



Original article

Short term results of intra-vitreous bevacizumab for the treatment of macular edema secondary to retinal vein occlusion

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Abstract

Introduction: Macular edema (ME) is the leading cause of visual impairment in retinal vein occlusion (RVO). **Objective:** To evaluate the efficacy and safety of intravitreal bevacizumab (Avastin; Genentech) on ME secondary to RVO. **Materials and methods:** A prospective, interventional study was conducted among patients with ME due to RVO from June 2008 to February 2010. Intravitreal bevacizumab (1.25 mg/0.05 ml) was given at 4 to 6 weekly intervals until the ME subsided. Complete ophthalmic evaluation and measurement of central retinal thickness (CRT) by optical coherence tomography (OCT) were performed at baseline and follow up visits. **Results:** Thirty four eyes (18 CRVO and 16 BRVO) were included in the study. The mean duration of visual symptoms and follow up period were 5.1 months (range 0.3 - 24 months) and 7.5 ± 4.8 months respectively. In CRVO, the CRT improved from $652 \pm 206 \mu\text{m}$ at the baseline to $257 \pm 132 \mu\text{m}$ ($p < 0.0001$) at the final follow up, and in BRVO, the CRT improved from $540 \pm 197 \mu\text{m}$ to $219 \pm 135 \mu\text{m}$ ($p < 0.0001$). The improvement in BCVA was significant at each follow up interval for BRVO; in CRVO, there was only a significant improvement between the baseline and the 6 weeks' follow up. BCVA was improved in 75 % cases of BRVO and in 61.6 % in CRVO at the final follow up. There were no ocular or systemic adverse effects. **Conclusion:** Intravitreal bevacizumab is an effective and safe drug for reducing ME and improving visual acuity secondary to RVO in the short term follow up.

Key-words: bevacizumab, branch retinal vein occlusion, central retinal vein occlusion, macular edema

Introduction

Retinal vein occlusion is a potential sight threatening retinal vascular problem second only to diabetic retinopathy in both the developed and developing countries like Nepal. Macular edema is often the cause for visual symptoms in both central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) (Mruthyunjaya & Fekrat 2006).

Argon laser treatment has shown some improvement in vision in cases of macular edema due to BRVO (The Branch Vein Occlusion Study Group 1984). Various studies have been published regarding the effectiveness of triamcinolone but its use is complicated by the significant side effects of raised intraocular pressure and cataract (Chen et al, 2006). In recent years, the use of intra-vitreous anti-vascular endothelial growth factor (VEGF) agents, like Bevacizumab (Genentech, USA), have been in increasing use with better results in ME following

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RVO (Abegg et al, 2008; Badala, 2008; Beutel et al, 2010; Gutiérrez et al, 2008; Fish, 2008; Hung et al, 2001; Iturralde et al, 2006; Kriechbaum et al, 2008; Manayath et al, 2009; Rensch et al, 2009; Pai et al, 2007).

There have been no similar studies in developing countries like Nepal. We hope this study will help evaluate the outcome of intra-vitreous Bevacizumab in macular edema secondary to branch and central retinal vein occlusion at our hospital set up.

Materials and methods

This was a prospective, interventional, nonrandomized case series conducted at a tertiary eye care centre in Nepal. Consecutive cases with macular edema (CRT > 249 μ m) and visual acuity worse than 6/12 secondary to either BRVO or CRVO who presented from July 2008 until February 2010 were included in the study. The patients with retinal vein occlusion having a prior history of treatment with laser therapy or intra-vitreous injections were excluded from the study. Those patients with uncontrolled hypertension, myocardial infarct or cerebrovascular accident within 3 months of presentation were also excluded. Informed consent was taken from the patients before enrollment in the study after fully explaining the possible risks and benefits of intra-vitreous Bevacizumab. Ethical approval was obtained from the Institutional Review Board of the Institute. The study was conducted according to the declaration of Helsinki.

Detailed history was taken regarding the demographics, chief complaints including the duration of problem, presence of systemic diseases like hypertension, diabetes mellitus, cardiac diseases and hyperlipidemia.

Ocular evaluation included presenting and best corrected visual acuity (BCVA), anterior and posterior segment examinations with the help of Haag Streit slit lamp and 90 D (Volk) lens. RVO was further evaluated to classify the BRVO and CRVO as ischemic or non ischemic. Ischemia was

determined clinically by BCVA less than 6/60, the presence of extensive cotton wool spots, disc edema and the presence of a relative afferent papillary defect. Except some selective cases, fundus fluorescein angiogram (FFA) was not done routinely in all cases in our series.

Central retinal thickness was assessed objectively with the help of OCT (Stratus OCT, USA) at baseline and every follow-up visits at 4 - 6 weeks intervals till the macular edema subsided. The intraocular pressure was taken with Goldmann applanation tonometry. Systemic blood pressure was measured at baseline, and at each follow up visit. Fasting and post prandial blood sugar and lipid panel tests were advised in all cases to find out the underlying systemic risk factors and to assess the level of control in diagnosed cases before intra-vitreous injection. Likewise, patients were advised to consult a physician and/or cardiologist for evaluation and control of systemic diseases.

The intra-vitreous Bevacizumab (Avastin; Genentech) was given in a dose of 1.25 mg/0.05 ml through pars plana with 27G or 30G needle at baseline and repeated at 4 - 6 week intervals until the macular edema subsided. The injection was given in the operation theatre with aseptic precautions under topical anesthesia (4% xylocaine). Topical ciprofloxacin eye drop four times a day and ciprofloxacin eye ointment was used at night time for a week after the intra-vitreous bevacizumab. Detailed ophthalmic evaluation including visual acuity, anterior and posterior segment evaluation, and assessment of macular edema was done at each follow up. Snellen visual acuity was converted to Log MAR for visual outcome analysis. The data was analyzed in SPSS version 11.5 (SPSS Inc. Chicago, IL, USA). Paired t-test was used for statistical analysis. A p-value of less than 0.05 was considered to be statistically significant in this study.

Results

Thirty-four eyes of 34 patients (CRVO 18 and BRVO 16) were included in the study. The ischemic CRVO comprised of two cases. The age ranged



from 23 - 79 years with the mean age of 55.8 ± 14.1 years. There were 15 males and 19 females. The duration of symptoms ranged from 3 weeks to 15 months with mean of 4.4 months. All patients completed 3 months of follow up with a mean follow-up period of 7.5 ± 4.8 months

Table 1: Age and duration of symptoms and follow-up of the patients (N=34)

Characteristics	Min.	Max.	Mean	SD (\pm)
Age (years)	23	79	55.8	14.1
Duration of visual symptoms (months)	0.03	15	4.4	4.7
Follow up period (months)	3	18	7.5	4.9

In cases with CRVO, the mean CRT was $652 \pm 206\mu\text{m}$ at baseline and decreased significantly to $432 \pm 229\mu\text{m}$ ($p = 0.006$), $300 \pm 148\mu\text{m}$ ($p < 0.0001$), $257 \pm 132\mu\text{m}$ ($p < 0.0001$) at 6 weeks, 3 months and last follow up respectively. Likewise, mean BCVA at baseline was 1.2 ± 0.5 log MAR, which was significantly improved to 0.99 ± 0.5 log MAR ($P = 0.0003$) at 6 weeks. The mean BCVA was also improved at 3 months, and last follow up (1.1 ± 0.6 log MAR ($p = 0.125$), and 0.9 ± 0.6 log MAR ($p = 0.056$) but these latter two findings were not significant (Table 2).

Table 2: Central retinal thickness and visual acuity change after Bevacizumab for CRVO (N = 18)

Duration	CRT (μm) (SD \pm)	p-value *	Mean BCVA (log MAR) (SD \pm)	p-value *
Baseline	652 (206)		1.2 (0.5)	
6 weeks	432 (229)	0.006	0.99 (0.5)	0.003
3 months	300 (148)	<0.0001	1.0 (0.6)	0.125
Last follow up	257 (132)	<0.0001	0.89 (0.6)	0.056

CRT=central retinal thickness, S.D=standard deviation, BCVA= best corrected visual acuity
 * compared to baseline

In cases with BRVO, the mean CRT was $540 \pm 197\mu\text{m}$ at baseline and decreased significantly to $351 \pm 122\mu\text{m}$ ($p < 0.0001$), $230 \pm 117\mu\text{m}$ ($p < 0.0001$) and $219 \pm 135\mu\text{m}$ ($p < 0.0001$) at 6 weeks, 3 months and last follow up respectively. Similarly, mean BCVA at baseline was 1.0 ± 0.6 log MAR, which was significantly improved to 0.7 ± 0.5 log MAR ($P = 0.007$), 0.6 ± 0.5 log MAR ($p = 0.004$), and 0.5 ± 0.50 log MAR ($p = 0.003$) at 6 weeks, 3 months, and last follow up respectively (Table 3).

Table 3: Central retinal thickness and visual acuity change after Bevacizumab for BRVO (N=16)

Duration	CRT (μm) (SD \pm)	p-value *	Mean BCVA (log MAR) (SD \pm)	p-value *
Baseline	540 (197)		1.0 (0.6)	
6 weeks	351 (122)	<0.0001	0.7 (0.5)	0.007
3 months	230 (117)	<0.0001	0.6 (0.5)	0.004
Last follow up	219 (135)	<0.0001	0.5 (0.5)	0.003

CRT=central retinal thickness, S.D=standard deviation, BCVA= best corrected visual acuity
 * compared to baseline

In our series, during the last follow-up, visual acuity was improved in 12 eyes (61.6%), remained the same in 4 eyes (22.2%) and worsened in 3 eyes (16.7%) with CRVO. In BRVO visual acuity improved in 12 eyes (75%), remained stable in 3 cases (18.8%), and worsened in 1 case (6.2%).

There were no ocular or systemic adverse effects.

Discussion

In our series of 34 cases, the macular edema and visual acuity significantly improved without any ocular or systemic adverse effects at the short term follow up. The visual benefit was greater for patients with BRVO than with CRVO.

The mean age of patients in our series was 55.8 ± 14.1 years. This mean age of the patients with RVO was similar to the previous studies on RVO from the same hospital (Thapa et al 2010), but younger than studies from other countries (Gutiérrez et al 2008; Iturralde et al 2006). The average number of intra-vitreous Bevacizumab injections received in our series was 2.4 and 2 cases (6.2%) had recurrent macular edema at the last follow up. This number of injections is similar to that reported by Iturralde et al (2006) over a similar study period. The recurrence rate compares favorably with triamcinolone with one recent paper reporting a 100% recurrence of ME following an initial response (Patel et al 2008).

The mean duration of RVO in our series was similar to some of the reported series (Gutiérrez et al 2008; Iturralde et al 2006) but longer than the series by Rensch et al (2009). The follow up period of patients was similar to some of the reported studies (Fish 2008; Rensch et al, 2009). Unlike our series, there are few studies with longer follow-up periods (Manayath et al, 2009; Pai et al 2007) and shorter follow up periods (Hung et al 2001; Iturralde et al, 2006).

We found a significant reduction in central retinal thickness for both the CRVO and BRVO related macular edema at each follow up visit. Likewise, the BCVA was significantly improved at each follow up visit for patients with ME secondary to BRVO. In CRVO the vision was significantly improved between baseline and the 6 week follow up visit, but this was not maintained at the 3 month and final follow up visit.

Previous studies from other countries have similar findings regarding a significant reduction in CRT and visual acuity improvement following the use of intra-vitreous bevacizumab for ME secondary to BRVO (Abegg et al, 2008; Gutiérrez et al, 2008; Hou et al, 2009; Hung et al, 2001; Iturralde et al, 2006; Kriechbaum et al, 2008; Rensch et al, 2009) and CRVO (Beutel et al, 2010; Kriechbaum et al, 2008; Manayath et al, 2009; Pai et al, 2007). In our series,

the pattern of visual improvement was also found to be similar to previous studies from other countries (Fish 2007; Iturralde et al, 2006; Manayath et al, 2009).

One issue that may reduce the impact of Bevacizumab upon visual acuity in RVO is ischemia. In this series there were 2 cases with ischemic CRVO. The BCVA was improved by one line in one case and stable in another case where as the CRT was significantly reduced in both the cases of ischemic CRVO. The poor visual recovery in ischemic CRVO was similar to the previous studies with both intra-vitreous Bevacizumab and triamcinolone (Ip et al, 2004; Lim et al, 2011). Retinal pigment epithelial change, epiretinal membrane formation and recurrent macular edema were the main causes among the cases for poor visual recovery.

Studies reporting the changes in BCVA and CRT following the use of IVTA have been mixed in their findings. Patel et al (2008) reported a combined improvement in BCVA and CRT of 62%, whereas in this study 100% of patients experienced a reduction in CRT and more than 70% had an improvement in BCVA. Hou et al (2009) reported similar efficacy when they compared triamcinolone with bevacizumab for branch retinal vein occlusion.

None of our patients had any adverse reactions like raised intraocular pressure, intraocular inflammation, endophthalmitis or retinal detachment, a finding which is common in other studies (Badala, 2008; Gutiérrez et al, 2008; Hung et al, 2001; Iturralde et al, 2006). This favourable adverse effect profile is also better than triamcinolone with one paper reporting that 54% of cases experienced an increase in intra-ocular pressure and 46% required treatment (Patel et al, 2008). This high level of ocular hypertension in our context is difficult to manage due to limited patient access and their inability to afford topical medications or surgical intervention.

There are a number of limitations to this study. The main one is that there was no control group in order to make outcome comparisons. The cohort was



small with an average follow up period of only 7.5 months. A larger cohort with a longer follow up would add strength to our data. There were also few patients who underwent FFA. This makes the determination of ischemia less certain, but its presence is known to predict a poor final BCVA despite the resolution of ME.

Although the present study confirms the previous findings from other countries, it is important to demonstrate similar efficacy within the Nepalese population. The findings lend support for a long-term, prospective, randomized controlled trial with an adequate number of patients in order to assess the long term safety and comparative efficacy of intra-vitreous Bevacizumab.

Conclusion

Intra-vitreous Bevacizumab is an effective and safe drug for reducing macular edema and improving visual acuity secondary to retinal vein occlusion in short term follow up at our hospital set up.

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