Published in final edited form as:
Arch Dis Child Fetal Neonatal Ed. 2011 July ; 96(4): F249–F253. doi:10.1136/adc.2010.191023.

Acute Physiological Effects of Packed Red Blood Cell Transfusion in Preterm Infants with Different Degrees of Anemia

Laura K. Fredrickson[1], **Edward F. Bell**[1], **Gretchen A. Cress**[1], **Karen J. Johnson**[1], **M. Bridget Zimmerman**[2], **Larry T. Mahoney**[1], **John A. Widness**[1], and **Ronald G. Strauss**[1,3]

[1]Department of Pediatrics, University of Iowa, Iowa City, Iowa, USA

[2]Department of Biostatistics, University of Iowa College of Public Health, Iowa City, Iowa, USA

[3]Department of Pathology, University of Iowa, Iowa City, Iowa, USA

Abstract

Objective—The safe lower limit of hematocrit or hemoglobin that should trigger a red blood cell (RBC) transfusion has not been defined. The objective of this study was to examine the physiological effects of anemia and compare the acute responses to transfusion in preterm infants who were transfused at higher or lower hematocrit thresholds.

Methods—We studied 41 preterm infants with birth weights 500-1300 g, who were enrolled in a clinical trial comparing high ("liberal") and low ("restrictive") hematocrit thresholds for transfusion. Measurements were performed before and after a packed RBC transfusion of 15 ml/kg, which was administered because the infant's hematocrit had fallen below the threshold defined by study protocol. Hemoglobin, hematocrit, red blood cell count, reticulocyte count, lactic acid, and erythropoietin were measured before and after transfusion using standard methods. Cardiac output was measured by echocardiography. Oxygen consumption was determined using indirect calorimetry. Systemic oxygen transport and fractional oxygen extraction were calculated.

Results—Systemic oxygen transport rose in both groups following transfusion. Lactic acid was lower after transfusion in both groups. Oxygen consumption did not change significantly in either group. Cardiac output and fractional oxygen extraction fell after transfusion in the low hematocrit group only.

Conclusions—Our results demonstrate no acute physiological benefit of transfusion in the high hematocrit group. The fall in cardiac output with transfusion in the low hematocrit group shows that these infants had increased their cardiac output to maintain adequate tissue oxygen delivery in response to anemia and, therefore, may have benefitted from transfusion.

Keywords

Neonatology; haematology; circulatory; physiology; clinical procedures

Correspondence to Edward F. Bell, MD, Department of Pediatrics, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52240. edward-bell@uiowa.edu. Telephone: 319-356-4006. Telefax: 319-356-4685.

Competing Interests None.

Introduction

Transfusion with red blood cells is a common treatment for neonatal anemia. Approximately 300,000 small preterm infants are transfused annually, and the majority of very low birth weight (VLBW) infants (<1500 g) receive at least one RBC transfusion in the first weeks of life.[1,2] These large numbers rank small preterm infants as the most heavily transfused population of any hospitalized patient group. Several trials have examined the criteria used to guide transfusions and their impact on outcome,[3-5] yet clear guidance on the indications for transfusions remains elusive.[6,7] Little is known about the adaptive responses to anemia in VLBW infants and the effects of transfusion at various levels of anemia on the delivery and utilization of oxygen.[8-11] Consequently, transfusion guidelines are inconsistent, and transfusions are administered to premature infants often and repeatedly, using poorly defined indications. Despite the dearth of evidence regarding risks and benefits of allowing infants to be more anemic, there has been a trend toward use of more restrictive transfusion guidelines.[12-15] There is a critical need for further examination of both the adaptive responses to anemia of varying degree and the acute physiologic responses to transfusion at different levels of anemia.

To better understand the physiologic effects of anemia and the responses to transfusion, we performed paired measurements of lactic acid, cardiac output, and oxygen consumption before and after a standardized RBC transfusion in preterm infants who were participating in a randomized clinical trial comparing liberal (high hematocrit) and restrictive (low hematocrit) thresholds for transfusion.[3] We hypothesized that pretransfusion cardiac output and fractional oxygen extraction would be increased in the more anemic infants and would decrease following transfusion.

Methods

Patients

Preterm infants with birth weights between 500 and 1300 g who were enrolled (1992-1997) in the Iowa transfusion trial[3] were eligible for the current study if they had reached their hematocrit threshold for transfusion and were being mechanically ventilated via endotracheal tube - with fractional inspired oxygen concentration (F_iO_2) ≤0.50 and no detectable leak around the endotracheal tube - or if they required no respiratory support or supplemental oxygen. Airway leak was assessed by auscultation of the upper airway and carbon dioxide measurement in air sampled from the mouth. Infants with high F_iO_2 were excluded because of the impact of higher F_iO_2 on the accuracy of oxygen consumption measurement.[16] Infants with significant shunting through a patent ductus arteriosus or interatrial communication were excluded. Written consent was obtained from one or both parents. The study was approved by the University of Iowa institutional review board and registered with a national clinical trials registry (clinicaltrials.gov NCT00369005).

Study Design

The patients had been randomly assigned to be transfused using a “high” hematocrit transfusion threshold (liberal transfusion criteria) or “low” hematocrit transfusion threshold (restrictive transfusion criteria), as previously described.[3] Briefly, allocation of transfusion group was done by randomization within three birth weight strata: 500-750 g, 751-1000 g, and 1001-1300 g. The transfusion thresholds for all infants enrolled were dependent on the infants' requirements for respiratory support, which was used as a simplified indicator of overall condition. Infants who were mechanically ventilated were transfused if the hematocrit fell below 46% in the liberal group and 34% in the restrictive group. Infants requiring no ventilation assistance or supplemental oxygen were transfused if the hematocrit

fell below 30% in the liberal group and 22% in the restrictive group. There was also an intermediate phase of illness in the original trial,[3] in which infants were receiving nasal continuous positive airway pressure (CPAP) or supplemental oxygen without pressure support; infants in this phase were not eligible for the present study because of the technical difficulty of conducting oxygen consumption measurements in such infants.

The hematocrit was measured on a prescribed schedule from arterial blood samples or from capillary blood collected from free-flowing heel punctures, which were performed by using an automated capillary-sampling device (Tenderfoot Preemie or Tenderfoot Micro-preemie; ITC, Edison, NJ).[17] Hematocrit was measured each morning for those infants requiring assisted ventilation and twice weekly for infants not requiring assisted ventilation or supplemental oxygen. If the hematocrit was below the infant's transfusion threshold, the measurement was repeated. If the repeat hematocrit was also below the threshold, a transfusion of 15 ml/kg of packed RBCs was ordered. The RBCs were leukocyte reduced by filtration immediately after collection and stored in additive solutions for up to 42 days. The RBCs in solution were centrifuged shortly before transfusion to a hematocrit of 80 to 85%. The transfusion was administered by continuous infusion over 5 hours using a syringe pump.

Laboratory analyses and physiologic measurements were performed once it was determined that the infant would receive a transfusion but before the transfusion was begun. Blood was drawn for hemoglobin, hematocrit, red blood cell count, reticulocyte count, lactic acid level, and plasma erythropoietin. The hemoglobin, hematocrit, RBC count, reticulocyte count, and lactic acid level were measured in the hospital's clinical laboratories using standard methods. Erythropoietin level was determined by using a double-antibody radioimmunoassay.[18] Oxygen consumption was measured continuously for 2 to 4 hours using a portable, computerized indirect calorimetry system (MGM/jr, Utah Medical Products, Salt Lake City, UT) for infants receiving assisted ventilation,[16] and an open circuit, ventilated hood system for non-ventilated infants.[19] The measurement error for both systems is less than 5%.[16,19] Cardiac output was determined by using 2-dimensional and pulsed Doppler echocardiography.[20,21] This method has been validated in newborn infants.[22] The method offers technical challenges, and its reliability is operator dependent.[23,24] All cardiac output measurements were performed by a single echocardiographer and interpreted by a single cardiologist. Oxygen saturation was monitored continuously by pulse oximetry (N-200 or N-395; Nellcor, Hayward, CA) during the measurements of oxygen consumption and cardiac output. F_iO_2 was recorded periodically and averaged during the measurements of oxygen consumption and cardiac output. Arterial oxygen content and systemic oxygen transport were calculated using mean oxygen saturation assuming the oxygen-carrying capacity of hemoglobin to be 1.34 ml/g. Mixed venous oxygen content was calculated from oxygen consumption, cardiac output, and arterial oxygen content. Fractional oxygen extraction was calculated as oxygen consumption divided by systemic oxygen transport. These same measurements and calculations were repeated the following morning, after the transfusion.

Data Analysis

The target sample size was 44 infants, 22 per group, based on the number needed to demonstrate a decrease in fractional oxygen extraction of the size detected in the study of Alverson *et al*,[8] 0.07, with similar pooled standard deviation 0.09, 2-sided α 0.05, and β 0.20. This report includes all infants for whom the measurements of cardiac output and oxygen consumption were successfully completed, a total of 41 infants.

Laboratory and physiological measurements were compared between the high and low hematocrit groups before transfusion using unpaired t tests. A linear mixed model analysis

for repeated measures was used to test for changes from pre- to post-transfusion within each group and also to test for differences in mean response between the high and low hematocrit groups. The fixed effects in the model were transfusion group (high hematocrit threshold and low hematocrit threshold), time (pre and post), and group-time interaction. The test for group-time interaction effect corresponds to testing whether the change from pre- to post-transfusion differed between the high and low hematocrit groups. In addition, to test for specific comparisons of interest (i.e., comparing mean values between the high and low groups before and/or after transfusion, and testing for change from pre to post within each group), a test of mean contrast was performed using estimates from the fitted mixed model. To account for the number of tests performed (2 to test for between group difference; 2 to test for time effect), Bonferroni's method was used to adjust the p-values, with a Bonferroni-adjusted p-value <0.05 considered as statistically significant.

For some of the variables, the distribution was skewed, with most of the data values having low values and a few extreme high values. To normalize the data distribution, logarithmic transformation was applied to the values, and the log-transformed data were used in the analysis. For these variables, the mean estimates were computed by back-transformation of the log means.

Results

Of the 100 infants enrolled in the randomized clinical trial,[3] 41 were enrolled also in this study, 22 in the high hematocrit group and 19 in the low hematocrit group. Those not enrolled were excluded for the following reasons: they were being treated with nasal CPAP or supplemental oxygen, for which methods to measure oxygen consumption were not available; the necessary study equipment and personnel were not available; insurmountable technical problems rendered the cardiac output or oxygen consumption measurements uninterpretable; or the parents did not consent. Patient characteristics were similar between infants in the high hematocrit and low hematocrit groups (Table 1).

Before transfusion, the hemoglobin, hematocrit, RBC count, arterial oxygen content, systemic oxygen transport, and mixed venous oxygen concentration were significantly higher in the high hematocrit group than in the low hematocrit group (Table 2). Reticulocyte count, blood lactic acid, plasma erythropoietin, cardiac output, mean F_iO_2, and mean oxygen saturation were not significantly different between high and low groups. Fractional oxygen extraction was significantly higher in the low hematocrit group than in the high hematocrit group. Oxygen consumption was also higher in the low hematocrit group, but not significantly so (P=0.235).

After transfusion, hemoglobin, hematocrit, RBC count, arterial oxygen content, systemic oxygen transport, and mixed venous oxygen content remained higher in the high hematocrit group than in the low hematocrit group (Table 2). Reticulocyte count, blood lactic acid, plasma erythropoietin, cardiac output, oxygen consumption, mean F_iO_2, and mean oxygen saturation were not significantly different between groups. Fractional oxygen extraction was higher in the low hematocrit group than in the high hematocrit group following transfusion.

Both groups of infants experienced significant increases in hemoglobin, hematocrit, RBC count, arterial oxygen content, systemic oxygen transport, and mixed venous oxygen content following transfusion (Table 2). There was no significant change with transfusion in reticulocyte count, plasma erythropoietin concentration, oxygen consumption, mean F_iO_2, or mean oxygen saturation for either group. Cardiac output and fractional oxygen extraction fell after transfusion in the low hematocrit only; cardiac output fell from 301 ± 101 to 253 ± 66 ml/min per kg (P=0.048), and fractional oxygen extraction fell from 0.31 ± 0.11 to 0.24 ±

0.12 (P=0.003). There was no significant change in cardiac output or fractional oxygen extraction with transfusion in the high hematocrit group. Blood lactic acid level was significantly lower following transfusion in both groups.

There was no significant difference between the transfusion groups in the magnitude of change after transfusion in any of the following: hemoglobin, hematocrit, RBC count, reticulocyte count, blood lactic acid, plasma erythropoietin concentration, cardiac output, arterial oxygen content, oxygen consumption, systemic oxygen transport, fractional oxygen extraction, mean oxygen saturation, and mixed venous oxygen content. There was a statistically significant (P=0.020) but clinically unimportant difference in the change in mean F_iO_2, which increased slightly after transfusion in the liberal group (from 0.31 to 0.32) and decreased slightly in the restrictive group (from 0.32 to 0.31).

Discussion

In this study examining the cardiovascular and metabolic adaptive responses to anemia and the acute physiological responses to transfusion in infants transfused at higher or lower hematocrit thresholds, we found that small preterm infants have appropriate adaptive responses to anemia and that these responses can be mitigated by transfusion, at least in those infants whose hematocrits were allowed to fall to lower levels before transfusion.

As a result of the study transfusion protocol, the low hematocrit group had significantly lower hemoglobin, hematocrit, RBC count, arterial oxygen content, systemic oxygen transport, and mixed venous oxygen content before transfusion. Moreover, because the infants in both groups received the same volume of transfusion, 15 ml/kg, these values remained lower in the low hematocrit group after transfusion. With similar arterial oxygen saturation, the lower hemoglobin in the low group results in lower arterial oxygen content, which, unless offset by decreased oxygen consumption, leads to lower systemic oxygen transport and mixed venous oxygen content. In our study, the groups had similar oxygen consumption, so the mixed venous oxygen content was lower in the low hematocrit group, both before and after transfusion. With less oxygen available in the blood, the larger fractional oxygen extraction in the low hematocrit group was necessary in order to deliver to the tissues the oxygen needed for normal aerobic metabolism.

The significant increases in hemoglobin, hematocrit, RBC count, arterial oxygen content, systemic oxygen transport, and mixed venous oxygen content following transfusion in both groups were expected, as these occur with any RBC transfusion. RBC transfusion is used as treatment for anemia to increase oxygen carrying capacity by increasing hemoglobin concentration, with the goal of increasing oxygen supply to the tissues. The higher pre-transfusion fractional oxygen extraction in the low hematocrit group indicates the need for more efficient oxygen use in these anemic infants, and the fall in their fractional oxygen extraction indicates a more generous oxygen supply after transfusion. With more oxygen available after tranfusion, a smaller fraction must be extracted to supply the tissues. The decrease in cardiac output seen after transfusion in the low hematocrit group, but not in the high hematocrit group, indicates that the infants in the low group had increased their cardiac output in an effort, only partly successful, to maintain their systemic oxygen transport. Other investigators have also found that cardiac output decreases after transfusion in anemic preterm infants.[9,10,25] Significant change was neither expected nor observed in reticulocyte count, plasma erythropoietin concentration, mean F_iO_2, or mean oxygen saturation. Oxygen consumption did not change with transfusion in either group. Had oxygen consumption been elevated in the low hematocrit group before transfusion, as a result of increased cardiac work for example, a decrease might have been anticipated with transfusion, as described previously by several other groups of investigators.[8,26] Blood lactic acid decreased after

transfusion in both groups, suggesting that tissue hypoxia may have been present before transfusion.

Infants transfused at a lower hematocrit threshold responded differently to transfusion than those transfused at a higher threshold. The decrease in cardiac output and fractional oxygen extraction after transfusion in the low hematocrit group indicate possible physiological benefit from transfusion that was not experienced by infants in the high hematocrit group. In particular, benefit may result from correcting the metabolic cost of increased cardiac work in the most anemic patients, allowing redirection of energy from this purpose to others, including energy storage for growth. The increased cardiac output and fractional oxygen extraction seen in the more anemic group of infants before transfusion are expected signs of compensation. It is not known, however, whether the most critically ill preterm infants – whom we did not study – have this same adaptive capability.

With sufficient anemia, cardiac output and fractional oxygen extraction are increased in preterm infants, and these values normalize after transfusion. These changes are not seen in infants who are transfused at higher hematocrits. Because of the technical challenges of measuring oxygen consumption, we were not able to study infants with the full range of illness severity. Consequently, these results should be interpreted with caution.

What is already known on this topic?

- Elevated cardiac output, oxygen consumption, and fractional oxygen extraction have been reported inconsistently in anemic preterm infants; some reports have described decreases in one or more of these with transfusion.
- Previous investigations have not focused on the degree of anemia as it affects these measures and their response to transfusion.

What this study adds

- We examined the physiological adaptations to anemia in preterm infants enrolled in a trial comparing two sets of hematocrit thresholds for transfusion.
- Cardiac output and fractional oxygen extraction fell after transfusion in the low hematocrit group but not in the high hematocrit group.

Acknowledgments

This study was supported by National Institutes of Health grants P01 HL46925 and M01 RR00059. We thank the parents who permitted their infants to participate in this study, and we thank the physicians and nurses of the University of Iowa Children's Hospital NICU, without whose cooperation this study would not have been possible.

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Table 1

Patient characteristics

	High Hematocrit Group (n=22)	Low Hematocrit Group (n=19)
Birth weight* (g)	895 (551-1230)	920 (630-1230)
Gestational age* (wk)	27 (24-33)	27 (24-30)
Postnatal age at study* (d)	24 (6-85)	30 (24-31)
Weight at study* (g)	1046 (758-2020)	1130 (797-1800)
Number of males	11	11
Number mechanically ventilated at time of study	18	16

*Values given are median and range

Table 2

Laboratory and physiological measurements before and after transfusion

	High Hematocrit Group			Low Hematocrit Group		
	Pre-Transfusion	**Post-Transfusion**	***P****	**Pre-Transfusion**	**Post-Transfusion**	***P****
Hemoglobin, g/dl	13.6 (1.0)	16.3 (1.6)	<0.0001	9.1 (1.4) *a*	13.1 (1.4) *b*	<0.0001
Hematocrit, %	39 (7)	48 (5)	<0.0001	27 (4) *a*	38 (4) *b*	<0.0001
RBC count, × 10^6/μl	4.1 (0.7)	5.4 (0.6)	<0.0001	2.9 (0.5) *a*	4.2 (0.6) *b*	<0.0001
Reticulocyte count, × 10^3/μl	53 (20)	62 (19)	0.412	53 (16)	61 (21)	0.586
Blood lactic acid, mmol/l	1.1 (0.2)	0.7 (0.1)	<0.0001	1.1 (0.2)	0.9 (0.2)	0.032
Plasma erythropoietin, mU/ml	16 (6)	14 (6)	0.596	16 (7)	14 (5)	0.609
Cardiac output, ml/min per kg	291 (98)	277 (91)	0.402	301 (101)	253 (66)	0.048
Arterial oxygen content, ml/dl	16 (2)	20 (3)	<0.0001	12 (2) *a*	17 (2) *b*	<0.0001
Oxygen consumption, ml/min per kg	8.1 (1.5)	8.1 (1.1)	>0.99	10.0 (1.7)	9.0 (1.1)	0.279
Systemic oxygen transport, ml/min per kg	44 (7)	57 (12)	0.004	33 (4) *a*	41 (5) *b*	0.001
Fractional oxygen extraction	0.20 (0.08)	0.17 (0.08)	0.250	0.31 (0.11) *a*	0.24 (0.12) *b*	0.003
Mean F_iO_2	0.31 (0.09)	0.32 (0.10)	0.561	0.32 (0.11)	0.31 (0.12)	0.055
Mean oxygen saturation, %	96 (3)	96 (3)	0.563	96 (3)	95 (2)	0.333
Mixed venous O_2 content, ml/dl	13 (2)	17 (2)	<0.0001	8 (2) *a*	13 (3) *b*	<0.0001

Values are mean (SD)

*Pre-Transfusion vs Post-Transfusion

a $P<0.05$, Pre-Transfusion Low vs Pre-Transfusion High

b $P<0.05$, Post-Transfusion Low vs Post-Transfusion High