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Low dose versus conventional dose of intravitreal bevacizumab injection for retinopathy of prematurity: a case series with paired-eye comparison

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ABSTRACT.

Purpose: **To compare the clinical outcomes of intravitreal bevacizumab (IVB) injection, with different dosing (0.25 mg/0.01 ml versus 0.625 mg/0.025 ml) in each eye of the same patient with retinopathy of prematurity (ROP).**

Methods: **Intravitreal bevacizumab (IVB) was injected into eight patients with stage 3+ in zone I or posterior zone II ROP (16 eyes). Bevacizumab, with different dosing (0.25 mg/0.01 ml and 0.625 mg/0.025 ml), was injected into the vitreous cavity of each eye.**

Results: **Among the 16 eyes treated with IVB, six eyes had zone I ROP and 10 eyes had zone II ROP. The mean birthweight was 800 ± 139 g (range, 533–955 g), and the mean gestational age was 25.9 ± 1.2 gestational weeks (range, 24.4–28.7 weeks). The postmenstrual age at initial treatment was 37.2 gestational weeks (range, 33.7–41 weeks). The mean follow-up was 312 ± 50 days (median, 305 days; range, 238–376 days). All eyes showed regression of plus sign after IVB injection within 1 week and revascularization to the ora serrata at the time of final visit. There was no difference in the time of anatomical achievement between the eyes with different doses. None of the patients received any additional IVB injection or laser photocoagulation. After the regression of ROP, tractional retinal detachment and macular ectopia were not observed in any patients during follow-up.**

Conclusions: **There was no difference in the short-term clinical outcomes of stage 3+ ROP in zone I or II between the eyes with low dose and conventional dose of IVB.**

Key words: anti-VEGF therapy – intravitreal bevacizumab – retinopathy of prematurity – vascular endothelial growth factor

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Introduction

Retinopathy of prematurity (ROP) is a major concern for premature infants because it can lead to severe visual impairment. Based on the results of the Early Treatment of Retinopathy of Prematurity (ETROP) study conducted a decade ago, early use of conventional laser therapy to treat type I prethreshold ROP has been regarded as a standard therapy (Early Treatment For Retinopathy of Prematurity Cooperative Group 2003). Because vascular endothelial growth factor (VEGF) plays a major role in the pathogenesis of ROP (Smith 2008), the use of anti-VEGF agents, including bevacizumab, for the management of ROP has been proposed and used by some researchers. After the recent Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) trial reported a beneficial effect of bevacizumab in comparison with conventional laser therapy (Mintz-Hittner et al. 2011), treatment with intravitreal bevacizumab (IVB) has gained a wider acceptance (Harder et al. 2013; Moran et al. 2014). However, there are many concerns regarding the possible ocular and systemic side-effects of anti-VEGF treatment, especially in premature infants. Although post-mortem biopsy showed relative safety profiles for IVB (Kong et al. 2008), VEGF has been shown to influence neuronal growth and lung maturation (Compernolle et al. 2002; Nishijima et al. 2007). In addition, Sato et al. (2012) showed that IVB could escape from the eye, resulting in reduced serum levels of VEGF in infants.

In the BEAT-ROP study, a dosage of 0.625 mg was used, but others advocate that a much lower dosage could be sufficient to treat ROP (Harder et al. 2013; Spandau 2013). Because ROP typically occurs in both

eyes, the accumulating effect of anti-VEGF could be more dangerous when bevacizumab is injected in both eyes or when repeated injections are given. Besides organogenesis failure, the late recurrence of ROP after IVB injection was reported in some cases (Jang et al. 2010; Lee et al. 2012; Karaca et al. 2013). All of these patients received 0.625 mg of bevacizumab or higher doses, in both eyes. This suggests that the high level of VEGF had an important role in stimulating fibrosis-related pathways and in causing tractional retinal detachment. Considering the potential adverse effects of suppressing VEGF levels in both local and systemic environments, in premature infants, lower doses of bevacizumab in the ROP eye would be desirable if equivalent efficacy could be achieved.

In the present study, we investigated whether a lower bevacizumab dose (0.25 mg/0.01 ml) could provide comparable benefits to the bevacizumab dose used in the BEAT-ROP study (0.625 mg/0.025 ml) for the management of stage 3+ ROP, in Zone I or Zone II posterior disease. Different dosing was employed in each eye of an infant with ROP, and short-term efficacy and adverse effects were investigated.

Patients and Methods

This study was approved by the Institutional Review Board of Shinchon Severance Hospital and was conducted in adherence to the tenets set forth in the Declaration of Helsinki. Our study included eight children who were consecutively treated for stage 3+ ROP disease, in zone I or zone II. Before treatment, we discussed with the parents of all affected children the possibility of using off-label IVB as an alternative to conventional standard laser treatment performed according to the international guidelines of the ETROP. Intravitreal bevacizumab (IVB) dosing was randomly selected for each eye and was administered in the operating room under general anaesthesia with intubation. Sometimes, ROP did not appear to be equally severe between both eyes, albeit the same stage and zone were designated according to the diagnostic criteria of the International Classification of Retinopathy of Prematurity. In such cases (patient number 2, 5, and 6), the higher conventional dose was used in more severe-looking eyes for ethical concerns. Slit-lamp, fundus examination and wide fundus photography were performed prior to the IVB. Bevacizumab (0.25 mg/0.01 ml or 0.625 mg/0.025 ml) was injected through the pars plicata into the vitreous cavity with a 30-gauge needle and inserted 1 mm posterior to the corneal limbus of both eyes. After injection of bevacizumab, the syringe is carefully removed from the eye to avoid the regurgitation of bevacizumab. All surgical procedures were performed by one experienced surgeon (CSL). After the IVB, routine ophthalmic examinations were repeated once or twice a week for 3 weeks, and patients were followed every 1–4 weeks until full vascularization of the retina was observed. If the patient did not respond positively to IVB treatment in 2 or 3 weeks, a second injection of IVB or conventional laser photocoagulation was considered.

The postoperative ophthalmological examinations were performed without anaesthesia or sedation. After instillation of mydriatics, the child was held by a nurse, topical anaesthesia (lidocaine hydrochloride eye drops) was applied, eyelids were retracted by a lid retractor, and the fundus, including its periphery, was examined using a binocular ophthalmoscope. We defined recurrence as any of the following: recurrent plus disease, recurrent neovascularization or progression of traction despite treatment. Major complications were defined as corneal opacity requiring corneal transplant, lens opacity requiring cataract surgery, preretinal or intravitreal haemorrhage requiring vitrectomy, tractional retinal detachment after IVB.

Results

The study included 16 eyes of eight children with a mean birthweight of 800 ± 139 g (mean ± standard deviation; median, 836 g; range, 533–955 g) and a mean gestational age of 25.9 ± 1.2 weeks (median, 25.7 weeks; range, 24.4–28.7 weeks). Six patients were male (75%), and two patients were female (25%). All children showed stage 3+ ROP in zone I or zone II. Among 16 eyes, 10 eyes were zone II stage 3 with plus and six eyes were zone I stage 3 with plus. The mean age at the time of the IVB injection was 37.2 gestational weeks (median, 36.9 weeks; range, 33.7–41 weeks). The mean follow-up was 312 ± 50 days (median, 305 days; range, 238–376 days). Clinical characteristics and anatomical outcomes of each patient after IVB are provided in Table 1.

All eyes showed decreased vascular dilation and tortuosity within 7 days after the IVB injection, a resolution of any tunica vasculosa lentis if present within 7 days, and a resolution of the retinal neovascularization within 2–3 weeks. There was no difference in the time of these anatomical achievements between the eyes with different dosing. During the follow-up period, no recurrence of ROP was found and none required a second IVB injection or additional laser photocoagulation. Late tractional retinal detachment and macular ectopia did not occur in any patients. All infants received a single IVB as primary and sole treatment. One infant (patient number 8) developed significant vitreous haemorrhage in lower dose injected eye 7 weeks after IVB injection despite prior prompt resolution of ROP. The 25-gauge lens-save vitrectomy successfully treated vitreous haemorrhage that did not resolve within 3 weeks. At the time of surgery, no sign of ROP reactivation was noted after vitreous haemorrhage was cleared, and vitreous haemorrhage was presumed to be due to Terson syndrome associated with intraventricular haemorrhage, which preexisted before ROP treatment. We did not detect any other ophthalmologic or systemic side-effects of the IVB injection during the follow-up periods.

Discussion

The present study showed that all patients who received a single low dose (0.25 mg) of IVB in one eye versus a 'standard' dose (0.625 mg) of IVB in the other eye showed favourable anatomical outcomes, as indicated by the complete regression of plus disease, absorption of vitreous haemorrhage if present, regression of a tunica vasculosa lentis and vascularization of the avascular area. Additional retinal laser photocoagulation or a repeated IVB injection was not necessary in any patients. Similar efficacy of two different doses in one subject was observed, and any significant systemic adverse

Table 1. Clinical characteristics of patients with retinopathy of prematurity who received intravitreal injection of bevacizumab.

Patient	GA (weeks)	Birthweight (g)	GA at injection (weeks)	ROP stage	TVL present	IVB dose	Comorbidity	Follow-up (days)	Clinical outcome at final recorded visit
1	26	890	38 + 5	Zone II, stage 3+	OD: – OS: –	OD: 0.25 mg OS: 0.625 mg	HMD, VSD, Inguinal hernia	371	Near full vascularization, OU
2	28 + 5	650	39 + 1	Zone II, stage 3+	OD: + OS: +	OD: 0.25 mg OS: 0.625 mg	HMD, BPD, ASD, VSD	356	Full growth of vessel at ora serrata, OU
3	25 + 5	760	36 + 4	Zone I, stage 3+	OD: – OS: –	OD: 0.25 mg OS: 0.625 mg	HMD, BPD, PDA ligation, IVH	376	Near full vascularization, OU
4	25 + 1	862	35 + 4	Zone II, stage 3+	OD: + OS: +	OD: 0.625 mg OS: 0.25 mg	HMD, BPD	284	Near full vascularization, OU
5	25 + 4	553	41	Zone II, stage 3+	OD: + OS: +	OD: 0.625 mg OS: 0.25 mg	HMD, BPD, NEC, PDA ligation	319	Full growth of vessel at ora serrata, OU
6	25 + 6	955	33 + 5	Zone I, stage 3+	OD: + OS: +	OD: 0.625 mg OS: 0.25 mg	HMD, IVH, ICH, Hydrocephalus	291	Near full vascularization, OU
7	24 + 3	810	37 + 2	Zone I, stage 3+	OD: + OS: +	OD: 0.25 mg OS: 0.625 mg	HMD, PFO, IVH, Bowel perforation	262	Near full vascularization, OU
8	25 + 5	920	35 + 5	Zone II, stage 3+	OD: + OS: +	OD: 0.25 mg OS: 0.625 mg	HMD, ASD, PDA, IVH	238	Full growth of vessel at ora serrata, OU

GA= gestational age, TVL = tunica vasculosa lentis, IVB = intravitreal bevacizumab, OD = oculus dexter, OS = oculus sinister, OU = oculus uterque, HMD = hyaline membrane disease, VSD = ventricular septal defect, BPD = bronchopulmonary dysplasia, ASD = atrial septal defect, PDA = patent ductus arteriosus, IVH = intraventricular haemorrhage, NEC = necrotizing enterocolitis, ICH = intracranial haemorrhage, PFO = patent foramen ovale.

event was not observed. One infant developed significant vitreous haemorrhage that required vitrectomy in the eye with lower dose bevacizumab. Although Terson syndrome was the most likely cause of vitreous haemorrhage in this infant, bevacizumab may have been responsible for the development of vitreous haemorrhage, as its association has been previously noted (Wu et al. 2008, 2011). Bevacizumab treatment could lead to resolution of new vessels that may exert forces on neovascularization and cause bleeding. However, vitreous haemorrhage following IVB was typically resorbed within a few weeks without causing significant damage (Wu et al. 2008, 2011). Our patient developed abrupt and significant vitreous haemorrhage that completely obscured the view of the retina and did not resolve within 3 weeks. Furthermore, it occurred in the eye receiving the lower dose, not in the fellow eye receiving the higher dose, which thereby faces increased risk of vitreous haemorrhage associated with bevacizumab. On the contrary, it could be argued that undertreatment with a lower dose of bevacizumab caused ROP progression that led to the development of vitreous haemorrhage. However, this was unlikely because the prompt resolution of ROP with vascularization was seen up until 1 week before development of vitreous haemorrhage. In addition, there was no sign of ROP progression while examining the eye after vitreous haemorrhage was removed at the time of surgery. This infant had preexisting intraventricular haemorrhage before IVB injection. All comorbidities in all patients listed in Table 1 existed before IVB injection.

Since the BEAT-ROP study (Mintz-Hittner et al. 2011), IVB injection for ROP has gained wide popularity in clinics. However, the risk of potential systemic side-effects of VEGF blockade in the fast-growing tissue of a premature infant has not been sufficiently elucidated (Harder et al. 2013). Angiogenesis plays a major role in the development of most organs and neural tissues, particularly in young infants. Intravitreal injected anti-VEGF was found in the general circulation and reduced systemic VEGF concentrations for weeks to months (Sato et al. 2012; Hoerster et al. 2013). In terms of the dosage relationship between the vitreous concentration of bevacizumab and the serum concentration of bevacizumab, the lowest possible dosage of bevacizumab should be used for infants with ROP.

After the BEAT-ROP study, several studies reported late recurrence of the ROP following intravitreal anti-VEGF injection (Jang et al. 2010; Lee et al. 2012; Patel et al. 2012). The stimulation of fibrosis after IVB injection had been suggested for the possible mechanism of delayed onset retinal detachment. Karaca et al. (2013) also reported tractional retinal detachment in the injected eye, while the untreated eye was free of traction. They suggested that high bevacizumab levels, in the injected eye, might have a fibrosis-promoting effect, based on the observation of a single case. We did not observe the late recurrence or tractional retinal detachment in both eyes during follow-up periods. But, it must be noted that our study was limited by the relatively short follow-up periods for adequate assessment of late complications. If the accumulating effect of 0.625 mg of intravitreal bevacizumab could stimulate the fibrogenic pathway in eyes with ROP, the clinician must consider these late occurring retinal detachments in bilateral high-dose injections.

There are several limitations to be considered in this study. With regard to bilateral effects of unilateral IVB injection, Karaca et al. (2013) reported four patients with unilateral injection of bevacizumab who showed bilateral regression of ROP, though this was more prominent in the treated eyes. It was evident that high doses of bevacizumab entered the systemic circulation and reduced the angiogenesis activity in untreated eyes. However, in the aforementioned study, it could not be determined if a leakage from contralateral eyes was sufficient for complete resolution of disease activity in the untreated eyes, because all of the uninjected eyes subsequently underwent photocoagulation (Karaca et al. 2013). Additional limitations of our study include the small number of patients, and the relatively short follow-up periods. Hu et al. (2012) reported that five eyes of nine patients progressed to having retinal detachment after IVB injections, at a median age of 55 gestational weeks (range, 49–69 weeks). We cannot definitively conclude that the 0.25 mg dose of IVB in one eye and the 0.625 mg dose of IVB in the other eye were free of late ocular complications. Systemic adverse events could not be compared because the study was designed to inject a different dose in the same patient. Additionally, the randomization of the eyes was not entirely complete because in three patients, the ROP extent was deemed different in each eye, and higher doses were used in more severe eyes. However, these differences were not significant as the stage and zone of ROP were determined to be the same between both eyes in these patients.

In conclusion, a 0.25 mg/0.01 ml low dose of IVB showed similar short-term clinical outcomes in patients with stage 3+ zone I or II ROP, compared to 0.625 mg/0.025 ml of IVB. Further investigations, in randomized clinical trials, are required to determine the optimal dose of IVB to suppress the progression of ROP, while avoiding serious local and systemic side-effects.

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