Estimating blood needs for very-low-birth-weight infants

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BACKGROUND: Red blood cell (RBC) transfusions are crucial for the care of very-low-birth-weight (VLBW) infants. These infants frequently require multiple, small-volume RBC transfusions, with potential exposure to multiple donors. Optimal protocols provide dedicated RBC units to reduce exposures and avoid RBC wastage.
STUDY DESIGN AND METHODS: This study was a retrospective, single-institution review of RBC transfusions in VLBW infants. The RBC volume transfused during the entire hospitalization (VTH) and that transfused at 35 days were determined for all infants, 401 to 1250 g at birth, admitted to a Level III neonatal intensive care unit from January 1, 2000, through December 31, 2002. Multivariable models identified perinatal factors associated with volume transfused.
RESULTS: The 640-infant cohort had a median birth weight (BW) of 818 g and gestational age (GA) of 26 weeks. Most infants (546 or 85%) required at least one RBC transfusion. Median number of RBC transfusions was 3 (range, 0-30) and median volume transfused was 82 mL (range, 9-737 mL). Of 328 infants who received all transfusions within a 35-day period, only 5 (1.5%) required at least 200 mL. VTH was inversely related to BW and GA. Multivariable models identified BW, GA, age at first transfusion, and use of inotropes as variables associated with higher volume transfused.
CONCLUSION: Few VLBW infants use an entire RBC unit. One dedicated unit shared by two or more infants should meet their transfusion needs. GA, BW, and markers of illness severity predict increased RBC volume requirements.

Less than two decades ago, survival of extremely premature infants was rare. Today, smaller, more immature neonates survive[1] due to advances in supportive care that includes safe and effective blood replacement therapy. Rapid senescence of newborn (HbF) red blood cells (RBCs), insufficient erythropoiesis, and iatrogenic, phlebotomy-related blood losses contribute to the need for RBC transfusions in very-low-birth-weight (VLBW) infants. Newborn infants with cardiopulmonary or infectious complications of prematurity commonly receive multiple small-volume RBC transfusions.[2-5]

Until recently, VLBW infants received fresh RBC units, generally less than 7 days old, to avoid transfusing RBCs with low levels of 2,3-diphosphoglycerate and higher levels of extracellular potassium. Multiple investigators, however, have shown that transfusion of RBCs stored for as long as 35 to 42 days is safe and does not cause metabolic acidosis or hyperkalemia in VLBW infants.[6-10] The longer, usable shelf-life period for RBC units allows for transfusion of aliquots from the same, dedicated RBC unit until the newborn is discharged or the unit is depleted.[11]

Previous studies have demonstrated the feasibility of dedicated RBC unit protocols for VLBW infants.[7-10,12-15] Reserving blood units to individual patients is achievable,

ABBREVIATIONS: BW(s) = birth weight; GA(s) = gestational age(s); IVH = Intraventricular-parenchymal hemorrhage; PDA = patent ductus arteriosus; VLBW = very-low-birth-weight (infants); VT35 = total volume of blood given in the 35-day period after the first transfusion; VTH = total red cell volume transfused during their hospital stay.

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yet widespread application could lead to blood wastage. An optimal, neonatal, dedicated RBC unit protocol should include the predicted transfusion volume needed by VLBW infants at varying gestational ages (GAs) and/or birth weights (BWs) based on the presence or absence of risk factors for increased transfusion requirements.

Our objectives were to determine the volume of blood transfused to VLBW infants during their entire neonatal hospitalization and to identify perinatal and early neonatal clinical conditions that influence the total RBC volume transfused.

MATERIALS AND METHODS

Patient population

We studied all infants admitted to the University of Alabama at Birmingham Hospital, Regional Neonatal Intensive Care Unit, with birth weights between 401 and 1250 g, from January 1, 2000, to December 31, 2002. We obtained antenatal and postnatal patient characteristics, the number of RBC transfusions, and the total RBC volume transfused during their hospital stay (VTH) from an electronic clinical archive and medical records. For infants who received at least one transfusion, we also determined the total volume of blood given in the 35-day period after the first transfusion (VT35). The University of Alabama at Birmingham Hospital's Institutional Review Board for Human Use approved this clinical research protocol.

Blood transfusions

Although the decision to transfuse RBCs was based on an individualized, clinical assessment of each infant, attending neonatologists followed similar institutional guidelines for transfusion. Specifically, RBC transfusions were considered for mechanically ventilated infants in the acute phase of the respiratory distress syndrome when the hemoglobin (Hb) level was lower than 12 g per dL. For infants who required supplemental oxygen for respiratory insufficiency, RBC transfusions were considered when the Hb level was lower than 10 g per dL, and in stable infants who did not require supplemental oxygen, transfusions were considered when the Hb level was lower than 7 g per dL. Erythropoietin (EPO) was not used for prophylaxis or treatment of anemia during the study period.

The standard RBC volume per transfusion at our institution was 20 mL per kg based on body weight at the time of transfusion. Aliquots for transfusions were prepared in the hospital's transfusion service utilizing a sterile connecting device to attach a filter and syringe to the original unit. RBCs transfused to infants were stored either in AS-1 or CPDA-1 throughout the study period. All RBC units were leukoreduced before storage, cytomegalovirus-negative, and irradiated, but not concentrated, before transfusion.

Study definition of patient characteristics

- Maternal hypertension: if it preceded or started during the pregnancy.
- Premature prolonged rupture of membranes: that which occurred before 37 weeks of gestation and for more than 24 hours before delivery.
- Antenatal steroids: one or more doses administered before delivery to induce lung maturation.
- Resuscitation in the delivery room: any maneuvers, including bag and mask ventilation, endotracheal intubation, chest compressions, and/or medications.
- Nasal continuous positive airway pressure: continuous positive distending airway pressure given through nasal cannulae.
- Intermittent mandatory ventilation: ventilatory support performed through a pressure-limited, time-cycled ventilator.
- Inotropes: use of any vasoactive drug to support cardiovascular function.
- Patent ductus arteriosus (PDA): confirmed by echocardiogram.
- Intraventricular-parenchymal hemorrhage (IVH): diagnosed by head ultrasonography and interpreted based on the classification of Papile and coworkers[16] (Grades III and IV considered severe IVH).
- Pneumothorax: diagnosed clinically and/or radiologically.

Statistical analysis

Because the VTH and VT35 data were not normally distributed, a base 10 log transformation was applied. Univariate regression models identified perinatal and early neonatal clinical conditions associated with log VTH and log VT35. Variables with p values of 0.2 were included in multivariable models and nonsignificant variables were removed in a backward stepwise fashion. Final models for log VTH and log VT35 are presented. VTH and VT35 were also dichotomized with a cut point of 200 mL. This cut point was chosen because it represents the estimated transfusable volume from a RBC unit undergoing repeated, small-volume aliquot removals. Univariate and then multivariable logistic regressions modeling the probability of VTH and VT35 being at least 200 mL were then fit. All statistical analyses were performed with computer software (SAS Version 9.0, SAS Institute, Cary, NC).

RESULTS

Patient population

The RBC transfusion characteristics of 640 infants were analyzed. The median birth weight was 818 g (interquartile range, 668-1013 g) and the median GA was 26 weeks (interquartile range, 25-28 weeks). Of the total, 546 (85%)

patients received transfusions a median of 3 times (range, 1-30 times), for a total of 2847 transfusions administered during the study. Characteristics of the transfused infants are presented in Table 1.

The median VTH was 82 mL (range, 9-737 mL) and the median age at the first transfusion was 4 days (range, 0-59 days). Only 61 infants (11 percent of those transfused) received a VTH in excess of 200 mL. The median VTH was inversely related to the BW and GA (Fig. 1). The median VT35 was 63 mL (range, 9-285 mL). Of 328 infants who received all RBC transfusions within a 35-day period, only 5 (1.5%) required more than 200 mL.

Ninety-five patients (15%) never received transfusions during the hospitalization. Of those, 12 infants died, with 10 succumbing within the first 3 hospital days. When compared to VLBW infants who required RBC transfusion, surviving infants who never received transfusions were larger (median BW, 1070 g vs. 840 g at birth, $p < 0.001$) and later gestation (median GA, 29 weeks vs. 27 weeks, $p < 0.001$) and required less assisted ventilation, intermittent mandatory ventilation, and continuous positive airway pressure (all $p < 0.005$).

To determine whether the anticoagulant or additive solution had an effect on the total transfusion needs, we identified infants who were administered exclusively CPDA-1 or AS-1 blood and received all RBC transfusions within 35 days. CPDA-1 and AS-1 blood were used almost equally with a ratio of 1.07:1.00 for the 135 infants who met the above criteria. There was a nonsignificant increase of 0.3 mL of blood transfused to infants receiving only AS-1 blood.

TABLE 1. Characteristics of 546 VLBW infants transfused

Prenatal characteristics	
Premature prolonged rupture of membranes (%)	17
Maternal hypertension (%)	28
Cesarean delivery (%)	53
Antenatal steroids (%)	73
Postnatal characteristics	
Median GA in weeks (range)	26 (22-40)
Median birth weight in grams (interquartile range)	818 (668-1013)
Male (%)	49
African-American (%)	52
Apgar score at 5 min < 7 (%)	40
Resuscitation in the delivery room (%)	74
Nasal continuous positive airway pressure (%)	53
Intermittent mandatory ventilation (%)	75
Inotropes (%)	28
Pneumothorax (%)	6
PDA (%)	37
Grade III and/or IV IVH (%)	23
Transfusion characteristics	
Median age at first transfusion in days (range)	4 (0-59)
Median total volume transfused in mL (range)	82 (9-737)
Median volume transfused in 35 days in mL (range)	63 (9-285)

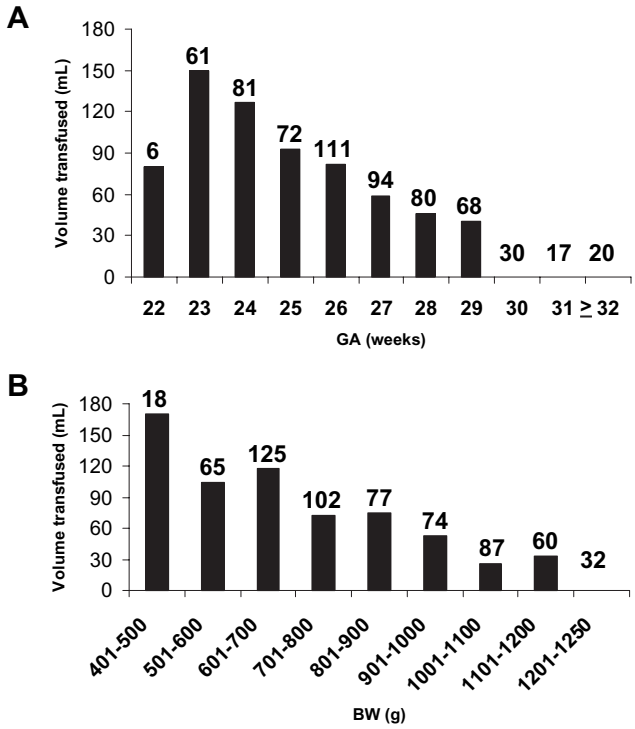

Fig. 1. Median volume transfused by GA (A) and by BW (B) in 640 VLBW infants. Numbers over the bars indicate the total number of infants included in each BW or GA category.

Multivariable models

BW, age at first transfusion, use of nasal continuous positive airway pressure, PDA, and the presence of Grades III and/or IV IVH were significantly associated with a higher VTH (Table 2). Similarly, BW, age at first transfusion, use of inotropes, PDA, and severe IVH were significantly associated with VT35.

Logistic regression analyses identified BW, age at first transfusion, inotrope requirement, and PDA as variables independently associated with VTH of at least 200 mL (Table 3). The single variable independently associated with RBC transfusion exceeding 200 mL for VT35 was GA.

DISCUSSION

The transfusion needs of individual VLBW infants vary considerably. During hospitalization, some but not all of these infants will receive multiple small-volume transfusions. We reasoned that assessing risk factors and clinical conditions before the first transfusion would improve our ability to estimate the RBC transfusion needs of VLBW infants. Such estimation of blood use could identify infants

who will require more RBC transfusions and who would benefit from having a dedicated RBC unit to decrease donor exposures. Similarly, risk-based estimates of blood use could identify those infants who are likely to require only one or no RBC transfusions for whom dedicating an entire RBC unit would be unnecessary and wasteful.

A number of observational studies[4,5,17-19] and randomized trials[20-22] have provided some insight into number and total volume of transfusions VLBW infants receive, as well as factors that modify transfusion practices in hospitalized infants (summarized in Table 4). The absolute number and total volume of transfusions for VLBW infants has fallen considerably in the past two decades, and there is marked variation between centers.[11,23] Relatively few reports have quantified the volume of RBCs transfused for the entire hospital stay (VTH) as we have done, and even fewer have examined clinical conditions associated with greater transfusion needs.

Our findings agree with prior studies that showed smaller and more immature infants have higher transfusion requirements.[20,21,24,25] We found a stepwise increase in the VTH transfused with shorter gestation and lower BW. Because of the large number of infants in our population, we showed that this relationship holds true even when analyzed in weekly GA and 100-g BW increments. The exception was for infants born at 22 weeks' GA, which is considered the threshold of viability and is associated with a mortality rate within the first 72 hours exceeding 90 percent.[1] Fewer infants at this GA survive long enough to require RBC transfusions. Larger infants with GA of more than 29 weeks or weighing more than 1200 g at birth were unlikely to require any transfusion.

TABLE 2. Variables from backward, stepwise regression used to create the multivariable model to predict transfusion volume in VLBW infants*

Variable	Estimate	p Value
BW (per 100-g interval)	–0.033	<0.0001
Age at first transfusion	–0.006	<0.0001
Nasal continuous positive airway pressure	0.078	0.008
PDA	0.135	<0.0001
Grade III and/or IV IVH	0.103	0.002

* Nonsignificant variables were eliminated in the regression analysis. Only significant variables are listed in the table. Variables with negative estimates predicted less total blood transfusion volume while those with positive estimates predicted increased total blood transfusion volume.

TABLE 3. Variables from backward, stepwise multivariable logistic regression model to predict blood transfusion volume of at least 200 mL in VLBW infants*

Variable	OR	95% CI
BW (per 100-g interval)	0.733	0.592-0.908
Age at first transfusion (days)	0.916	0.851-0.986
Inotropes	2.121	1.181-3.809
PDA	1.928	1.089-3.412

* Only significant variables are listed in the table. Variables with an odds ratio (OR) of less than 1 predicted a lower probability that an infant would receive at least 200 mL transfusion volume, whereas variables with ORs of more than 1 predicted a higher probability of at least 200 mL transfusion volume.

TABLE 4. Published studies reporting RBC transfusion volume given to VLBW infants

Year	First author	Number	BW (g)	Type of study	Period	RBC volume	Comments
1989	Donowitz[26]	75	500-2500	RRR		148*	
1998	Alagappan[27]	80	≤1250	HC	Before guidelines	156*	Increasingly restrictive transfusion guidelines
					After guidelines	119*	
1996	Widness[18]	150	≤1250	RRR	1982	82*	
					1989	85*	
					1993	50*	
1995	Shannon[21]	157	≤1250	RCT		37†	Control group value, 42-day study period
1997	Kling[25]	66	≤1500	RRR		48†	
1998	Bednarek[4]	825	≤1500	PO		38-96†	BW and illness severity affected volume
2000	Maier[5]	256	500-999	RRPD	1989	131†	Increasingly restrictive transfusion guidelines
					1991	98†	
					1995	37†	
2001	Beeram[28]	476	501-1500	RRR		41†	
2001	Franz[19]	140	<1250	RRPD		14†	
2001	Franz[19]	66	<750	RRPD		71†	Observation period Days 7-64

* Total volume (mL) of blood transfused,
† Volume as a function of BW (mL/kg BW).
Abbreviations: RRR = retrospective medical record review; HC = historical cohort; RCT = randomized controlled trial; PO = prospective observational study; RRPD = retrospective review of a prospectively collected data set.

Previous studies have also examined clinical variables influencing blood transfusions and found that GA, 5-minute Apgar score, transfusion during the first week, phlebotomy blood loss, and the Score for Neonatal Acute Physiology were significantly associated with greater transfusion requirements.[24,25] The best predictor of blood transfusion, alone or combined, however, appeared to be GA of less than 30 weeks.[24] In our population, we also found that earlier age at first transfusion and markers of severity of illness such as need for assisted ventilation, PDA, and severe intracranial hemorrhage were independent predictors of greater VTH. These latter predictors may be especially useful for estimation of eventual blood use because they are typically present early in the hospital course of VLBW infants and frequently before the first RBC transfusion is given.

Although 42 days is the usual shelf life of an AS-preserved unit,[2,10,12] the 35-day period we used is clinically relevant because products are typically 5 to 7 days old when received by the transfusion service. We chose 200 mL as the volume of each unit because this approximates the effective, usable volume of a multiply aliquoted blood unit.[8] Because we found that only 11 percent of transfused infants required more than 200 mL of RBCs during their hospital stay and even fewer (1.5%) used more than 200 mL for VT35, it would be an inefficient use of resources to "dedicate" a single unit to every hospitalized VLBW infant.[9]

The fact that our patient population was from a single center has both positive and negative implications. From one perspective, it limits variation in clinical practice, because there were accepted institutional guidelines to be followed by all attending neonatologists. Although we did not evaluate their adherence to the guidelines, the large number of patients studied would likely control for physician variation. Furthermore, none of our patients received EPO, which indicates good internal validity. In contrast, our data may not be fully applicable to centers where such adjunctive therapies are commonly used.

How much blood do hospitalized VLBW infants need? Although we showed that the total volume transfused increases with decreasing GA, only rarely do VLBW infants require an entire RBC unit when using conservative RBC transfusion practices. A single, dedicated RBC unit shared by two or more infants will likely meet their transfusion needs, while limiting donor exposures. This practice would also minimize blood wastage in hospitals caring for these infants. Factors that helped predict increased volume of blood used by VLBW infants were GA, BW, and markers of illness severity. Communication between the clinician and the hospital transfusion service is essential to decide whether a single or shared dedicated unit would be optimal for a given patient. We urge centers caring for such infants to perform internal reviews of transfusion practices and needs for these unique patients and, from those data, create a protocol for assigning one or more infants to a dedicated RBC unit.

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