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Original Article NEONATOLOGY

Evaluation of babies with retinopathy of prematurity following intravitreal bevacizumab administration

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ABSTRACT

OBJECTIVE: In Turkiye, the increased likelihood of survival of small premature babies has resulted in a higher incidence of retinopathy of prematurity (ROP), which causes severe visual impairment in childhood. Early diagnosis and timely and proper treatment of ROP can prevent vision loss. This paper discusses cases of ROP treated with bevacizumab.

METHODS: Patients treated with bevacizumab for ROP were evaluated retrospectively. Systolic and diastolic blood pressure values were recorded 1 day before and 2 weeks after bevacizumab administration. The Bayley III test, hearing test, eye examination, and neurological evaluation were performed.

RESULTS: The mean composite Bayley III test scores for cognition, language, motor, social-emotional, and adaptive domains in 10 patients who received bevacizumab for ROP were 75±10.8, 73.4±15.4, 71.2±10.2, 88±23.7, and 65.4±13.8, respectively. The mean values of the day before the injection and the values of the 14 days after the injection were compared, it was seen that there was a significant increase in systolic blood pressure values, especially at the end of 1st day and 1st week after the surgery. Neurological examination results were abnormal in 50% of the cases. Vision problems were detected in 40% of the cases. About 30% of the babies failed the hearing test.

CONCLUSION: Caution needs attention in the care of neonates until further studies of the long-term benefits and effects of bevacizumab therapy are completed.

Keywords: Bevacizumab; newborn; retinopathy of prematurity.

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Retinopathy of prematurity (ROP), a well-known cause of childhood blindness, is a proliferative vasculopathy of the developing retinal vessels in premature babies [1, 2]. The development of the retina, which progresses from the optic nerve to the periphery during pregnancy, becomes deficient depending on the degree of prematurity [3]. Neovascularization in the later stages of ROP can cause retinal traction and retinal detachment, which can impair vision [4, 5].

VEGF, a key factor in fetal angiogenesis, plays a key role in the progression of ROP by causing neovascularization [1, 4, 6, 7]. While cryotherapy was used for the ablation of the avascular retina to treat ROP in the 1980s, laser therapy replaced cryotherapy in the 1990s [6, 8].

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Laser and cryotherapy treatments destroy most of the cells in the retina that produce vascular endothelial growth factor (VEGF) [5]. Therefore, treatments with fewer complications have been sought. Since bevacizumab (Anti-VEGF) treatment does not destroy the peripheral retina, it prevents some of the late complications associated with ablative therapy [2]. In the BEAT-ROP study, monotherapy with intravitreal bevacizumab (IVB) injection was shown to be more effective than conventional laser photocoagulation in the treatment of disease in Zone I [7].

Although the literature supports the efficacy of bevacizumab in ROP, the suppression of serum VEGF levels following treatment has raised concerns about the systemic effects of antiangiogenic therapy [2, 4, 9, 10]. Given bevacizumab's long half-life and potential antiangiogenic effect on the eye, it is critical to document its effect on the entire body in preterm babies with ongoing organogenesis. If the antiangiogenic effect occurs at the cerebral level, it may hinder brain development and cause motor, cognitive, and language disorders [1].

IVB has emerged as a significant and promising, albeit controversial, treatment option for ROP. It is less difficult to administer than ablative treatment; the procedure takes less time, does not require special equipment, and can be used with short-acting topical anesthesia, avoiding the need for general anesthesia or sedation [2, 10]. Bevacizumab treatment should be considered in advanced diseases such as the newly defined aggressive posterior ROP (APROP), for which there is limited evidence about the efficacy of laser therapy [2].

This article aims to evaluate neurodevelopment using the Bayley III test in cases with ROP treated with bevacizumab in our clinic.

Highlight key points

- Although laser photocoagulation is the gold standard for ROP treatment, the fact that IVB agents are easier to administer, yield a faster response to treatment, do not narrow the visual field, and can be used in cases where the cornea is opaque, the vitreous is cloudy, and the pupil is not dilated, is an advantage.
- Bevacizumab may harm a developing preterm baby since it enters the systemic circulation upon intravitreal injection and affects vascular growth factors, which are important in organogenesis.
- In the first 18 months, the language and cognitive scores of our patients were relatively better than their motor development.
- Hypertension is one of the most common side effects of systemic bevacizumab therapy in adults. However, it has not been well defined in infants receiving intravitreal therapy yet.

MATERIALS AND METHODS

Patients with ROP who received bevacizumab and were followed up in the Neonatal Intensive Care Unit between November 2014 and December 2018 were evaluated. The study was launched with the Umraniye Training and Research Hospital Clinical Research Ethics Committee approval, dated May 16, 2018, and numbered 74. The study included premature babies with a corrected age of 1–42 months. Patients with congenital anomalies or severe congenital heart disease, as well as those born in or followed up on by another hospital before being referred to our hospital, were excluded from the study.

All babies were examined for ROP per guideline recommendations [11]. APROP was diagnosed based on the International ROP Classification [12]. IVB treatment was administered to patients with APROP.

Bevacizumab monotherapy was administered to babies using the methods recommended in the BEAT-ROP study [5]. All injections were performed in the operating room. Following topical anesthesia with 0.5% proparacaine HCl and 5% povidone-iodine administration on the ocular surface, 0.3 mg of bevacizumab (Altuzan, 100 mg/4 mL vial, Roche, Turkiye) was injected into the vitreous cavity. A positive response to IVB therapy was defined as tunica vasculosa lentis, plus disease and disease stage regression, and progression of retinal vessels to the peripheral retina. Additional injections of IVB were administered in cases where re-activation of ROP was observed, such as the possibility of disease recurrence or recurrence of proliferative components. To assess neovascularization of the peripheral retina, patients were examined on post-op day 1, week 1, and week 2, and at monthly intervals thereafter.

The data for the cases treated with IVB were extracted from the medical records using standard definitions. The study complied with the principles of the Declaration of Helsinki. Intraventricular hemorrhage (IVH) was graded according to Papile criteria [13], and periventricular leukomalacia (PVL) was graded according to the study by de Vries et al. [14]. Necrotizing enterocolitis (NEC) was assessed according to the Modified Bell criteria [15]. Bronchopulmonary dysplasia (BPD) was defined as the requirement for supplemental oxygen at postmenstrual

Table 1. Demographic characteristics and neonatal morbidities of the cases

	Case									
	1	2	3	4	5	6	7	8	9	10
Birth week	23w+6d	26w	25w	28w	26w	26w	28w	22w	22w	22w
Body weight (gr)	515	710	651	1215	845	520	700	560	608	520
Lenght (cm)	27	31	30	38	37	30	29	31	29	31
Head circumference (cm)	19	26	25	25	26	21	24	21	21	20
Gender	F	M	M	F	F	F	M	F	M	F
Antenatal bleeding	+	–	–	+	–	+	–	+	–	–
Fetal distress	+	+	–	+	–	–	+	–	–	–
PPROM	–	–	+	–	+	–	–	–	–	–
Placental abruption	–	–	–	+	–	–	–	–	–	–
Maternal hypertension	–	+	–	–	–	–	+	–	–	–
Gestational diabetes	–	+	–	–	–	–	–	–	+	–
Antenatal steroid	+	+	+	–	+	–	–	–	–	+
Postnatal steroid	+	–	+	–	+	+	+	+	+	+
BPD	+	–	+	–	+	+	+	+	+	+
PDA treatment	Med.	Med.	Lig.	Med.	Med.	–	Med.	Med.	Lig.	Lig.
Sepsis	+	–	+	–	–	+	+	–	+	+
IVH	Right grade 2	–	–	–	–	Grade 4	–	–	–	+
PVL	–	–	–	+	–	–	–	–	+	–
NEC	+	–	–	–	+	–	+	–	+	+
Anti–VEGF count	1	1	2	1	2	1	1	1	1	1
Length of stay in hospital (day)	130	154	162	57	110	106	83	102	297	262
Discharged home with oxygen	–	–	–	–	–	–	–	–	+	+
Death after discharge	–	–	–	–	–	–	–	–	+	–

M: Male; F: Female; Med: Medical; Lig: Ligation; PPROM: Preterm premature rupture of membranes; BPD: Bronchopulmonary dysplasia; PDA: Patent Ductus Arteriosus; IVH: Intraventricular hemorrhage; PVL: Periventricular leukomalacia; NEC: Necrotizing enterocolitis; Anti-VEGF: Anti-vascular endothelial growth factor.

week 36 [16]. Late-onset sepsis was defined as having a positive blood culture for bacteria and fungi 72 h after birth [17]. Hemodynamically significant patent ductus arteriosus (PDA) was evaluated by a pediatric cardiologist with echocardiography in the first 24–72 h.

Systolic and diastolic blood pressure values were recorded during the 2 weeks starting from the day before bevacizumab administration.

Patients were evaluated on a systemic and neurological level. Eye examination and hearing test results were extracted from the records retrospectively.

When the research started, families were contacted and informed about the study. Written consent was obtained from the parents. The child and mother were taken to a quiet place where the child could act comfortably. The Bayley III Test was performed by face-to-face interview using test materials. Scores were recorded on Bayley III special forms. The Bayley III scale was administered by a certified Pediatric pecialist who was included in the study team and was blinded to patients' previous treatments.

Bayley III Scale of Development

The Bayley III test, which is used as a scale of neurological development, is an approved and standardized developmental assessment for infants aged 1–42 months. The primary purpose of the test is to identify children with developmental delays. The Bayley III Test assesses children in five domains: cognitive, language, motor, social-emotional, and adaptive. The language scale includes receptive and expressive language, and the motor scale

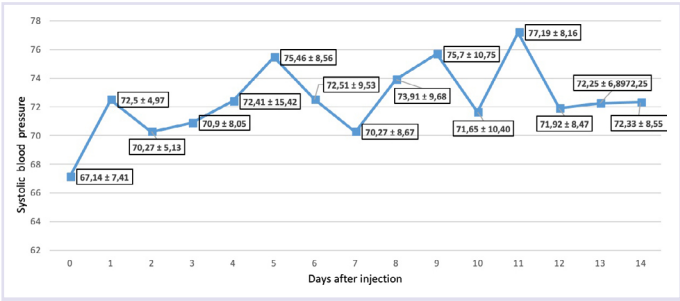

FIGURE 1. The systolic blood pressure values.

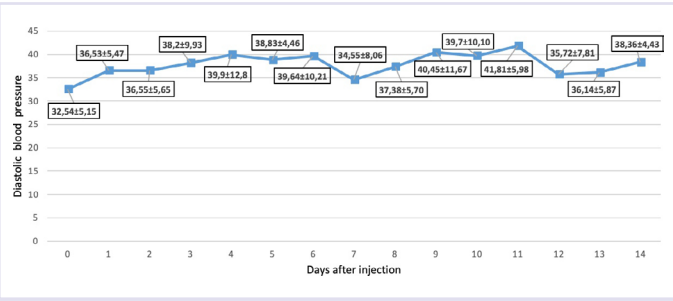

FIGURE 2. The diastolic blood pressure values.

TABLE 2. Bayley Test, neurological and eye examination, hearing test results of the cases

	Case									
	1	2	3	4	5	6	7	8	9	10
Adjusted age	2.5 mth	5 mth	23 mth	26 mth	24 mth	42 mth	25 mth	6 mth	15.5 mth	1 mth 12 day
Cognitive (85–115)	85	65	70	85	80	75	65	85	55	85
Language (85–115)	91	77	62	79	68	77	59	100	47	74
Motor (85–115)	79	76	76	64	76	73	70	82	46	70
Social emotional (85–115)	110	80	55	80	95	100	110	125	65	60
Adaptive (85–115)	75	73	52	57	61	63	56	99	59	59
Abnormal neurological examination	–	–	–	–	+	+	+	–	+	+
Abnormal eye exam	+	–	–	–	–	+	+	–	+	–
Hearing test	–	Pass	Pass	Pass	Pass	Fail	Pass	Pass	Fail	Pass

includes fine motor and gross motor subtests. The cognitive scale helps determine sensorimotor development, objective association, content formation, memory, and conceptual skills. The three types of scoring in the Bayley III test are scaled scores, composite scores, and percentiles. The composite score is the average of the graded scores of the subtests. The mean is 100, and its standard deviation is 15 points. In this study, cognitive, language, motor, social-emotional, and adaptive development levels were evaluated using a composite score [1, 18].

Statistical Analysis

All data were presented in the form of a mean±standard deviation. The non-parametric test (Wilcoxon Signed-Rank Test) was used to determine the statistical significance between the study groups. $p<0.05$ was considered significant. Statistical packages for the social sciences (SPSS) (SPSS for Windows 17.0; SPSS, Chicago, Illinois, USA) software was used in the computation of the data on the computer.

RESULTS

Between November 2014 and December 2018, bevacizumab was administered to 10 babies hospitalized at 24–32 weeks for the treatment of APROP. Table 1 shows the baseline demographics and neonatal morbidities of all enrolled babies. Only one of the cases (22 w, 520 g) had no antenatal risk factors. Half of them received antenatal steroids. Eight babies received postnatal steroids. Only one of those who received antenatal steroids did not require steroids in the postnatal period. When we evaluated their neonatal morbidities, BPD was present in 80%, hemodynamically significant PDA in 90% (30% ligation, 60% medical treatment), NEC in 40%, PVL in 20%, and IVH in 20%. Bevacizumab was administered for the 2nd time to 20% of 10 patients diagnosed with APROP. One of the two patients who were discharged home with supplemental oxygen died during the follow-up.

The systolic and diastolic blood pressures of our patients in the last 14 days before the intervention were

evaluated, and it was seen that the values were within the normal limits without any difference between the days. The mean values of the day before the injection and the values of the 14 days after the injection were compared, it was seen that there was a significant increase in systolic values, especially at the end of the 1st day and the 1st week after the surgery ($p<0.05$) (Figs. 1, 2).

The neurological examination, eye examination, hearing test, and Bayley III assessment results of the cases are given in Table 2. The results of the neurological examination were abnormal in 50% of the cases, and the results of the eye examination were abnormal in 40% of the cases. One patient's hearing test results were unavailable; two patients failed the tests; and seven patients did not have any hearing problems. In patients who received bevacizumab, the mean composite Bayley III test scores for cognition, language, motor, social-emotional, and adaptive domains were 75±10.8, 73.4±15.4, 71.2±10.2, 88±23.7, and 65.4±13.8, respectively. Bayley scores were found to be low in babies with PVL, eclampsia in the antenatal history, and additional risk factors for prematurity such as grade 4 intracranial hemorrhage and PDA ligation.

DISCUSSION

IVB treatment has emerged as a significant and promising, albeit controversial, treatment option for ROP. Although laser photocoagulation is the gold standard for ROP treatment, the fact that IVB agents are easier to administer, yield a faster response to treatment, do not narrow the visual field, and can be used in cases where the cornea is opaque, the vitreous is cloudy, and the pupil is not dilated is an advantage. Possible disadvantages are a temporary decrease in serum VEGF levels and the risk of brain, lung, and kidney damage [18]. The American Academy of Pediatrics emphasized that IVB therapy can be considered in Zone I stage 3 ROP+ 'plus' disease, but more research is needed on its dose, optimal timing, safety, and efficacy [18].

Investigating the long-term neurodevelopmental effects of bevacizumab treatment, Morin et al. [1] found that it was associated with lower motor scores and higher rates of severe neurodevelopmental deficiency in preterm babies. However, when Kennedy and Mintz-Hittner [8] compared IVB and laser treatments, they found no significant difference between the two groups in their neurological evaluations when the corrected age was 18–22 months. The fact that there was no systematic difference in the patients who received both treatments in the Kennedy and Mintz-Hittner study since the patients were randomized, and the fact that the Morin et al. [1] study was a non-randomized study in which the physicians' choice of treatment was compared to laser therapy, may explain these disparities. When a decision had to be made between IVB and laser therapy, sick babies may have been treated with IVB preferentially due to the lack of need for mechanical ventilation, general anesthesia, and transport to the operating room.

In a study conducted in Toronto, the neurodevelopmental and visual results of IVB and laser therapy were compared at the corrected age of 18–24 months, and it was thought that the lack of a significant difference between the two groups was due to the systemic absorption being too low to show any significant clinical effect [7].

In the study of Lien et al. [4], which evaluated 61 cases and performed neurological evaluations 2 years after the treatment, no difference was found in neurodevelopmental outcomes between laser and IVB. Supporting this result, we found that the scores were within the normal range in four of the five domains of the Bayley III assessment in two cases born at 515 g (case 1) at week 23 and 560 g at week 22 (case 8).

Cases treated for ROP have a smaller birth weight and more complications than other premature infants followed up in the neonatal intensive care unit. Therefore, they are more disadvantaged in terms of neurological development. Two of our cases, whose body weights were 608 g (case 9) and 520 g (case 10), had a significantly longer hospitalization period than our other patients (297 days and 262 days, respectively). In the Bayley III assessment of these two cases, we found that the scores were significantly lower in all five domains. Both patients had a history of frequent hospitalizations after discharge. The patient, with a birth weight of 608 g, died at the age of two due to chronic complications.

The BEAT-ROP study [5] is a prospective, randomized, nonblinded study comparing IVB and laser therapy. It has been reported that regression of retinal neovascular changes can be achieved at a lower dose of IVB (0.375 mg) than the standard dose. After the BEAT-ROP study, the use of IVB in the treatment of ROP increased. Since 2014, IVB treatment has been the treatment of choice in our unit for ROP. As a result, the lack of a laser therapy arm is a limitation of our study.

Studies using fluorescein angiography in eyes with ROP have shown vascular leakage and a ruptured blood-ocular barrier. Bevacizumab concentrations peak-

ed 2 weeks after injection, whereas VEGF concentrations were lower a week after injection, with a negative correlation with bevacizumab concentrations [19]. In studies, bevacizumab was detected in circulation for approximately 8 weeks [9, 20]. Organogenesis continues during the treatment of ROP in preterm babies. VEGF is neurotropic and neuroprotective in the brain, helps maintain the blood-brain barrier, and is also required for normal neural retinal development independent of angiogenesis in the eye. It has been suggested that bevacizumab may harm a developing preterm baby since it enters the systemic circulation upon intravitreal injection and affects vascular growth factors, which are important in organogenesis [19].

Sankar et al.'s [6] Cochrane analysis, published in 2018, includes six clinical studies of 383 infants. When IVB and ablation therapies were compared, it was discovered that those with zone I involvement had a significantly lower risk of recurrence, while those with zone II involvement had a higher risk of recurrence. They highlighted the need to conduct more research to assess the effect of IVB on structural and functional outcomes in childhood as well as its delayed systemic effects, including adverse neurodevelopmental outcomes. In our study, seven out of ten cases had zone II involvement, and two of them required a second IVB administration.

In the study of Morin et al., [1] Bayley-3 language and motor composite scores were consistently low in the group treated with IVB, and the difference was statistically significant only for motor development. Similar cognitive scores were obtained in both groups. The rates of severe neurodevelopmental disorders were also found to be higher in the IVB group. Brain development continues to be an active process during the first 18 months of life, especially with significant changes and rapid gains in motor skills. As a result, any event that disrupts cerebral development has been thought to manifest with delays in this area first, before abnormalities in language or cognition appear. Motor development scores were below normal in all of our cases. But half of these cases were babies over 18 months old. In the first 18 months, the language and cognitive scores of our patients were relatively better than their motor development.

Lien et al. [4] found that psychomotor development delay at Month 24 was significantly higher in those treated with IVB+laser when they compared IVB, laser, and IVB+laser therapies. The adverse effects on neurodevelopment in the IVB+laser group were thought to be caused by increased anti-VEGF transfer into the systemic circulation following laser therapy. However, these patients were said to have poor neurological outcomes due to lower gestational age and birth weight or additional serious systemic comorbidities at baseline. One of our cases, whose body weight and birth week were higher (1215 g at 28 weeks) (case 4), who had a shorter hospital stay but was diagnosed with PVL, had a cognitive score at the lower limit and lower than normal scores in the other four domains. More research is needed to objectively evaluate the effect of IVB on the neurodevelopment of premature babies.

According to current evidence, IVB therapy is just as effective as laser photocoagulation for achieving acute ROP regression. However, due to delayed retinal vascularization, careful and long-term follow-up is required. Following the intravitreal injection, serum VEGF levels are suppressed for at least 8–12 weeks. The effects of lower systemic VEGF levels on the developing organ systems of premature babies are unknown, and there is limited long-term data on potential systemic and neurodevelopmental effects following the use of IVB for the treatment of ROP. Agents that suppress VEGF should be used with caution and awareness of known or potential adverse effects [21].

Hypertension is one of the most common side effects of systemic bevacizumab therapy in adults. However, it has not been well defined in infants receiving intravitreal therapy yet. In the study of Twitty et al., [22] systemic hypertension was observed 10 days after bevacizumab administration in an infant born at 25 weeks of gestation with stage 3 ROP. In the adult study of Rasier et al., [23] hypertension was detected after the IVB administration. Regarding hypertension as a side effect of systemic bevacizumab therapy, we assessed the systolic and diastolic blood pressures of our patients in the last 14 days before the intervention, and it was seen that the values were within the normal limits without any difference between the days. When the mean values of the day before the injection and the values of the 14 days after the injection were compared, it was seen that there was a significant increase in systolic values, especially at the end of the 1st day and the 1st week after the surgery, according to the literature. Due to the limited number of participants in our study, statistically significant differences might be less. We could not assess the hypertension of patients in their 3rd week because of the discharge. Further studies are needed on the effect of bevacizumab on infant hypertension.

Due to the large range of post-gestational ages during the Bayley test process, it is very difficult to compare the results of the patients. This is the limitation of our study.

Conclusion

Increased survival of low-birth-weight infants will lead to more ROP cases requiring treatment. Babies with a posterior disease, such as those in our study, are at a high risk of adverse neurodevelopmental problems because they are born extremely prematurely. As a result, we believe that IVB does not cause abnormal neurodevelopmental outcomes on its own. There are numerous examples in the history of neonatology of therapies being adopted based on short-term benefits without knowing the long-term consequences. Ultimately, more research is needed to determine the short- and long-term effects, as well as the safety, of intravitreal agents that suppress VEGF in premature babies.

Ethics Committee Approval: The Umraniye Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 16.05.2018, number: 74).

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