



ARTICLE



Respiratory outcomes in preterm infants following intravitreal bevacizumab for retinopathy of prematurity—a 10-year matched case study

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OBJECTIVES: To evaluate respiratory outcomes in preterm infants with retinopathy of prematurity (ROP) following intravitreal bevacizumab injection (IVB).

METHODS: This single-centre study enrolled preterm infants with a gestational age (GA) < 34 weeks or a birth weight (BW) < 1500 g with bilateral type 1 ROP who received a single IVB, and a treatment-free control group matched by GA, postmenstrual age, and respiratory status at the time of the IVB. The primary outcome was serial respiratory changes in mean airway pressure (MAP), fraction of inspired oxygen (FiO₂), and respiratory severity score (RSS, MAP × FiO₂) during the 28-day post-IVB/matching period and overall respiratory improvement at day 28 and at discharge. The duration of supplemental oxygen therapy following IVB/matching was documented.

RESULTS: A total of 5578 infants were included. Seventy-eight infants were enrolled in the IVB group, and another 78 infants were matched as the control group. Both groups had downward trends in the MAP, FiO₂, and RSS over the study period (all $P < 0.001$), but there were no between-group differences in these measures. The percentage of overall respiratory improvement was similar between the IVB and control groups, so was the duration of invasive and in-hospital oxygen ventilation. A lower percentage of oxygen dependence at discharge in the IVB group ($P = 0.03$) remained significant after adjusting for GA and BW.

CONCLUSIONS: This is a matched case study to evaluate respiratory outcomes in preterm infants following IVB for ROP. We found that the IVBs did not compromise respiratory outcomes in preterm infants during the 28-day post-IVB period and at discharge.

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INTRODUCTION

Retinopathy of prematurity (ROP) is a leading cause of infancy blindness worldwide. Intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents have become the treatment of choice in treating severe ROP, although this usage has not been clinically approved [1, 2]. The largest ROP study, the Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity (BEAT-ROP) study, has shown that intravitreal bevacizumab injection (IVB) has a significant benefit in treating severe ROP over conventional interventions in peripheral retinal vascularization [2]. Little reliable safety data in humans regarding the function of vascular-enriched organs or vital organs following IVB have been reported [1, 3, 4].

Lung tissues were found to express highest amount of VEGF among all organs in rats [5]. In one study, anti-VEGF therapy resulted in mRNA overexpression of VEGF and VEGF receptors in the rats' lungs and pulmonary hypertension [4]. In human preterm infants, intravitreally injected anti-VEGF agents enter systemic

circulation and suppress plasma VEGF levels for up to 2 months [6–10]. Whether systemic leakage of the anti-VEGF agents affects the maturation and function of vital organs is of concern to neonatologists and ophthalmologists.

Respiratory outcomes following intravitreal anti-VEGF therapy in preterm infants have not been well investigated in the past. Some prior studies mentioned respiratory condition as a possible side effect of IVB [1, 2, 11]. Nevertheless, these prior studies did not clarify or specify respiratory condition and oxygen requirement parameters in the patients. Changes in the grading of oxygen supplementation are critical and intricate for preterm infants following intravitreal anti-VEGF therapy instead of merely recording the duration of ventilation. To address this issue, infants with delicately matched respiratory status before IVB were needed to assess the changes in respiratory condition following IVB. The respiratory outcomes were compared between ROP infants receiving IVB and preterm infants free from ROP treatment.

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METHODS

Study design and participants

We retrospectively reviewed preterm infants with a gestational age (GA) < 34 weeks or a birth weight (BW) < 1500 g admitted to the neonatal intensive care unit (NICU) at Chang Gung Memorial Hospital, Linkou, Taiwan from May 2008 to January 2017. Preterm infants with a diagnosis of bilateral type 1 ROP [12, 13] and underwent IVB treatment were assessed for eligibility. Infants with a major anomaly or a known genetic disease that might negatively affect respiratory function [14], those receiving additional laser treatment, those receiving ≥ 2 sessions of IVB, those receiving any intravitreal medication other than bevacizumab, any intraocular surgery, and those who did not require supplemental oxygen therapy on the day of treatment were excluded. After the study group was identified, they were matched with a control group at a 1:1 ratio based on the following criteria: GA ± 1 week, postmenstrual age (PMA) ± 7 days, category of ventilation mode, in oxygen-dependent order, the use of high-frequency oscillatory ventilation (HFOV), conventional mechanical ventilation or noninvasive ventilation (nasal intermittent positive pressure ventilation and continuous positive airway pressure (CPAP) and nasal cannula) and respiratory status by means of the respiratory severity score (RSS, mean airway pressure (MAP) \times fraction of inspired oxygen (FiO₂)) [15] $\pm 10\%$ on the day of IVB. We matched GA instead of BW because type 1 ROP is associated more with GA than BW [16, 17]. The patients in the control group may have had ROP, but none met the type 1 ROP treatment criteria [12, 18]. The control infants had the same exclusion criteria applied as those in the IVB group.

Clinical demographics, including GA, BW, sex, delivery method, multiple birth, Apgar scores, antenatal steroid use, and maternal chorioamnionitis, were documented. Prior to IVB, comorbidities that might have affected respiratory outcomes were recorded, including administration of exogenous surfactant for respiratory distress syndrome (RDS), severe intraventricular haemorrhage (IVH, stage ≥ 3), patent ductus arteriosus (PDA) requiring surgical ligation, necrotizing enterocolitis (NEC), culture-proven sepsis and bronchopulmonary dysplasia (BPD). The ROP status at IVB/match, non-systemic adverse events following IVB, serious adverse events, and death for both groups were documented.

Intravitreal bevacizumab injections

As our team previously described, the technique used for IVB and the treatment protocol for type 1 ROP were executed [8, 11, 19]. With proper antiseptic preparation, 0.625 mg (0.025 ml) of bevacizumab (Avastin; Genentech, Inc., San Francisco, CA) was injected intravitreally with a 30-gauge needle through the pars plicata. After the injection, retinal artery perfusion was checked, and the patients received the topical antibiotic levofloxacin (Cravit; Santen Pharmaceutical Co, Osaka, Japan) for 7 days. After IVB, we followed up the patients every 1 to 2 weeks based on their age and ROP severity until retinal vascularization was 2 discs in diameter or fewer away from the ora serrata.

Respiratory outcomes

The goal of assisted oxygen therapy in the NICU is to maintain arterial oxygen saturation >88% with adequate ventilation [20]. Treatment strategies for intubation, extubation to CPAP from mechanical ventilation, reintubation, and weaning from CPAP all followed international guidelines [21–24]. Using the respiratory status on the day of IVB/match as baseline (Day 0), serial respiratory status changes in terms of MAP, FiO₂ and RSS 3, 7, 14, 21, and 28 days later were the primary outcomes. Effective FiO₂ for infants on nasal cannula was documented according to reference conversion tables [25]. In addition, overall respiratory improvement 28 days after matching, defined as extubation, downgrading of ventilatory mode, reduction in MAP > 25%, or a decrease in FiO₂ > 25% [26], was evaluated. The time to extubation and the duration of supplemental oxygen therapy after matching were also compared.

Statistical analysis

For between-group comparisons, categorical variables were analysed using the chi-square test, while continuous variables were analysed using the independent *t* test. For serial changes in respiratory status, repeated-measures ANOVA was performed to test within-group differences. Non-normal distribution variables were tested using Mann–Whitney U test. All factors related to respiratory outcome with *P* value < 0.1 were pooled into a multivariate regression analysis and a backward selection was applied. Statistical analyses were performed using SPSS software (IBM SPSS

Statistics for Windows, Version 20.0. Armonk, NY). A *P* value < 0.05 was considered statistically significant.

RESULTS

Study participants

There were 5578 eligible preterm infants during the 10-year period, 135 of whom had bilateral type 1 ROP and underwent IVB. Forty-nine of them were excluded due to the administration of additional intraocular procedures. Four infants were excluded due to no requirement of supplemental oxygen at the time of IVB, 3 infants were excluded due to data corruption, and 1 infant was excluded due to death within 28 days after IVB. Consequently, a total of 78 infants were enrolled as the IVB group, and another 78 infants from the same database were matched as the control group. The flowchart of enrolment is illustrated in Fig. 1. There was no significant difference in GA (25.9 ± 1.5 weeks vs 25.7 ± 1.4 weeks), PMA at the time of matching (35.9 ± 2.0 weeks vs 35.7 ± 1.8 weeks), or postnatal age (69.8 ± 24.7 days vs 68.0 ± 14.8 days) at the time of matching between the IVB and control groups (both *P* > 0.05). The IVB group had a greater BW (833 ± 165 g vs 773 ± 145 g, *P* = 0.02), a higher incidence of surgical ligation for PDA, more cases of severe IVH and advanced ROP. In the control group, 57 (73.1%) infants had ROP, but none of them had type 1 ROP. All patients in the control group showed regression in their ROP and did not meet the treatment criteria for type 1 ROP during follow-up. The results are demonstrated in Table 1. After a single IVB, all infants in the IVB group demonstrated ROP regression, and showed no signs of reactivation during follow-up visits.

Respiratory outcomes

Regarding respiratory outcomes, Fig. 2 represents the frequency distribution of preterm infants needing supplemental oxygen therapy during the 28-day interval post-IVB/match. The IVB group had significantly fewer infants requiring supplemental oxygen therapy than the control group on day 14 (73.1% vs. 88.6%; *P* = 0.02). Infants in the IVB group required similar degrees of supplemental oxygen therapy on Day 7 (91.0% vs. 94.9%,

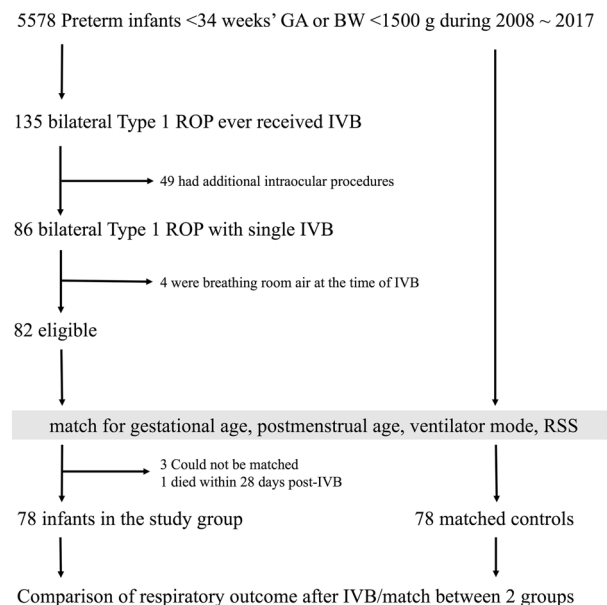


Fig. 1 Study flowchart of infant enrolment. BW birth weight, GA gestational age, IVB intravitreal bevacizumab, NICU neonatal intensive care unit, ROP retinopathy of prematurity, RSS respiratory severity score.

Table 1. Demographics, systemic risk factors, and ROP conditions between the 2 study groups.

	IVB (n = 78)	Control (n = 78)	P value
Gestational age (weeks)	25.9 ± 1.5	25.7 ± 1.4	0.41
Birth weight (g)	833 ± 165	773 ± 145	0.02
PMA at IVB/Match (weeks)	35.9 ± 2.0	35.7 ± 1.8	0.68
Postnatal age (day)	69.8 ± 24.7	68.0 ± 14.8	0.23
Male, No. (%)	48 (61.5)	48 (61.5)	1.00
Multiple birth, No. (%)	21 (26.9)	18 (23.1)	0.58
Caesarean delivery, No. (%)	42 (54.6)	41 (52.6)	0.81
Apgar score			
1 min	5.1 ± 2.0	5.1 ± 2.2	0.85
5 min	7.1 ± 1.6	7.0 ± 2.0	0.86
Maternal chorioamnionitis, No. (%)	15 (19.2)	22 (28.2)	0.16
Maternal steroid use, No. (%)	52 (66.7)	57 (73.1)	0.52
ROP stage, No. (%)			<.001
No ROP	0 (0)	21 (26.9)	
1	0 (0)	31 (39.7)	
2	6 (7.7)	24 (30.8)	
3	72 (92.3)	2 (2.6)	
ROP zone, No. (%)			<0.001
1	6 (7.7)	0 (0)	
2	72 (92.3)	42 (53.9)	
3	0 (0)	15 (19.2)	
Plus disease, No. (%)	74 (94.9)	0 (0)	<0.001
BPD severity, No. (%)			0.15
No BPD	1 (1.3)	0 (0)	
mild	31 (39.7)	21 (26.9)	
moderate	19 (24.4)	30 (38.4)	
severe	27 (34.6)	27 (34.6)	
RDS requiring surfactant, No. (%)	65 (83.3)	59 (75.6)	0.23
PDA ligation, No. (%)	52 (66.7)	39 (50.0)	0.04
IVH stage ≥3, No. (%)	16 (20.5)	6 (7.7)	0.02
NEC, No. (%)	10 (12.8)	8 (10.3)	0.62
Culture-proven sepsis, No. (%)	47 (60.3)	44 (56.4)	0.63

Data are the mean ± standard deviation or no. (%) unless otherwise mentioned.

BPD bronchopulmonary dysplasia, IVB intravitreal bevacizumab, IVH intraventricular haemorrhage, NEC necrotizing enterocolitis, PDA patent ductus arteriosus, PMA postmenstrual age, RDS respiratory distress syndrome, ROP retinopathy of prematurity.

$P = 0.35$), Day 21 (66.7% vs. 76.9%, $P = 0.16$), and Day 28 (56.4% vs. 68.0%, $P = 0.14$), compared with those in the control group.

A downward trend in MAP, FiO_2 and RSS over time was seen in both the IVB and control groups ($P < 0.001$), but there were no between-group differences. The trends in serial respiratory status are presented in Fig. 3. In general, most infants in both groups showed respiratory improvement on day 28 and at discharge. The two groups were comparable in MAP (IVB, 5.0 (5.0–5.0) vs. control, 5.0 (5.0–5.0)

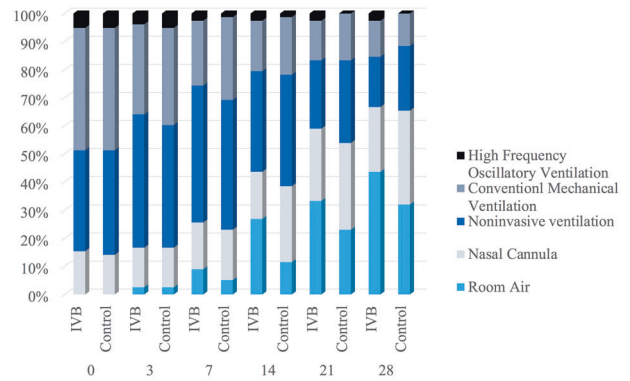


Fig. 2 Percentages of infants requiring supplemental oxygen therapy during the 28-day interval after intravitreal injection of bevacizumab or matching. Supplemental oxygen therapy was defined as that requiring any of the following ventilation modes: high-frequency oscillatory ventilation, conventional mechanical ventilation, and noninvasive ventilation (nasal intermittent positive pressure ventilation and continuous positive airway pressure and nasal cannula).

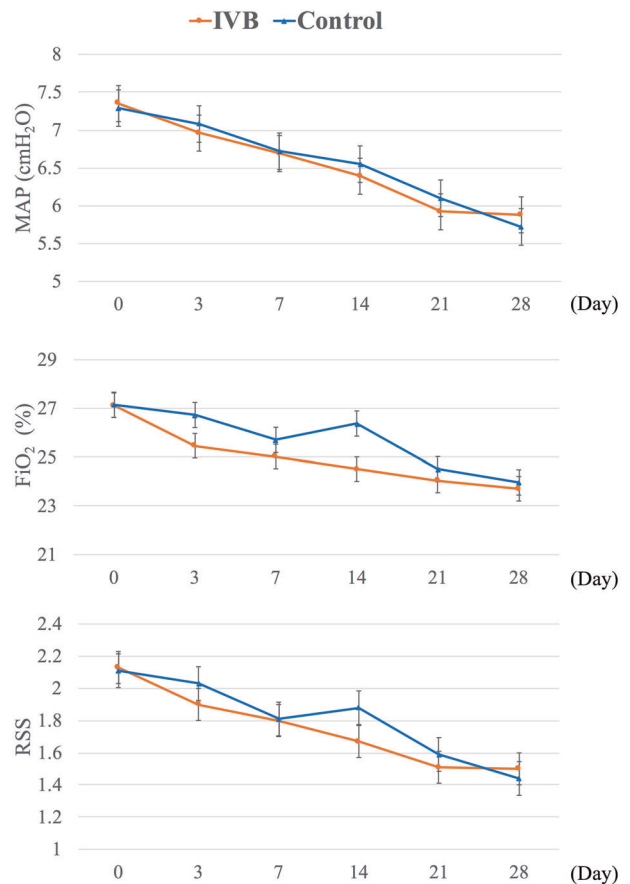


Fig. 3 Serial changes in mean airway pressure (MAP), fraction of inspired oxygen (FiO_2), and respiratory severity score (RSS). In both groups, MAP, FiO_2 , and RSS showed significant downward trends post intravitreal injection of bevacizumab/match (repeated-measures ANOVA, all $P < 0.001$). However, there were no between-group differences.

cmH_2O , $P = 0.73$), significantly different FiO_2 (IVB, 21.0 (21.0–21.0) vs. control, 21.0 (21.0–23.0) %, $P = 0.02$) and RSS (IVB, 1.1 (1.1–1.1) vs. control, 1.1 (1.1–1.2), $P = 0.02$) at discharge. The respiratory outcomes 28 days after IVB/match and at discharge are presented in Table 2.

Table 2. Respiratory outcomes between the 2 study groups.

	IVB (n = 78)	Control (n = 78)	P value
Respiratory status on day 28			
Extubation, No. (%)	66 (84.6)	69 (88.5)	0.48
Downgrade of respiratory support, No. (%)	61 (78.2)	65 (83.3)	0.42
Overall respiratory improvement, No. (%)	65 (83.3)	67 (85.9)	0.69
No need for supplemental O ₂ , No. (%)	34 (43.6)	25 (32.1)	0.14
In-hospital respiratory condition			
Intubation days	70.4 ± 38.0	66.9 ± 30.4	0.16
In-hospital supplemental O ₂ days	107.1 ± 40.2	109.1 ± 35.6	0.52
Post-IVB/match supplemental O ₂ days	39.1 ± 38.2	41.1 ± 30.7	0.75
Use of HFOV, No. (%)	67 (85.9)	61 (78.2)	0.21
Mortality, No. (%)	1 (1.3)	0 (0)	0.32
Respiratory status at discharge			
Respiratory support, No. (%)			0.72
Room air	62 (79.5)	50 (64.1)	
Nasal cannula	11 (14.1)	20 (25.6)	
Noninvasive ventilation	2 (2.6)	5 (6.4)	
Conventional mechanical ventilation	3 (3.9)	3 (3.9)	
MAP (cmH ₂ O), median (IQR)	5.0 (5.0–5.0)	5.0 (5.0–5.0)	0.73
FiO ₂ (%), median (IQR)	21.0 (21.0–21.0)	21.0 (21.0–23.0)	0.02
RSS, median (IQR)	1.1 (1.1–1.1)	1.1 (1.1–1.2)	0.02
Downgrade of respiratory support, No. (%)	76 (97.4)	71 (91.0)	0.09
Overall respiratory improvement, No. (%)	77 (98.7)	72 (92.3)	0.05
No need for supplemental O ₂ , No. (%)	62 (79.5)	50 (64.1)	0.03

FiO₂ fraction of inspired oxygen, HFOV high frequency oxygen ventilation, IQR interquartile range, IVB intravitreal bevacizumab, MAP mean airway pressure, RSS respiratory severity score.

Data are the mean ± standard deviation or median (IQR) or no. (%) unless otherwise mentioned.

Overall, there was no difference with regard to either the total or post-IVB/match duration of intubation or in the matter of oxygen requirements. However, more infants in the IVB group tolerated room air than in the control group at discharge (79.5% vs. 64.1%, $P = 0.03$), and the significance remained after adjusting for GA and BW. Whether an infant required oxygen at discharge was not associated with GA, BW, severe IVH, and PDA ligation (all $P > 0.05$).

One infant died 56 days after her IVB due to disseminated intravascular coagulopathy and hemodynamic instability. No ocular adverse events occurred in the IVB group.

DISCUSSION

In this study, we did not detect negative impacts on respiratory outcomes in terms of respiratory parameters in the IVB group or on the total duration of intubation and oxygen use during the 28-day post-IVB period. More preterm infants in the IVB group tolerated room air at discharge.

Prior studies have rarely discussed about the respiratory outcomes following intravitreal anti-VEGF treatment in ROP infants. The BEAT-ROP team found no differences in lethal respiratory outcomes between infants treated with IVB and those treated by laser [2]. The CARE-ROP team reported a longer duration of supplemental oxygen therapy for patients receiving higher doses of intravitreally injected ranibizumab [1]. Fan et al. [11] found that preterm infants with ROP, regardless of whether they received IVB treatment, had a significantly longer duration of ventilation than preterm infants without ROP. We also showed the duration of supplemental ventilation was comparable between ROP infants with or without IVB treatment [11]. However, all these studies did not aim to focus

on the comparison of respiratory function either before and after IVBs or with and without IVBs. Furthermore, oxygen requirements are affected by numerous prematurity-related comorbidities [15, 24, 26–29]. For example, intubation and general anaesthesia are often required before laser treatment to avoid cardiopulmonary decompensation upon a stressful event [2, 30, 31]. To reduce such confounding factors, we compared infants receiving IVB with those free from ROP treatment instead of with those receiving laser therapy. In addition, we stratified respiratory support into 4 classes to better access oxygen requirement in both groups. Subjects being compared on the same level of respiratory condition and oxygen requirement would better reflect their respiratory outcomes following IVBs.

After a dedicated matching process, the IVB and control groups had comparable GAs, PMAs and respiratory statuses. IVB group were found to be slight heavier than the control group (61 g or 7% difference). Why this happened? Poor systemic condition (usually associated with low BW) was associated with worse respiratory status and ROP [29, 32]. If IVB and control group had similar BW, the respiratory function of the control group will be better. To have a similar respiratory status (matched between IVB and control group), infants in the control group, would consequently be lighter to have a comparable respiratory status with IVB group. Respiratory status at discharge was not associated with GA nor BW in univariate analysis. The occurrence of major neonatal morbidities between 2 groups was comparable, especially those associated with poor respiratory outcomes (e.g., RDS [33, 34], NEC [35] or sepsis [33, 34]). Surgical ligation for PDA and severe IVH have been recognized as risks for ROP [36], and we reasonably found that more infants in the IVB group had severe IVH or were more likely to require ligation for PDA. However, respiratory status

at discharge was not associated with severe IVH nor PDA ligation in univariate analysis.

VEGF is crucial to vascularization and angiogenesis in the developing lung [4, 37–41]. Angiogenesis and alveolarization occur at GA between 32 weeks and 35 weeks and last until at least 3 years of age [37, 39, 40, 42]. In pup studies, VEGF inhibition decreased pulmonary angiogenesis and alveolarization, contributing to pulmonary hypertension [43, 44]. VEGF transgenic mice were found to develop pulmonary haemorrhage, alveolar remodelling, and higher neonatal mortality [41]. Matrix metalloproteinases (MMPs) degrade the lung basement membrane; in their study, the IVB group demonstrated statistically increased lung MMPs and a greater incidence of pulmonary haemorrhage and decreased alveolarization [39]. IVB might lead to adverse side effects in the lung until puberty in rats [39].

Interestingly, in contrast to previous studies [1, 4, 39, 45], IVB-treated preterm infants even demonstrated favourable respiratory outcomes in terms of certain parameters in this study. We found that significantly fewer preterm infants in the IVB group required supplemental oxygen therapy than in the control group on day 14 (73.1% vs. 88.6%; $P = 0.02$). No between-group difference in oxygen requirement was observed during the 28-day interval and in-hospital stay post IVB/match. Moreover, respiratory improvement was more prevalent in the IVB group, and more infants in the IVB group could tolerate room air at discharge.

We proposed several hypotheses to explain these findings. First, lung development composes of extracellular matrix modelling, alveolarization, and angiogenesis, modulated by several growth and transcription factors, including VEGF, interleukin-1 β , nuclear factor-kB, MMPs, fibroblast growth factors, and transforming growth factor- β 1 [46, 47]. Their interaction with one another is readily affected by oxygen toxicity, inflammation, infection, and mechanical ventilation, and any imbalance which would trigger pathophysiological mechanisms [46]. Although VEGF pathway plays an important role in angiogenesis in the developing lung, bone morphogenetic proteins are found to influence pulmonary angiogenesis via an alternative pathway [48]. Therefore, VEGF is not the one and only growth factor that would mediate angiogenesis process [46–48]. This could help explain that significant respiratory distress was not observed in the IVB-treated group.

Second, after IVB, effective serum bevacizumab might be too low to have such a significant impact on pulmonary function as we previously assumed. Intravenous injections of bevacizumab at 5–10 mg/kg every 2–3 weeks in paediatric solid tumour patients did not lead to the development of any adverse drug reactions on respiratory dysfunction [49]. The dose of bevacizumab for paediatric solid tumours is much higher than that of ROP treatment upon administration of 1.25 mg IVB and 0.5 mg IVB with corresponding highest serum bevacizumab levels of 1002 ± 352.7 ng/ml and 424 ± 237.8 ng/ml, respectively [7]. Compared with the intravenous administration of bevacizumab in paediatric solid tumour patients, circulating levels of bevacizumab were much lower in ROP patients with IVB. It is possible to infer that vital organs would be minimally damaged at such levels of serum bevacizumab. In accordance with previous studies [2, 3, 11], no permanent or life-threatening side effects associated with IVB treatment were noticed. There was one mortality in the IVB group that was not considered to be related to the use of anti-VEGF. Patients in the IVB group showed similar respiratory outcomes despite having more serious preterm-related comorbidities in the perinatal period.

Third, IVB might not cause drastic harm to the preterm infants because their lungs were more mature at the time of IVB. In an animal study, VEGF inhibition therapy exerted less substantial histological and biochemical changes as the newborn mice matured; the dependence on VEGF gradually lessened after four weeks postnatally [40]. Human lungs have developed alveolar

sacs and ducts by GA 36 weeks [37]. Up to GA 40 weeks, alveolarization, the final stage of lung maturation, is well developed. Additionally, surfactant increasingly matures up to approximately 30 weeks' gestation [50]. We propose that systemic anti-VEGF treatment might have minimal impact on vital organ function such as respiration in preterm infants if they receive it at late postnatal ages. Mintz-Hittner et al. demonstrated a lack of toxic respiratory distress in preterm infants receiving IVB at a mean PMA of around 35 weeks, although a larger sample size is required to determine whether bevacizumab is harmful to preterm infants [2]. Similarly, we disclosed comparable respiratory outcomes in preterm infants receiving IVB at a PMA of approximately 36 weeks.

There are limitations of the current study. First, only short-term data were provided in this study. Long-term outcomes remain unknown. Although some parameters of respiratory outcomes approached marginal significance, more cases are required to confirm the result. However, type 1 ROP is a relatively uncommon disease which causes difficulty in cases recruitment. In addition, daily blood gas samples were not taken from all the patients, and certain medications may affect respiratory outcomes, such as intravenous or inhaled steroids, which was not specified in this study. Furthermore, serum VEGF levels were not available in this study. Prior animal studies assessed tissue mRNA [3, 4] or performed histologic staining [3] to ascertain the organ-specific effect of anti-VEGF therapy. Such specimens cannot be obtained in human studies for ethical issues. Alterations in growth factors, such as VEGF, in bronchoalveolar lavage fluid might be related to delayed lung development in preterm infants [51]. Future studies, including analyses of bronchoalveolar lavage fluid, might provide additional evidence of the extent of lung maturation in infants treated with IVB. In treating severe ROP, 2 other commonly used anti-VEGF medications, ranibizumab and aflibercept, exhibit distinctive pharmacokinetics and systemic effects [9]. Further investigations of respiratory outcomes between these 3 medications would be helpful for decision making, with a focus not only on the treatment efficacy but also on the respiratory side effects of each medication.

In conclusion, our study shows short-term respiratory function was not compromised after IVB in type 1 ROP patients. Favourable respiratory outcomes were observed at specific time points and more infants could tolerate room air at discharge in the IVB group; however, larger studies are required in the future.

SUMMARY

What was known before

- Intravitreal bevacizumab (IVB) has gained preference in treating type 1 retinopathy of prematurity (ROP), although systemic leakage of the anti-VEGF agents was detected.
- Whether IVBs would affect lung maturation and respiratory function in preterm infants has not been well investigated.

What this study adds

- This matched-case study found that preterm infants with bilateral type 1 ROP receiving IVB had similar respiratory outcomes in terms of respiratory parameters or on the total duration of intubation and oxygen use during the 28-day post-IVB period compared with the treatment-naïve controls.
- Our short-term study shows respiratory outcomes were not compromised after IVB in type 1 ROP patients, which will decrease concern on negative effect of IVB on respiratory outcomes in preterm infants.

DATA AVAILABILITY

Due to sensitivity concerns, the data supporting the study's conclusions are not publicly accessible, but can be obtained from the corresponding author upon request. The data are held in a secure, controlled-access storage facility at Chang Gung Memorial Hospital.

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AUTHOR CONTRIBUTIONS

YCH was responsible for conceptualization/design, investigation, methodology, data curation, formal analysis, and drafting the initial manuscript. KHH was responsible for conceptualization/design, investigation, methodology, data curation, formal analysis, and editing of the manuscript. SMC was responsible for investigation, data curation, supervision/oversight, resources, and review of the manuscript. MCC and RL were responsible for investigation, methodology, data curation, supervision/oversight, and resources. KJC, YSH, and LCC were responsible for investigation, data curation, supervision/oversight, resources, and review of the manuscript. HJT was responsible for methodology, data curation, formal analysis, and editing of the manuscript. WWC was responsible for conceptualization/design, investigation, methodology, data curation, supervision/oversight, resources, funding acquisition, and editing of the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital in Linkou, Taiwan (IRB201900571B0) and was conducted in accordance with the Declaration of Helsinki. Patient consent for publication was not required.

ADDITIONAL INFORMATION

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