre-operative median CMT of 495.00μm (Min 254, Max 1208μm) (Z= -5.91, p <001) but failed to show significant improvement from CMT after 1 month of first dose 289.00μm (Min 64μm, Max 790μm) (Z= -0.17, p =0.86).

Third Dose Outcomes ***(Figure 1)***

Among the 63 eyes that received the second dose, records after one month following the third dose were available for 41 eyes (65.07% of 63 eyes that received the second dose). At one month following third dose, the median BCVA was LogMAR 0.60 (Min 0.00, Max 1.77), which improved from preoperative median BCVA of LogMAR 1.00 (Min 0.30, Max 2.28) (Z= -3.62, p<0.001) but failed to show

improvement from the BCVA after 1 month of first dose, LogMAR 0.60 (Min 0.17, Max 1.98) (Z= -0.44, p=0.65) and BCVA after 1 month of second dose, LogMAR 0.60 (Min 0.17, Max 1.98) (Z=-0.03, p=0.97). The median CMT at one month following third dose improved to 292.00μm (Min 107μm, Max 813μm) from preoperative CMT of 494μm (Min 285μm, Max 1208) (Z= -4.17, p <001) but failed to improve from the CMT after 1 month of first dose of 295μm (Min 128μm, Max 790μm) (Z= -0.50, P= 0.61) and that after 1 month of second dose of 290.00μm (Min 134μm, Max 763μm) (Z= -0.21, p =0.83).

Bivariate linear correlation analysis (Table 2) showed that preoperative BCVA in LogMAR correlated positively with the final visual outcome, indicating that better preoperative BCVA was associated with better final visual outcome. Baseline CMT helped to predict the visual outcome only until one month of first and second dose of IVB. Likewise young age at RVO was also associated with better visual outcome. A modest positive correlation was seen between age at RVO and the CMT at one month of the first and second dose of IVB (ρ =.21, p<0.01, and ρ=.24, p=0.02, respectively). No significant correlation was seen between age at RVO and the CMT following the third dose of IVB.

Table 1: Demographic features of the patients

Demographic data	
Mean age of patients	56.6 ± 11.51 years (24-84 years)
Gender	53 (57.6%) male, 39 (42.4%) female
Number of eyes	94 eyes of 92 patients (52 right eye, 42 left eye); 2 patients had bilateral involvement
Associated Risk factors	**Number of patients (%)**
Hypertension	49 (53.3%)
Diabetes	11 (12%)
POAG	2 (2.2%)
Dyslipidemia	2 (2.2%)
Type of RVO	**Number of eyes (%)**
STBRVO	40 (42.5%)
ITBRVO	19 (20.2%)
CRVO	19 (20.2%)
Macular BRVO	12 (12.8%)
Inferior HRVO	3 (3.2%)
Superior HRVO	1 (1.1%)

Note:

POAG = Primary open angle glaucoma
RVO = Retinal vein occlusion
BRVO = Branch retinal vein occlusion
STBRVO = Superotemporal BRVO
ITBRVO = Inferotemporal BRVO
CRVO = Central retinal vein occlusion
HRVO = Hemiretinal vein occlusion

Table 2: Bivariate Correlation between baseline parameters and the visual outcome at different follow-up

Factors	Correlation with BCVA at various follow-ups			
		1 month after 1st IVB	1 month after 2nd IVB	1 month after 3rd IVB
Age at Presentation	ρ	.25	.27	.29
	P value	<0.01	0.01	0.02
	N	94	63	41
Baseline BCVA	ρ	.71	.68	.52
	P value	<0.001	<0.001	<0.001
	N	94	63	41
Baseline CMT	ρ	.30	.27	.11
	P value	<0.01	0.01	0.23
	N	94	63	41

Note: ρ = Spearman rank correlation coefficient
N = number of eyes

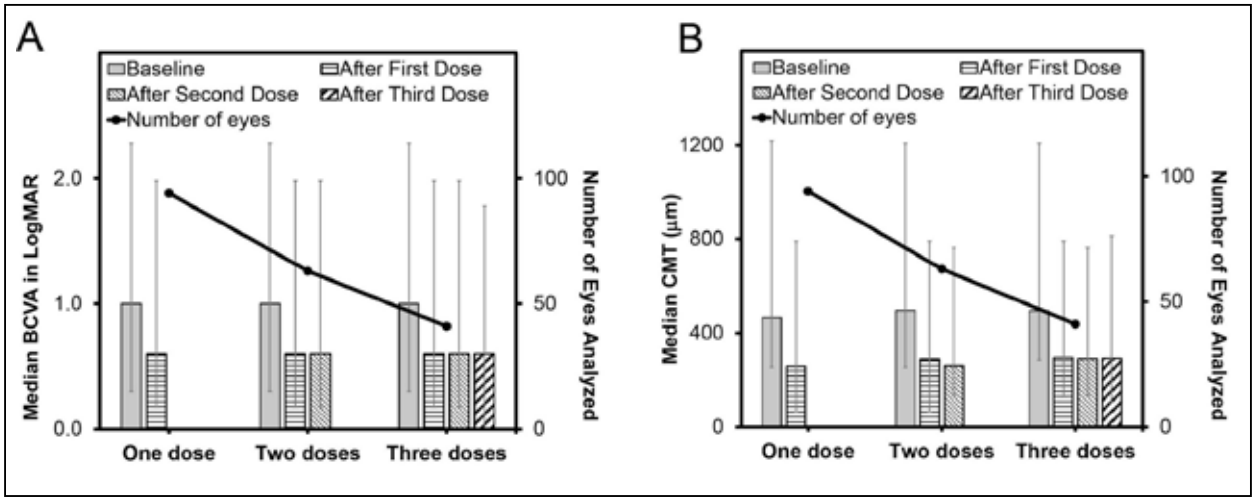

Figure 1: The effect seen on median BCVA in LogMAR (A) and median CMT (µm) (B) at one month follow-up following each dose of IVB given a month apart. The error bar in the graph shows the range of the data.

Discussion

The mean age (56.6 ± 11.51 years) of the patients in our study was slightly lower than the findings from a hospital based case control study by Thapa et al (2010). The mean age of their cases was 61.1 ± 12.3 years. BRVO (75.6%) was the most common type of RVO in our study which is similar to the findings (71.1%) by Thapa et al (2010). However, in a population based cross sectional study by Thapa et al (2017), BRVO comprised 92.73% of all the cases of RVO.

The most involved anatomical site in our study was superotemporal (42.5%). In the studies by Zhao et al (1993) and Thapa et al (2010) also, superotemporal quadrant was the most involved site, 66% and 63.9%, respectively. The frequent involvement of the superotemporal quadrant has been attributed to the presence of more arterio-venous crossings in this quadrant

than any other part of the retina (Zhao et al, 1993; Weinberg et al, 1993). Hypertension was the most associated risk factor in our patients (53.3%) with RVO, which is consistent with other studies like Ponto et al (2015) and Lee et al (2013). In the study by Thapa et al (2017) and Thapa et al (2010), hypertension was present in 45.45% and 57.3% patients respectively.

This study showed that eyes with RVO treated with IVB demonstrated significant anatomic and functional improvement. Patients showed a significant decrease in macular thickness and an improvement in visual acuity following IVB. Similar findings have been reported in various case series studies on BRVO (Rabena et al, 2007; Abegg et al, 2008; Thapa et al, 2012); CRVO (Iturralde et al, 2006); and RVO (Stahl et al, 2007). However, all these studies show variability in injection frequencies, follow up time and treatment interval.

We observed that the first dose of IVB was associated with the maximum reduction in median CMT accompanied by maximum improvement in visual acuity. Both the median macular thickness and LogMAR visual acuity did not change significantly on repeated doses of IVB. Kondo et al (2009) noted similar findings in their study where visual acuity and macular thickness improved significantly only at 1 month following first dose IVB. Stahl et al (2007) studied the effect of a single dose of IVB in RVO. They observed peak improvement in visual acuity within 3 to 6 weeks of the first dose of IVB and suggested repeat doses of IVB only after 6 to 9 weeks depending upon the OCT and visual acuity findings. We thus believe that if a case of RVO is planned for panretinal/ grid laser treatment, it should best be performed at 1 month of first dose of IVB, because at this time central macular thickness can be assumed to be the least, and thus the risk of a laser- induced increase of macular edema is expected to be the lowest.

We observed a modest positive correlation between change in CMT and change in BCVA in logMAR, (ρ) = 0.28, p=0.014), at one month after the first dose of IVB. In our study the baseline BCVA in logMAR was worse in eyes with thicker baseline CMT (ρ) = 0.33, p<0.001). Siegel et al (2012) also found a positive correlation between baseline visual acuity in logMAR and baseline CMT. We also observed that the pre-operative BCVA was the best predictor of final visual outcome (Table 2). Kim et al (2017) and Yunoki et al (2012) also commented that the baseline visual acuity helped to predict the final visual outcome. However, both the studies were done in cases with BRVO. The Central Vein Occlusion Study Group also found that the baseline visual acuity strongly predicted the final visual acuity in cases of CRVO (Vein, 1997). We also observed that young age at the time of RVO was a prognostic factor for better visual outcome. Jaissle et al (2011) too commented that age at BRVO was a significant predictive factor for final visual outcome where the young patients had better visual outcome.

Making a statement regarding the number of re-injections required to achieve a stable condition is beyond the scope of this study because of the short follow-up period and variability in injection frequencies. The optimum dosing and number of intravitreal injection of bevacizumab in RVO is still undetermined. In one study, Kondo et al (2009) found that a single injection of bevacizumab was sufficient for the treatment of approximately one fourth of the patients with macular edema secondary to BRVO.

Before deciding on a repeat dose of IVB, the negative long-term effects that the anti-VEGFs might have on collateral vessel formation needs to be addressed. There is still a lack of a randomized clinical trial (RCT) to prove the long-term safety of bevacizumab (Ehlers and Fekrat, 2011). Considering the pathophysiology of the disease; RVO is a one-

time insult (Adjievska et al, 2017). We thus believe that scheduled repeated monthly doses of IVB might not be necessary; and might be given on pro re nata basis when associated with macular edema (CMT ≥ 250 μm) and/or poor vision BCVA (≤ 20/40) (log MAR 0.301); only at the treating surgeon's discretion until further evidences from RCTs on IVB establishes a standard treatment protocol.

As reported in other series we did not observe any serious ocular or systemic complications such as severe rise in intraocular pressure, endophthalmitis, retinal tear, retinal detachment, cataract formation, hypertensive crisis or thromboembolic events (Thapa et al, 2012; Rabena et al, 2007; Prager et al, 2009; Mehany et al, 2010). Hence IVB seems to be safe and effective in treatment of RVOs. Our study has limitations. The lack of control group precludes us from understanding the natural history of the disease. The other limitations are its nonrandomized and retrospective nature. However, we excluded eyes that had already received some forms of treatments earlier or during the study period. This adds to the strength of our study.

Conclusion

IVB is a safe and effective treatment for decreased visual acuity secondary to macular edema caused by retinal vein occlusion. The most beneficial effect of IVB is seen one month after the first dose. The efficacy of subsequent doses of IVB could not be established in this study.

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