

# Hypotension Associated With Intravitreal Bevacizumab Therapy for Retinopathy of Prematurity

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Intravitreal bevacizumab therapy in preterm infants for retinopathy of prematurity (ROP) can be associated with hypotension. We report twin preterm infants who developed hypotension within 1 day after intravitreal bevacizumab therapy for ROP. Before receiving the medication, their clinical statuses were stable and similar. The dose, procedure, and premedication were the same; however, twin B presented with hypotension for 3 days. Although bevacizumab-related hypotension has been described in product information (incidence rate 7%–15%), this is the first case report of intravitreal bevacizumab for ROP inducing hypotension. Physicians should be aware of intravitreal bevacizumab therapy-related hypotension when treating ROP. We suggest conducting a postmarketing active surveillance on the systemic adverse effects of this regimen in preterm infants.

Bevacizumab is an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, approved as an additional medication with other chemotherapy drugs for the treatment of metastatic cancer.<sup>1</sup> It has been used off-label to decrease retinal thickening in age-related macular degeneration and to diminish intraoperative complications in diabetic retinopathy patients.<sup>2,3</sup> In addition, randomized trials have shown improvement of the retina and reduced zone I disease progression with intravitreal bevacizumab therapy for retinopathy of prematurity (ROP) in preterm infants.<sup>4</sup>

Systemic cardiovascular complications of intravenous bevacizumab have been reported, including hypertension, thromboembolic events, cardiac ischemia, cerebrovascular ischemia, and bleeding.<sup>5</sup> Although local intravitreal bevacizumab therapy might minimize the systemic side effects, cardiovascular adverse effects such as hypertension

have been observed in some studies.<sup>6</sup> In theory, bevacizumab will elevate blood pressure by reducing nitric oxide synthase in endothelial cells, decreasing vascular permeability.<sup>7</sup> Thus, bevacizumab-related hypotension needs more attention because this mechanism is unexpected, although it has been mentioned in product information, presenting an incidence rate of 7% to 15%.<sup>8</sup> One retrospective study in Japan also reported that 25 colorectal patients with cancer presented a temporary blood pressure drop within 90 minutes of intravenous bevacizumab.<sup>9</sup> Neither systemic adverse events nor hypotension effects were reported in clinical trials after treatment with bevacizumab for ROP<sup>4,10,11</sup>; however, the serum level of bevacizumab has been detected after intravitreal injection in preterm infants.<sup>12</sup> To provide more safety information for bevacizumab in preterm infants, we report a case of twin preterm infants treated

## abstract

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Ms Wu cared for the cases, noted the adverse effects relative with bevacizumab, and drafted the initial manuscript; Dr Yang carried out the initial analyses and reviewed and revised the manuscript; Drs C-H Lin and Y-J Lin critically reviewed the manuscript; Dr Cheng coordinated and supervised data collection, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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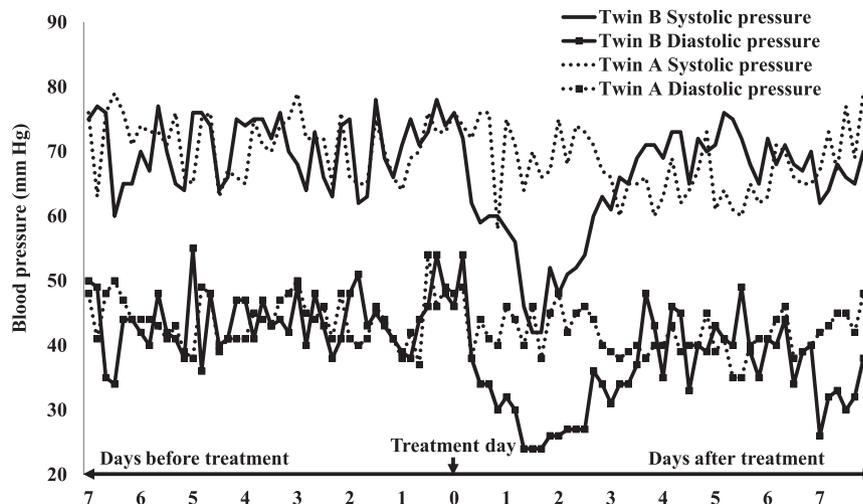
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with intravitreal injection of bevacizumab for ROP, after which 1 infant showed posttreatment hypotension that persisted through the day.

## CASE REPORT

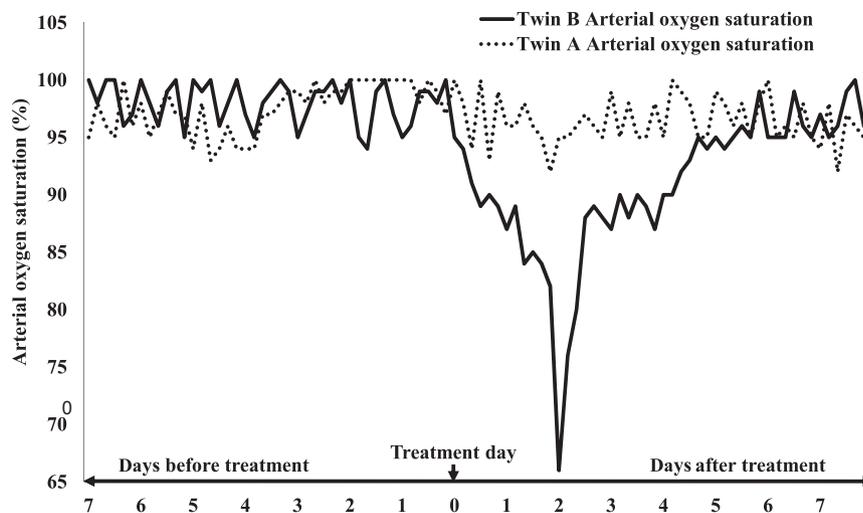
### Twin B: Hypotension After Therapy With Bevacizumab

Twin (B), a male infant, was born at 26 weeks' gestation with a birth weight of 800 g. Bilateral immature retina was found at 6 weeks after birth. At 9 weeks, the ROP had progressed to stage 3, zone 1. Intravitreal injection of bevacizumab (0.625 mg/0.025 mL) was performed in each eye under intravenous ketamine (0.3 mg) and local atropine (0.25%). At the same time, a local steroid (betamethasone) and an antibiotic (levofloxacin) were administered for inflammation and infection prevention. Up to this time, the patient had been stable and had only received parenteral nutrition for growth and metoclopramide 0.2 mg/kg every 8 hours for gastroesophageal reflux during the previous month. Feeding intolerance, hypotension (42/24 mm Hg), and desaturation (arterial oxygen saturation 80.0%) were noted 22 hours after bevacizumab therapy. On the second day, blood pressure remained low (48/26 mm Hg) and feeding intolerance was not improved. In addition, Twin B suffered from shortness of breath with apnea (arterial oxygen saturation 66.1%) and lethargy and was intubated for mechanical ventilation. Because of the hypotension, he received dopamine, 8 mcg/kg per minute infusion, and prophylactic antibiotics with vancomycin, 10 mg/kg every 6 hours and ceftazidime 50 mg/kg every 8 hours. On the third day after bevacizumab therapy, his blood pressure returned to normal, and his general condition improved (Figs 1



**FIGURE 1**

Blood pressure of the patients 1 week before and after intravitreal bevacizumab therapy. Twin B was in stable condition before treatment. Hypotension (42/24 mm Hg) was noted within 1 day after bevacizumab therapy. On the second day, blood pressure remained low (48/26 mm Hg).



**FIGURE 2**

Arterial oxygen saturation of the patients 1 week before and after intravitreal bevacizumab therapy. Twin B was in stable condition before treatment. Desaturation (arterial oxygen saturation 80.0%) was noticed within 1 day after bevacizumab therapy. On the second day, arterial oxygen saturation remained low (66.1%).

and 2). On the sixth day, his condition had stabilized, and antibiotics and dopamine were discontinued. He was successfully extubated on the next day, and arterial oxygen saturation was normal. Eighteen weeks after birth, he was discharged from the NICU in stable condition.

### Twin A: No Hypotension After Therapy With Bevacizumab

Twin A, a female infant, was similar to her brother: 26 weeks' gestation

with 775 g birth weight. Bilateral immature retina was found 6 weeks after birth (ROP stage 3, zone 1). The treatment regimen was the same as her brother's: intravitreal injections of bevacizumab (0.625 mg/0.025 mL), with intravenous ketamine (0.3 mg), local atropine, betamethasone, and levofloxacin. She received vancomycin 10 mg/kg every 6 hours plus ceftazidime 50 mg/kg every 8 hours for suspected infection in the previous 5 days. Her

**TABLE 1** Patient Characteristics

Patient	Twin B	Twin A
Hypotension or desaturation after treatment	Yes	No
Gender	Male	Female
Gestational age at birth	26+3 wk	26+3 wk
Body wt at birth	800 g	775 g
Apgar score at birth	5–8	7–8
PDA with ibuprofen	Yes	Yes
PDA with surgical ligation	Yes	Yes
Pulmonary hypertension	Yes	Yes
ROP stage	Stage III zone I+	Stage III zone I+
Age at treatment	34+4 wk	34+4 wk
Body wt at treatment	1680 g	1435 g
Average wt gain	16.0 g/kg/day	12.0 g/kg/day
Ventilation status at treatment	NIMV	NIMV
Sedation for procedure	Ketamine	Ketamine
Intraventricular hemorrhage	Grade I	Grade II
Chronic lung disease	Yes	Yes
Feeding condition 1 week pretreatment	Milk 8 mL every 4 h	Milk 1 mL every 4 h
Parenteral nutrition 1 week pretreatment	Yes	Yes
Total fluid intake 1 week pretreatment	150 mL/kg/d	150 mL/kg/d
Infection 1 month pretreatment	No	Yes
Medications 1 week before treatment	Metoclopramide	Vancomycin, ceftazidime

NIMV, nasal intermittent mandatory ventilation; PDA, patent ductus arteriosus.

blood pressure (72/43 mm Hg) and arterial oxygen saturation (97.3%) were normal after treatment with bevacizumab. The blood pressure (average 70.1/43.7 mm Hg) and arterial oxygen saturation (average 95.6%) were stable during the 2 days after bevacizumab treatment (Figs 1 and 2). Antibiotics were stopped the second day after bevacizumab therapy because infection was no longer noted. Eighteen weeks after birth, she was discharged from the NICU in stable condition.

## DISCUSSION

ROP is a serious vasoproliferative disorder that occurs in the retina of preterm infants with incomplete retinal vascularization. ROP can lead to severe visual impairment or blindness.<sup>13</sup> Exposure to hyperoxia can result in delay of normal retinal vascular development and induce vascular obliteration, and, consequently, VEGF administration before 31 weeks' gestation.<sup>13</sup> VEGF and other cytokines may contribute to both normal retinal vessel growth and abnormal vascular disruption and subsequent neovascularization.

Increased permeability of these abnormal new vessels can result in retinal edema and hemorrhage. Bevacizumab is an anti-VEGF monoclonal antibody that inhibits the physiologic effects of VEGF to improve visualization of the retina and may facilitate disease regression.<sup>4</sup>

In published reports on the effectiveness of bevacizumab, there are no systemic complications attributable to intravitreal bevacizumab, such as blood pressure fluctuation, cardiopulmonary distress, or infection, in the treatment of ROP.<sup>10–12</sup> However, the medication can leak through the compromised blood–retina barrier with ROP and be detected in serum 2 days after injection.<sup>14</sup>

We report that only 1 preterm twin (twin B, but not twin A) suffered hypotension and desaturation after intravitreal bevacizumab therapy. Before the infants received the treatment, both had adequate weight gain, ~12.0 to 16.0 g/kg/day, under parenteral nutrition and breastfeeding (Table 1). There was no bacterial, viral, or fungal growth from culture of the central venous

catheter for total parenteral nutrition at 1 week before and after the infants received intravitreal bevacizumab. Neither had a hemorrhage event or loss intravascular volume components in the previous month. Vital signs for each were stable for 2 weeks before the regimen (Figs 1 and 2).

Clinical features of hypotension include low blood pressure, change in consciousness, desaturation, tachycardia, skin mottling, cool extremities, and decreased urine output. Factors associated with hypotension in neonates are various, including hemorrhage, loss of intravascular volume components (burns, nephrotic syndrome, diarrhea, vomiting, and diabetes), congenital heart disease, ischemia, dysrhythmias, pneumothorax, sepsis, and drug-induced hypotension.<sup>15</sup> Systemic anesthesia (ketamine) may induce hypotension and apnea. However, although both twins received the same ketamine treatment, only twin B developed hypotension and desaturation the day after intravitreal bevacizumab. The half-life of bevacizumab is 11 to 50 days, whereas the half-life of ketamine is approximately 2 to 3 hours. The hypotension occurred 22 hours after intravitreal treatment and thus is less likely to have resulted from ketamine. The time sequence between the therapy administration and the onset of adverse effects showed a high association between the intravitreal bevacizumab and the hypotension. Although metoclopramide-associated hypotension had been reported within 2 minutes after administration, twin B used metoclopramide 1 month before the incident without hypotension. Thus, intravitreal bevacizumab was considered the probable cause of hypotension in twin B, and this event was idiosyncratic and unexpected.

Off-label use of intravitreal bevacizumab therapy for ROP is increasing, despite the lack of studies on its safety. It is well known that bevacizumab may leak out of the eyes and enter the systemic circulation.<sup>12,14</sup> The safety of intravitreal bevacizumab for ROP concerns not only the eye but also systemic tissues. The potential for systemic adverse events exists and should not be ignored. Thus, the safety of intravitreal bevacizumab therapy in preterm infants with ROP should be established with further studies.

#### ABBREVIATIONS

ROP: retinopathy of prematurity  
VEGF: vascular endothelial growth factor

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