

Risk Factors of Transfusion in Anemia of Very Low Birth Weight Infants

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Purpose: Anemia of prematurity is frequent in preterm infants, for which red blood cell (RBC) transfusion remains the treatment of choice. In this study, we attempted to evaluate the characteristics and risk factors of anemia of prematurity, and suggest ways to reduce anemia and the need for multiple transfusions. **Materials and Methods:** Preterm infants weighing less than 1500 g (May 2008-May 2009) were divided into two groups depending on whether they received RBC transfusions (transfusion group and non transfusion group). Hemoglobin (Hb) concentration, phlebotomy blood loss, and the amount of RBC transfusion were analyzed. Risk factors of anemia and RBC transfusions were analyzed. **Results:** Fifty infants that survived were enrolled in the present study: 39 in the transfusion group and 11 in the non transfusion group. Hb concentrations gradually decreased by eight weeks. In the transfusion group, gestational age and birth weight were smaller, bronchopulmonary dysplasia and sepsis were more frequent, full feeding was delayed, parenteral nutrition and days spent in the hospital were prolonged, and phlebotomy blood loss was greater than that in the non transfusion group. **Conclusion:** Anemia of prematurity was correlated with increased laboratory blood loss, decreased birth weight, prolonged parenteral nutrition, and delayed body weight gain. Accordingly, reducing laboratory phlebotomy loss and parenteral nutrition, as well as improving body weight gain, may be beneficial to infants with anemia of prematurity.

Key Words: Anemia, erythrocyte transfusion, infant, premature

INTRODUCTION

Almost all infants experience various degrees of anemia, or physiologic anemia of infancy. Typically, hemoglobin (Hb) concentration decreases to between 9.5-11 g/dL around 10-12 weeks in healthy term infants;¹ the nadir rarely falls below 9 g/dL.² Preterm infants experience more profound and earlier onset of anemia than physiologic anemia of infancy, deemed anemia of prematurity (AOP).³ In AOP, mean Hb concentration reportedly falls to approximately 8 g/dL in infants with a birth weight of 1000-1500 g and to 7 g/dL for infants weighing less than 1000 g.⁴ One study reported that between 4-10 weeks of age, the nadir of Hb concentration falls to 8-10 g/dL in preterm infants weighing 1200-1400 g and 6-9 g/dL for preterm in-

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fants weighing less than 1200 g.³

Various causes are known to contribute to AOP. One is that in the first few weeks of life, blood is lost due to sampling for the many laboratory tests that premature infants undergo.⁵ As a result, nearly half of all red blood cell (RBC) transfusions are given in the first 2 weeks of life when neonatal illness is most severe and laboratory blood loss is greatest.⁶ The most premature infants, who are the most critically ill and have the smallest blood volume, experience the greatest laboratory blood loss, and experience more profound anemia. Erythropoiesis is suboptimal, too. The survival of RBC in premature infants is short (40 to 60 days in premature infants vs. 120 days in adults), and RBC mass expands rapidly according to growth in premature infants, as a result erythropoiesis is suboptimal in comparison to need.⁷ This suboptimal erythropoiesis is greatest in the smallest and least mature infants.⁸ The suboptimal erythropoiesis seen in premature infants is caused by the blunted synthetic response of hepatic oxygen sensor to hypoxia in premature infants. Deficiency of folate, vitamin B₁₂, or vitamin E may deteriorate AOP. Vitamin E is an antioxidant essential to maintain the integrity of RBC. And vitamin E protects RBC from lipid peroxidation and membrane injury. Consequently deficiency of vitamin E may contribute to AOP.

AOP is more severe in the smallest and least mature preterm infants even in the absence of phlebotomy blood loss.⁹ Infants delivered before 28 weeks gestation or with a birth weight of <1000 g are born before the bulk of iron is transported through the placenta from the mother to the fetus and before the marked erythropoietic activity of fetal marrow during the third trimester. This results in low iron stores and a small circulating mass of RBCs, finally resulting in a more severe and early onset AOP, even in the absence of phlebotomy blood loss.¹⁰

Despite many non-transfusion approaches in AOP, RBC transfusion still remains the treatment of choice of this transfusion-dependent anemia.¹¹ However, RBC transfusions pose a risk of viral transmission, such as cytomegalovirus, hepatitis virus and graft-versus-host disease in immunocompromised very low birth weight infants (VLBWIs), as well as alloimmunization and volume overloading.¹² In addition, RBC transfusions are costly and add to parental anxiety. Thus, it is critical to prevent AOP and minimize RBC transfusions. This study was conducted to describe the characteristics of AOP, evaluate the risk factors of AOP, and suggest ways of reducing RBC transfusions in preterm infants.

MATERIALS AND METHODS

Patients

The protocol of this study was reviewed and approved by the Institutional Review Board of the Busan Paik Hospital. VLBWIs weighing less than 1500 g admitted to the neonatal intensive care unit (NICU) of Busan Paik Hospital from May 2008 to May 2009 were enrolled. The infants were allocated to two groups depending on whether they received RBC transfusions (transfusion group and non-transfusion group). Infants were excluded if the infant had immune hemolytic disease, hydrops or a life-threatening congenital anomaly.

Study protocol

Clinical data were collected retrospectively from medical records. To identify factors that might influence anemia and transfusion, various perinatal and postnatal variables were evaluated. Demographic factors included gestational age, birth weight, sex, Apgar score at 1 and 5 minutes, small for gestational age (SGA), antenatal steroids therapy, and antepartum and postpartum maternal Hb concentration. Morbidity and outcome variables included respiratory distress syndrome (RDS), sepsis, non-laboratory blood loss, such as pulmonary hemorrhage and intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), postnatal day when full feeding was reached, duration of parenteral nutrition, rate of body weight gained on the 28th postnatal day, and amount of phlebotomy blood loss. Neonatal RBC transfusions are controversial and vary from center to center. The guidelines for RBC transfusion in our NICU are based on the general guidelines proposed by Strauss.¹³ Erythropoietin (EPO) is not used routinely in our NICU, because of cost. Intrauterine RBC transfusions using umbilical veins for severe fetal anemia were not carried out in this study. Decisions regarding ordering blood tests were left to the attending physicians depending on patient severity. Micro collection tubes were used for laboratory testing, and capillary tubes for capillary blood gas analysis.

SGA was defined as a birth weight less than the 10th percentile on Lubchenco growth curve.¹⁴ Antenatal steroids were administered to all pregnant women at risk of preterm delivery within 7 days, between 24 and 34 weeks' gestation with an intact membrane or between 24 and 32 weeks' gestation with a ruptured membrane. We administered two

Table 1. Demographic Factors

	Transfusion group (n=39)	Non transfusion group (n=11)	<i>p</i> value
Gestational age (wk ^{+day})	28 ⁺³ ±2 ⁺³	32 ⁺³ ±2 ⁺⁶	<0.001
Birth weight (g)	1056±231	1232±234	0.031
Male, n (%)	22 (56.4)	8 (72.7)	0.329
Apgar score at 1 min	6±1	6±2	0.272
Apgar score at 5 min	7±1	8±2	0.285
Small for gestational age, n (%)	8 (20.5)	7 (63.6)	0.017
Antenatal steroid therapy, n (%)	27 (69.2)	4 (36.4)	0.053

doses of 12 mg of betamethasone at 24 hour intervals intramuscularly. Sepsis was diagnosed upon clinical signs of systemic infection with a positive blood culture.¹⁵ BPD was defined as an oxygen dependency for the first 28 days of life.¹⁶ IVH and ROP were limited to those of a high grade (\geq Gr III) and a high stage requiring laser therapy, respectively. The postnatal day to reach full feeding was defined as the postnatal day to achieve 120 mL/kg/day of feeding. The rate of body weight gain on the 28th postnatal day was calculated using the following equation: (body weight on the 28th postnatal day-body weight at birth)/(body weight at birth) \times 100. Two mg/kg of elemental iron was supplemented to each infant after four weeks old.

Hb concentration, phlebotomy blood loss, and volume of RBC transfusion were analyzed weekly from birth to postnatal eight weeks, the completion period of this study.

Data analysis

Statistical analysis was performed using chi-square test or Fisher's exact test for dichotomous outcome data, and a t-test or Mann-Whitney U test for continuous data. Repeated measures ANOVA was performed to monitor changes in Hb concentration from birth to postnatal eight weeks. Relative risk (RR) with 95% confidence intervals using simple logistic regression analysis and coefficients (β) using multiple regression analysis were presented to evaluate factors that might influence transfusion. *P*-values <0.05 were considered indicative of significant differences. Statistical analysis was performed using MedCalc for Windows, version 11.5 (MedCalc Software, Mariakerke, Belgium).

RESULTS

Demographic factors

During the period of enrollment (May 2008, through May 2009), 50 VLBWIs who survived were enrolled. The mean gestational age and birth weight were 29⁺⁴±3⁺⁰ weeks (range:

24⁺⁵-35⁺² weeks) and 1095±240 g (range: 510-1500 g), respectively. Gestational age and birth weight were smaller in the transfusion group than the non-transfusion group (28⁺⁵±2⁺³ weeks vs. 32⁺³±2⁺⁶ weeks, *p*<0.001, 1056±231 g vs. 1232±234 g, *p*=0.031, respectively). Sex ratio and Apgar score at 1 and 5 minutes were not different between the two groups. SGA was more frequent in the non-transfusion group (20.5% vs. 63.64%, *p*=0.017). The administration of antenatal steroids was not significantly different between the two groups [69.2% (27/39) vs. 36.4% (4/11), *p*=0.053]. Maternal Hb concentration decreased after delivery, which was not different between the two groups [11.6 g/dL (antepartum) to 9.9 g/dL (postpartum) vs. 12.4 g/dL (antepartum) to 9.4 g/dL (postpartum), *p*=0.092].

In total, 78% (39/50) of enrolled VLBWIs received a single RBC transfusion, and 54% (27/50) received more than one transfusion. The mean number of RBC transfusions was 1.8. Thirty-nine infants were assigned to the transfusion group and 11 to the non-transfusion group (Table 1).

Hb concentration gradually decreased by eight weeks (*p*<0.001), and the difference for infants weighing 1000 g was marginally significant in consideration of group \times factor interaction (*p*=0.056) (Fig. 1).

Morbidities and clinical outcome variables

Compared to the non-transfusion group, BPD and sepsis were more frequent in the transfusion group (51.3% vs. 9.1%, *p*=0.012, and 35.9% vs. 0%, *p*=0.019, respectively). The postnatal day to reach full feeding was delayed in the transfusion group (23 vs. 13 days, *p*<0.001). Also, a prolonged duration of parenteral nutrition and days spent in the hospital (24 vs. 11 days, *p*=0.002, and 79 vs. 51 days, *p*<0.001, respectively) was observed in the transfusion group. There was greater phlebotomy blood loss in the transfusion group (37 vs. 16 mL/kg, *p*<0.001). RDS, PVL, NEC (\geq stage 2), ROP (requiring laser op), and the rate of body weight gain on the 28th day were not significantly different between the two groups. Non-laboratory blood loss, such as

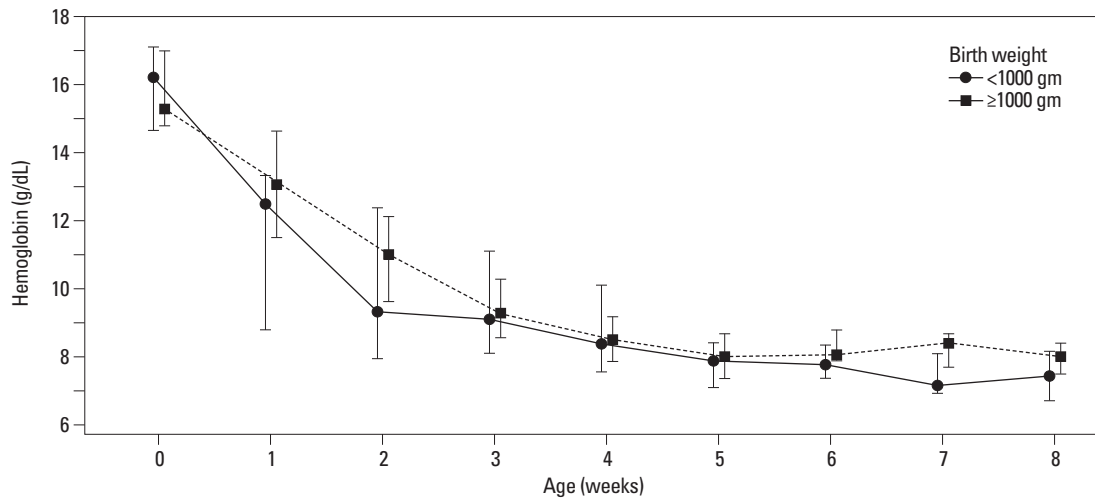


Fig. 1. Hemoglobin concentration from birth to postnatal 8th week. Dots (hemoglobin concentrations in infants whose birth weight was <1000 g are presented as circles, ≥1000 g as squares) represent median values of Hb concentration, and error bars represent 95% confidence intervals for the median. According to repeated measures ANOVA, Hb concentration gradually decreased over eight weeks. The difference in infants weighing 1000 g was marginally significant in consideration of group x factor interaction ($p=0.056$). Results of repeated measures ANOVA, results of tests assessed by Greenhouse-Geisser statistics. Between-subjects effects $p=0.149$, within-subjects effects $p<0.001$, group x factor interaction $p=0.056$.

Table 2. Morbidity and Outcomes

	Transfusion group (n=39)	Non Transfusion group (n=11)	<i>p</i> value
BPD, n (%)	20 (51.3)	1 (9.1)	0.012
Sepsis, n (%)	14 (35.9)	0 (0)	0.019
Days to reach full feeding (postnatal day)	23	13	<0.001
Duration of PN (days)	24	11	0.002
Hospital stay (days)	79	51	<0.001
Phlebotomy loss (mL/kg)	37	16	<0.001
RDS, n (%)	29 (74.4)	6 (54.5)	0.205
PVL, n (%)	3 (7.7)	0 (0)	0.343
NEC (≥ stags 2), n (%)	4 (10.3)	1 (9.1)	0.909
ROP (requiring laser op.), n (%)	5 (12.5)	0 (0)	0.211
Rate of body wt. gain at 28th day (%)	24	30	0.052
Pulmonary hemorrhage, n (%)	3 (7.7)	0 (0)	1.000
IVH (≥ grade 3), n (%)	6 (15.4)	0 (0)	0.317

BPD, bronchopulmonary dysplasia; PN, parenteral nutrition; RDS, respiratory distress syndrome; PVL, periventricular leukomalacia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; IVH, intraventricular hemorrhage.

pulmonary hemorrhage and IVH (≥ grade 3), were also not significantly different between the two groups (Table 2).

Risk factors of transfusion

The risk of needing RBC transfusion increased by 2.24 (1.13-4.43) times for infants with a gestational age of less than 28 weeks ($p=0.021$) and 2.09 (1.05-4.15) times for infants between 28 to 31 weeks ($p=0.037$), compared to infants of age equal to or greater than 32 weeks. The risk of RBC transfusion increased by 1.66 (1.02-2.71) times for infants of appropriate for gestational age (AGA) than SGA infants ($p=0.042$). This risk also increased by 1.60 (1.15-2.23) times in patients whose duration of parenteral nutri-

tion was equal to or longer than three weeks ($p=0.005$), and 1.52 (1.08-2.15) times in infants whose rate of body weight gain at the 28th postnatal day was less than 25% ($p=0.017$). The volumes of RBC transfusion also increased as follows: 60 mL/kg for gestational age <28 weeks, 22 mL/kg for gestational age 28 to 31 weeks, and 6.7 mL/kg for gestational age ≥32 weeks (Table 3).

Multiple regression analysis revealed that the volume of RBC transfusion decreased to 0.043 mL with an increased birth weight of one gram ($p=0.045$), suggesting that RBC transfusion volume increases by 4.3 mL when birth weight decreases by 100 g. Additionally, volume of RBC transfusion increased to 13.3 mL with increasing phlebotomy blood loss

Table 3. Risk of Transfusion According to Characteristics of the Subjects (Simple Logistic Regression Analysis)

	No. (%) of transfusion	RR (95% CI)	<i>p</i> value
Gestational age (wk ^{+day})	≥32 ⁺⁰	5/12 (41.7)	1.00
	28-32	20/23 (87.0)	2.09 (1.05-4.15)
	<28	14/15 (93.3)	2.24 (1.13-4.43)
Birth weight (g)	≥1000	26/35 (74.3)	1.00
	<1000	13/15 (86.7)	1.17 (0.88-1.54)
SGA	SGA	8/15 (53.3)	1.00
	AGA	31/35 (88.6)	1.66 (1.02-2.71)
Days to reach full feeding (postnatal day)	<20	20/29 (69.0)	1.00
	≥20	19/21 (90.5)	1.31 (0.99-1.74)
Duration of parenteral nutrition (days)	<21	15/25 (60.0)	1.00
	≥21	24/25 (96.0)	1.60 (1.15-2.23)
Rate of body wt. gain at 28th day (%)	≥25	14/23 (60.9)	1.00
	<25	25/27 (92.6)	1.52 (1.08-2.15)

RR, relative risk; 95% CI, 95% confidence interval of RR; *p* value, *p* value of RR; SGA, small for gestational age; AGA, appropriate for gestational age.

Table 4. Influencing Factors to Transfusion by Multiple Regression Analysis

	Coefficient (β)	Standard error	<i>p</i> value
Gestational age (wk ^{+day})	-0.377	0.251	0.141
Birth weight (g)	-0.043	0.021	0.045
Phlebotomy loss (mL/kg)	1.334	0.179	<0.001
Duration of parenteral nutrition (days)	1.012	0.327	0.003
Rate of body weight gain at 28th day (%)	-0.660	0.281	0.033

by 10 mL ($p<0.001$), 10.1 mL with prolonged parenteral nutrition by 10 days ($p=0.003$), and to 6.6 mL with a decreasing rate of body weight gain by 10% ($p=0.033$) (Table 4).

DISCUSSION

Immediately following birth, almost all infants experience varying degrees of anemia. The rapidity of developing anemia and its severity are determined by multiple physiologic and non-physiologic processes. The severity of developing anemia is most pronounced in the least mature preterm infants, and preterm infants are prone to developing severe cardiorespiratory and infectious illnesses, resulting in heavy laboratory blood loss during diagnosis and treatment.⁹

Our findings indicated that as gestational age and birth weight decreased, AOP became more severe and the risk of the need for RBC transfusions increased. When adjusted for gestational age and birth weight by multiple linear regression analysis, excessive blood loss from phlebotomy was the most important cause of anemia. In this study, the mean cumulative phlebotomy loss was 32 mL/kg (37 mL/kg in the transfusion group vs. 15 mL/kg in the non-transfusion group) by the completion of the study, which was the first eight weeks of life. Meyer, et al.¹⁷ previously reported a mean

cumulative phlebotomy loss of 22 mL/kg during hospital stay in extremely low birth weight infants (ELBWIs), which was less than our study. On the other hand, relatively large phlebotomy losses, ranging from 11 to 22 mL/kg per week among VLBWIs in the NICU, were reported during the first 6 weeks after birth in another previous study.⁹ Various factors may contribute to phlebotomy loss, including written guidelines that dictate the need for laboratory testing, behaviors among neonatologists regarding blood test ordering, the unavailability of cord blood sampling in postnatal labs at birth, and the unavailability of microtechniques for laboratory assays, among others. Accordingly, phlebotomy blood loss was previously reported as a primary cause of AOP, especially during the first few weeks of life.^{5,18} The need for RBC transfusions can be reduced by decreasing phlebotomy loss via the following: microsampling using capillary micro collection tubes, batching of blood labs, cord blood sampling in immediate postnatal labs, removing central lines as soon as possible, ordering labs judiciously, careful monitoring of phlebotomy loss, and the use of blood-testing devices operated at the bedside.¹⁹ According to a previous study, the introduction of a bedside point-of-care (POC) “analyzer” (a device that requires the permanent removal of blood) (iSTAT Corp, Princeton, NJ, USA) for blood gas analysis decreased phlebotomy loss to 30% and the number

of RBC transfusions to 43%, in comparison to a conventional pre-POC blood gas analyzer.¹⁸ In another study, an in-line POC “monitor” (a device that either returns blood to the infant after analysis or does not require blood removal) that withdraws blood through a central line to analyze blood gases decreased phlebotomy loss to 22%, RBC transfusion volumes to 33%, and transfusion frequency to 32%, compared to a conventional blood gas analyzer.⁵ These findings suggest that although there are several causes of AOP, the most important cause is excessive phlebotomy loss.

The total volume of RBC transfusions in this study was 39.4 ± 31.7 mL/kg among transfused infants, which is low in comparison to several other studies. Madan, et al.¹⁸ reported a volume of RBC transfusion of 78.4 mL/kg in a pre-POC group and 44.4 mL/kg in a post-POC group among ELBWIs.

Milking the umbilical cord,²⁰ delayed cord clamping,²¹ strict RBC transfusion guidelines,^{22,23} and the use of EPO³ might reduce the need for RBC transfusions in premature infants. Umbilical cord milking can retrieve up to 20 mL of placental blood.²⁴ In a previous report, umbilical cord milking, the milking of blood from approximately 20 cm of umbilical cord two to three times, increased initial Hb concentration and blood pressure, and reduced the need for RBC transfusions.²⁰ Moreover, umbilical cord milking did not lead to an increased risk of IVH in a previous study, which poses the potential to be an adverse effect of umbilical cord milking due to rapid volume overloading.²⁰ Additionally, the optimal timing at which to clamp the cord is under debate. Delayed cord clamping may lead to the need for placental transfusion, but may conflict with immediate resuscitation in preterm infants. On meta-analysis, delayed cord clamping between 30 and 120 seconds was shown to reduce the risk of IVH and the need for RBC transfusion compared to clamping within 30 seconds. These results might be due to an increased circulating blood volume and blood pressure secondary to placental transfusion.²¹

Concerns for Hb threshold for RBC transfusion remain unresolved. To complicate the matter, data from two large randomized control trials (RCT) revealed conflicting findings. One RCT concluded that more restrictive RBC transfusion guidelines were related to increased IVH, PVL, and apnea and bradycardia, compared to more liberal guidelines. Liberal and restrictive guidelines were defined as hematocrit levels maintained at >45% (liberal) and >34% (restrictive) in infants tracheally intubated for assisted ventilation, >38% (liberal) and >28% (restrictive) in infants with nasal-related continuous positive airway pressure or supplemental oxygen,

and >30% (liberal) and >22% (restrictive) in infants with neither positive pressure nor oxygen.²² The other RCT study suggested that restrictive guidelines did not increase the risk of death or IVH, PVL, BPD, or ROP. The restrictive guidelines were defined as Hb levels maintained at >10 g/dL during the first week and >6-7 g/dL after the second week of life in infants with neither positive pressure nor oxygen.²³ Some studies in support of the latter RCT concluded that RBC transfusions were associated with an increased risk of BPD and NEC,²⁵ or ROP.²⁶ In this study, BPD was increased in the transfusion group. Valieva, et al.²⁵ found that BPD was significantly increased according to increases in RBC transfusions among ELBWIs. Thus, RBC transfusions might be implicated in BPD, potentially due to increased oxidative stress caused by an increase in non-transferrin bound iron or inflammatory mediators present in stored blood products.^{27,28}

In the transfusion group, the day of reaching full feeding was delayed (23 vs. 13 days), and the volume of RBC transfusion was increased by 9.47 mL, which was delayed by 10 days. Additionally, a prolonged duration of parenteral nutrition was observed (24 vs. 11 days) in the transfusion group, and RBC transfusion volume increased by 10 mL upon a 10-day delay in the duration of parenteral nutrition. Moreover, the RR of RBC transfusion increased 1.60 times among patients whose duration of parenteral nutrition was longer than 3 weeks. Taken all together, we deduced the following: if full enteral feeding is delayed, the duration of parenteral nutrition and central venous catheter will be prolonged, and infection associated with central venous catheter and sepsis will increase, as observed in the present study, necessitating further blood tests. Finally, phlebotomy blood loss, anemia and RBC transfusion might increase, and body weight gain may be impeded due to delayed enteral feeding. Thus, we suggest that if full enteral feeding is achieved sooner, the need for RBC transfusions may be lessened. However, further prospective studies are needed to elucidate the relationships between aggressive enteral nutrition, anemia, and RBC transfusion.

An important cause of AOP is low EPO plasma level in premature infants.¹⁰ Preterm infants delivered before the third trimester are born prior to marked erythropoietic activity and before the bulk of iron is transported from mother to fetus through the placenta, resulting in a small circulating mass of RBCs and low iron stores.¹⁰ Decreased EPO levels in premature infants have been shown to be associated with the liver rather than the kidneys during the first few weeks

of life in premature births.¹ The liver is less sensitive to anemia than the kidneys, so hepatic EPO production to decreased RBCs is ineffective. The switching of EPO production from the liver to the kidneys is timed from conception, or post-conception age, and is not accelerated by preterm delivery. Thus, hepatic EPO production results in anemia in premature infants. EPO administration has been suggested for the treatment of AOP.³ Nevertheless, there are no data for the absolute indications, dosage, route of administration, timing of EPO, and effects of EPO administration. Some data suggested that EPO decreases the need for RBC transfusion,²⁹ although others have concluded that EPO does not decrease the need for RBC transfusion but rather increases adverse effects.¹⁷ Approximately 60% of fetal life iron stores are formed during the third trimester. Preterm infants born before the third trimester are typically iron deficient and exhibit decreased Hb formation, diminishing the efficacy of EPO administration in premature infants.³ As a result, EPO is not routinely used in treatment of the AOP, except in particular patients such as preterm infants born of Jehovah's Witness parents. Regarding cost effectiveness, EPO is not used in our NICU because, based on our experience, responses to EPO in AOP infants are minimal and the frequency of RBC transfusions is low in our NICU (1.84).

Other physiologic and non-physiologic factors may also contribute to AOP. Physiologic factors include a low set point of oxygen sensor (liver-to-kidney switch), rapid body growth, shortened RBC life span, and a left shift in oxygen dissociation curves at birth. Non-physiologic factors include those that are acquired and some that are iatrogenic, e.g. inadequate nutrient intake, such as protein, vitamins, and calories; non-laboratory blood loss; hemorrhage and infection. Laboratory blood loss is a non-physiologic contributor to AOP.⁹

The risk of RBC transfusion was decreased in SGA infants compared to AGA infants, and SGA occurred more frequently in the non-transfusion group in this study. Infants with SGA were more mature than AGA infants (gestational age 32⁺² weeks in SGA vs. 28⁺³ weeks in AGA), without any differences in birth weight (1078 g in SGA vs. 1102 g in AGA). Hb concentration at birth was higher in SGA infants than AGA infants (18.0 g/dL in SGA vs. 15.9 g/dL in AGA). Advanced gestational age and higher Hb concentration at birth in SGA infants might decrease the risk of RBC transfusion.

No objective criteria exist for administering RBC transfusions in premature infants. Currently, many NICUs allow

for hematocrits to fall to $\leq 21\%$ to reduce RBC transfusions. In a previous study, preterm infants with "not symptomatic" anemia and with a hematocrit of $\leq 21\%$ exhibited increased cardiac output and stroke volume, as well as large left ventricular end-diastolic and end-systolic dimensions, resulting in left ventricular dysfunction, and these abnormal parameters improved after RBC transfusion.³⁰ The decision to transfuse or not in "not symptomatic" preterm infants was left to the clinical judgment of the practitioner. Even though adaptations to anemia, such as increased cardiac output, were shown to improve after RBC transfusion, it remains to be seen whether chronic adaptations to anemia have long-term impacts, such as hypertension. Reducing RBC transfusion is not always the best course of action, and individualized RBC transfusion may be needed.

In conclusion, AOP was more severe in the smallest and least mature preterm infants, and RBC transfusion remains the only treatment for transfusion-dependent anemia. Thus, it is important to prevent this anemia by delayed cord clamping and cord milking at delivery, and reducing the amount of laboratory phlebotomy loss using cord blood sampling at admission, capillary micro collection tubes, and reducing frequencies of sampling. Even though these efforts were previously shown to prevent anemia, AOP is not completely preventable due to decreased erythropoietic activity. We found that improved neonatal intensive care and feeding strategies, such as achieving full enteral feeding earlier and reducing the duration of total parenteral nutrition, can reduce AOP and RBC transfusions. As the mechanism to reduce anemia is not known, further evaluation is needed.

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