Journal of the American Heart Association

ORIGINAL RESEARCH

Red Blood Cell Transfusion After Stage I Palliation Is Associated With Worse Clinical Outcomes

Felina K. Mille, MD; Aditya Badheka, MD, MS; Priscilla Yu, MD; Xuemei Zhang, MS; David F. Friedman, MD; John Kheir, MD; Sarah van den Bosch, MS; Antonio G. Cabrera, MD; Javier J. Lasa, MD, FAAP; Hannah Katcoff, MPH; Paula Hu, CCRC, RN, MSPH; Santiago Borasino, MD; Krissie Hock, RN, MSN, CNL; Jordan Huskey, BS; Jamie Weller, MD; Harsh Kothari, MD; Joshua Blinder, MD

BACKGROUND: Packed red blood cell transfusion may improve oxygen content in single-ventricle neonates, but its effect on clinical outcomes after Stage 1 palliation is unknown.

METHODS AND RESULTS: Retrospective multicenter analysis of packed red blood cell transfusion exposures in neonates after Stage 1 palliation, excluding those with intraoperative mortality or need for extracorporeal membrane oxygenation. Transfusion practice variability was assessed, and multivariable regression used to identify transfusion risk factors. After propensity score adjustment for severity of illness, clinical outcomes were compared between transfused and nontransfused subjects. Of 396 subjects, 323 (82%) received 930 postoperative red blood cell transfusions. Packed red blood cell volume (median 9–42 mL/kg [$P<0.0001$]), donor exposures (1–2 [$P<0.0001$]), transfusion number (1–3 [$P<0.0001$]), and pretransfusion hemoglobin (12.1–13 g/dL, $P=0.0049$) varied between sites. Cyanosis ($P=0.02$), chest tube output ($P=0.0003$), and delayed sternal closure ($P=0.0033$) increased transfusion risk. Transfusion was associated with prolonged mechanical ventilation (6 [interquartile range 4, 12] versus 3 [1, 5] days, $P=0.02$) and intensive care unit stay (19 [12, 33] versus 9 [6, 19] days, $P=0.016$). When stratified by number of transfusions (0, 1, or >1), duration of mechanical ventilation (3 [1, 5] versus 4 [3, 6] versus 9 [5, 16] days [$P<0.0001$]) and intensive care unit stay (9 [6, 19] versus 13 [8, 25] versus 21 [13, 38] days [$P<0.0001$]) increased for those transfused more than once. Most subjects who died were transfused, though the association with mortality was not significant.

CONCLUSIONS: Packed red blood cell transfusion after Stage 1 palliation is common, and transfusion practice is variable. Transfusion is a significant predictor of longer intensive care unit stay and mechanical ventilation. Further studies to define evidence-based transfusion thresholds are warranted.

Key Words: congenital heart disease ■ neonates ■ Norwood operation ■ red blood cell transfusion ■ single ventricle ■ stage I palliation

Limited oxygen delivery in critical illness may lead to end-organ dysfunction. It is well established that organ dysfunction is associated with prolonged intensive care unit (ICU) hospitalization and higher risk of death.[1–4] Neonates after congenital heart surgery have limited cardiovascular reserve due to myocardial immaturity, preload sensitivity, and a relatively fixed stroke volume, which may limit oxygen delivery.[5] Neonates with single ventricle physiology undergoing Stage I palliation (S1P), also known as the Norwood operation, face additional challenges, including lower ventricular mass with parallel

Correspondence to: Felina K. Mille, MD, Division of Cardiac Critical Care, Department of Anesthesiology and Critical Care Medicine, The Children's Hospital of Philadelphia, 3401 Civic Center Blvd., Room 8554 Philadelphia, PA 19104. E-mail: millef@email.chop.edu

This article was handled independently by Francis Miller, MD as a guest editor. The editors had no role in the evaluation of the manuscript or in the decision about its acceptance.

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Retrospective review of packed red blood cells transfusion in neonates after Stage I palliation showing significantly longer intensive care unit stay and longer duration of mechanical ventilation in transfused patients after propensity score adjustment for severity of illness.
- This is the first multicenter study on the topic and the first to stratify subjects by severity of illness.

What Are the Clinical Implications?

- This population has sometimes been thought to require a higher hemoglobin concentration to maintain adequate oxygen delivery.
- These findings, along with those published by Dr. Chollette et al showing that single ventricle patients can safely tolerate lower hemoglobin than previously thought, highlight the need for evidence-based transfusion thresholds in this population.

Nonstandard Abbreviations and Acronyms

ECMO	extracorporeal membrane oxygenation
ICU	intensive care unit
PRBC	packed red blood cells
S1P	Stage I palliation, Norwood operation

systemic and pulmonary circulations, obligate systemic cyanosis, and higher combined cardiac output. This further increases their risk of postoperative low cardiac output syndrome and death.[6,7]

Packed red blood cell (PRBC) transfusions increase hemoglobin concentration and thus oxygen carrying capacity of the bood.[8] Because oxygen delivery depends directly on cardiac output, hemoglobin concentration, and oxygen saturation, many practitioners target higher hemoglobin levels in cyanotic, single ventricle patients.[9] Neunhoeffer et al demonstrated that PRBC transfusion improved cerebral oxygenation and reduced cerebral oxygen extraction in infants undergoing surgery, including those undergoing single ventricle palliation.[10]

However, the potential benefits of PRBC transfusion must be weighed against associated risks. Transfusions are associated with multiorgan system dysfunction, transfusion associated acute lung injury, prolonged mechanical ventilator support, prolonged vasoactive infusion requirement, hospital-acquired infections, and increased mortality in critically ill children, including those recovering from cardiac surgery.[9,11–14] Furthermore, the TRIPICU (Transfusion Strategies for Patients in Pediatric Intensive Care Units) study failed to identify impaired oxygenation or worse outcomes with a restrictive PRBC transfusion strategy in a cohort of critically ill children, including a subset of acyanotic children undergoing cardiac surgery.[14,15] Cholette et al reported similar findings among subjects undergoing neonatal cardiac surgery and those recovering from bidirectional Glenn and Fontan palliations[16,17]

There are limited data informing PRBC transfusion practice in cyanotic neonates with single ventricle physiology, with the few, single-center studies yielding inconsistent findings. Kuo et al showed that PRBC transfusion given for hemoglobin below 12.3 g/dL improved diastolic blood pressure, arterial oxygen saturation, and cerebral near-infrared regional spectroscopy.[18] Gupta et al found no association between increasing PRBC transfusion and mortality, ICU length of stay, or duration of mechanical ventilation, whereas others found an association between higher hematocrit and mortality after S1P.[19,20]

Given the paucity of data informing PRBC transfusion after S1P, we sought to describe postoperative transfusion practices and to assess for associations between PRBC transfusion and patient outcomes. We hypothesized that PRBC transfusion practice after S1P is variable across centers and that PRBC transfusion is associated with worse clinical outcomes.

MATERIALS AND METHODS

Study Design

We performed a multicenter, retrospective cohort study of postoperative PRBC transfusion practice in all subjects undergoing S1P at 6 academic pediatric cardiac surgical centers. Contributing centers included The Children's Hospital of Philadelphia, Boston Children's Hospital, University of Iowa Stead Family Children's Hospital, Texas Children's Hospital, University of Alabama Birmingham, and University of Texas Southwestern Medical Center. All neonates aged <30 days who underwent S1P, with either a modified Blalock-Taussig shunt or a right ventricle to pulmonary artery (Sano) shunt, between January 1, 2012 and December 31, 2016 were included. Subjects with intraoperative mortality and those who required extracorporeal membrane oxygenator (ECMO) support during the study period were excluded. We chose to exclude those who required ECMO support because many institutions use ECMO-related blood product transfusion protocols. Subjects were identified from each center's surgical database. The study was approved by the

institutional review board at The Children's Hospital of Philadelphia and locally at each participating center. The need for informed consent was waived.

Data Collection

Demographic, preoperative, intraoperative, and postoperative variables were abstracted from available surgical and medical databases, as well as each institution's electronic medical record. The data that support the findings of this study are available from the corresponding author upon reasonable request. Preoperative data variables included demographic and diagnostic information and echocardiographic and clinical features associated with worse outcomes.[21–23] Intraoperative variables included the details of the surgical repair, cardiac support times, and intraoperative blood product administration. Postoperative data were collected for the first 14 days after surgery, from the time subjects left the operating room. This study period represents the mean postoperative cardiac intensive care unit stay after S1P at the lead author's center. Postoperative data variables, including severity of illness markers, such as peak vasoactive-inotropic score, peak lactate, and lowest arterial oxygen saturation, were collected.[24,25] Outcome data, including in-hospital mortality, duration of mechanical ventilation, ICU length of stay (LOS) were collected until death or hospital discharge.

All blood product transfusions given during the study period were recorded. This included the number of PRBC transfusions and total PRBC volume (in mL/kg), as well as the number of individual PRBC donor exposures. Pretransfusion hemoglobin and hematocrit were recorded; these were the last available values prior to PRBC order to define clinicians' transfusion threshold. Individual donor exposures were defined as number of unique PRBC unit numbers to which the subject was exposed.

No participating center had a PRBC transfusion protocol at the time of the study. Transfusions were administered at the treating clinicians' discretion. Indications for PRBC transfusion were inconsistently recorded in the medical record and, therefore, were not included in this study.

Outcome Measures

The primary exposure was PRBC transfusion during the first 14 postoperative days. Our primary outcome was postoperative ICU length of stay. Secondary outcomes were in-hospital mortality, duration of mechanical ventilation, and incidence of postoperative infection.

Statistical Analysis

Standard descriptive statistics were applied. Continuous variables are presented as median (interquartile range). Categorical variables are presented as numbers and percentages. Characteristics of subjects who did and did not receive PRBC transfusion were compared using the Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables. Variability in rates of transfusion was assessed using a chi-square test. The Kruskal–Wallis test was used to assess for between center variability in number of transfusions, donor exposures, and pretransfusion hemoglobin and hematocrits. Multivariable regression analysis identified independent risk factors for PRBC transfusion. Center, as a random intercept, was controlled for in the regression model. Propensity score stratification was used to balance the difference in baseline characteristics of transfused and nontransfused subjects for the outcome analysis. Patients were stratified into 5 subsets (strata) using quintiles of propensity score for transfusion. Characteristics included in the propensity score model were center, prematurity (<37 weeks gestational age), peak vasoactive-inotropic score, peak lactate, restrictive atrial septum, preoperative ventricular dysfunction, greater than mild preoperative atrioventricular valve regurgitation, delayed sternal closure, native ascending aorta <2 mm, cardiopulmonary bypass time, chest tube output on postoperative days zero and one, and birth weight <2.5 kg. Continuous outcomes such as length of ICU stay were compared using a linear mixed effect model, adjusting for propensity score strata as a fixed effect and center as a random intercept. Categorical outcomes, such as death or infection, were compared using stratified logistic regression controlling for propensity score strata and site. To attempt to assess whether worse outcomes were associated with PRBC transfusion or higher hematocrit value, as suggested in prior studies, we divided our cohort into 2 groups based on first quartile of hematocrit during the study period and compared study outcomes between these 2 groups. Then, log transformed duration of mechanical ventilation and ICU stays were compared using a mixed effect model, controlling for site, transfusion, and age at surgery.

RESULTS

Description of Transfusion Practice

Of 465 subjects who underwent S1P during the study period, 396 were included in our analysis. There were differences in baseline characteristics between centers (Table 1). Specifically, the incidence of chromosomal abnormalities and echocardiographic variables varied. This may be related to ascertainment bias. There were variations in the rates of delayed sternal closure, use of intraoperative fresh whole blood, and cardiac support times.

PRBC transfusion was common. A total of 323 subjects (82%) received 930 postoperative transfusions, with statistically significant (P<0.0001) variation in rates

Table 1. Patient Characteristics by Center

	Overall (N=396)	Site 1 (N=122)	Site 2 (N=91)	Site 3 (N=11)	Site 4 (N=81)	Site 5 (N=32)	Site 6 (N=59)	*P* Value
Age at surgery (d), mean	5 (4, 7)	5 (4, 7)	4 (3, 5)	8 (5, 11)	7 (5, 9)	6 (5, 7)	5 (4, 8)	<0.0001
Race								
White	241 (71%)	68 (56%)	26 (79%)	7 (64%)	69 (85%)	20 (63%)	51 (86%)	<0.0001
Black	44 (13%)	21 (17%)	3 (9%)	0 (0%)	3 (4%)	12 (38%)	5 (8%)	
Other	53 (16%)	33 (27%)	4 (12%)	4 (36%)	9 (11%)	0 (0%)	3 (5%)	
Sex								
Female	148 (37%)	49 (40%)	32 (35%)	3 (27%)	26 (32%)	14 (44%)	24 (41%)	0.7202
Male	248 (63%)	73 (60%)	59 (65%)	8 (73%)	55 (68%)	18 (56%)	35 (59%)	
Gestational age (wk), mean	39 (38, 39)	39 (38, 39)	39 (38, 39)	38 (38, 39)	39 (38, 39)	39 (38, 39)	39 (38, 39)	0.1331
Birth weight <2500 g	29 (7%)	9 (7%)	7 (8%)	2 (18%)	5 (6%)	2 (6%)	4 (7%)	0.8428
Chromosomal abnormality	56 (14%)	23 (19%)	8 (9%)	5 (45%)	2 (2%)	0 (0%)	18 (31%)	<0.0001
Genetic syndrome	30 (8%)	14 (11%)	2 (2%)	0 (0%)	4 (5%)	3 (9%)	7 (12%)	0.0783
Delayed sternal closure	159 (40%)	39 (32%)	31 (34%)	0 (0%)	77 (95%)	0 (0%)	12 (20%)	<0.0001
Ascending aorta size <0.2 cm^3	79 (22%)	18 (15%)	23 (26%)	3 (27%)	10 (14%)	14 (45%)	11 (26%)	0.0038
Ascending aorta Z score	−4 (−5, −2)	−4 (−5, −2)	−4 (−5, −2)	−4 (−5, −3)	−4 (−5, −2)	−5 (−5, −3)	−4 (−4, −2)	0.3461
Lowest oxygen saturation	62 (54, 67)	63 (57, 68)	59 (53, 65)	65 (61, 69)	55 (47, 64)	68 (60, 71)	65 (54, 68)	<0.0001
Preoperative moderate or severe atrioventricular valve regurgitation	34 (9%)	16 (13%)	5 (6%)	2 (18%)	9 (11%)	0 (0%)	2 (3%)	0.0491
Preoperative ventricular dysfunction	84 (21%)	14 (11%)	26 (29%)	1 (9%)	5 (6%)	6 (19%)	32 (54%)	<0.0001
Restrictive atrial septum								
No restriction	254 (65%)	78 (64%)	62 (68%)	10 (91%)	42 (55%)	28 (88%)	34 (58%)	0.0278
Mild restriction	123 (31%)	42 (34%)	25 (27%)	0 (0%)	31 (41%)	3 (9%)	22 (37%)	
Requiring intervention	14 (4%)	2 (2%)	4 (4%)	1 (9%)	3 (4%)	1 (3%)	3 (5%)	
Total cardiopulmonary bypass time	133 (98, 169)	85(78, 97)	163 (139, 206)	180 (162, 211)	131 (116, 147)	129 (115, 166)	184 (162, 200)	<0.0001
Cross clamp time	65 (48, 90)	44 (39, 51)	98 (74, 131)	0 (0, 56)	68 (59, 75)	59 (48, 69)	98 (88, 112)	<0.0001
Circulatory arrest time	15 (6, 41)	44 (39, 50)	15 (7, 25)	0 (0, 0)	4 (2, 6)	17 (4, 43)	9 (8, 13)	<0.0001
Peak postoperative lactate	7 (5, 10)	5 (2, 8)	10 (8, 12)	10 (7, 15)	7 (6, 8)	10 (5, 13)	6 (5, 7)	<0.0001
Maximum vasoactive-inotropic score	13 (8, 17)	8 (5, 10)	20 (15, 24)	22 (15, 29)	14 (12, 17)	17 (15, 21)	7 (5, 11)	<0.0001
Intraoperative use of whole blood	157 (41%)	102 (84%)	52 (57%)	0 (%)	3 (4%)	0 (0%)	0 (0%)	<0.0001
Chest tube drainage 2 d, mL/kg	35 (11, 60)	11 (7, 22)	53 (39, 70)	51 (35, 79)	73 (60, 93)	43 (36, 60)	9 (6, 15)	<0.0001

Table 2. Rates of PRBC Transfusion Vary Significantly Between Study Centers

	Overall (N=396)	Site 1 (N=122)	Site 2 (N=91)	Site 3 (N=11)	Site 4 (N=81)	Site 5 (N=32)	Site 6 (N=59)	*P* Value
Received PRBC transfusion	323 (82%)	89 (73%)	87 (96%)	11 (100%)	67 (83%)	27 (85%)	42 (71%)	<0.0001

The rates of packed red blood cell transfusion were uniformly high, but varied significantly between participating centers, ranging from 71% to 100% transfused. PRBC indicates packed red blood cell.

of transfusion between centers (Table 2). As shown in Table 3, the number of individual PRBC transfusions per patient ($P<0.0001$), total volume of PRBC transfusion ($P<0.0001$), and number of unique donor exposures ($P<0.0001$) also varied. Pretransfusion hemoglobin and hematocrit values were more uniform. Median pretransfusion hemoglobin ranged 12.1 to 13.0 g/dL ($P=0.0049$) and hematocrit ranged 37% to 38.4% ($P=0.054$) at all centers.

Risk factors for PRBC transfusion differed across centers. Univariate regression analysis performed for each center identified delayed sternal closure, lower oxygen saturation, chest tube drainage, and use of intraoperative whole blood as potential transfusion risk factors. On multivariable regression analysis of the entire cohort, oxygen saturation ($P=0.02$), delayed sternal closure ($P=0.0033$), and chest tube drainage ($P<0.0003$) were significant risk factors for PRBC transfusion (Table 4).

PRBC Transfusion and Outcomes

When transfused and nontransfused subjects were compared, transfusion was associated with prolonged mechanical ventilation (median 6 [interquartile range 4, 12] versus 3 [1, 5] days, $P=0.02$) and ICU LOS (19 [12, 33] versus 9 [6, 19] days, $P=0.016$). To assess for a dose-dependent association, all subjects (N=396) were divided into 3 groups: not transfused, 1 transfusion, and more than 1 transfusion during the study period. After correcting for propensity score strata, those receiving more than one transfusion had longer duration of mechanical ventilation and ICU LOS (Table 5). Median duration of mechanical ventilation differed between the groups (3 [1, 5] days for nontransfused, 4 [3, 6] days for one transfusion, and 9 [5, 16] days for >1 transfusion, $P<0.0001$). Similarly, subjects receiving more PRBC transfusions had significantly longer ICU LOS (median 9 [6, 19] versus 13 [8, 25] versus 21 [13, 38] days, $P<0.0001$). Most subjects who died (25 of 27) received PRBC transfusion, though there was no statistically significant association between PRBC transfusion and death ($P=1.00$). Rates of infection did not vary between transfused and nontransfused groups.

Hematocrit and Outcomes

When we divided the cohort based on subjects' average hematocrit (lower than the first quartile [<40] and not), subjects with higher mean hematocrits had longer duration of mechanical ventilation (6 [4–12] versus 5 [3–9] days, $P=0.029$) and longer ICU LOS (19 [11–32] versus 14 [9–25] days, $P=0.017$). However, this relationship disappeared after adjusting for surgical center and transfusion status, and mean hematocrit during the study period was not independently associated with study outcomes.

Table 3. Variation in Transfusion Practice Across Centers

Site	PRBC Transfusion Volume (median in mL/kg [IQR])	PRBC Transfusion Events Median (IQR)	PRBC Donor Exposures Median (IQR)	Pretransfusion Hemoglobin (Median in mg/dL [IQR])	Pretransfusion Hematocrit (%)
Overall	29.8 (15.2, 49.4)	2 (1, 3)	2 (1, 3)	12.8 (11.9, 13.7)	37.9 (35.6, 40.1)
1	25.6 (16.4, 42.9)	1 (1, 2)	1 (1, 2)	12.8 (12, 13.5)	38 (35.3, 40)
2	41.6 (16.4, 42.9)	3 (2, 5)	2 (1, 3)	13 (12, 13.9)	38.1 (35.9, 39.9)
3	35.7 (30.9, 101.9)	3 (3, 8)	1 (1, 3)	12.5 (11.6, 13.3)	38 (35, 40)
4	37.9 (25.2, 59.3)	3 (2, 4)	2 (2, 3)	13 (12.1, 14)	38.4 (35.7, 41.2)
5	32.6 (19.7, 56.1)	2 (1, 3)	2 (1, 3)	12.1 (11.6, 13)	37.1 (35.6, 40)
6	9.4 (0, 14)	1 (0, 1)	Data not available	12.4 (11.6, 13.3)	37 (34, 39.5)
P value	<0.0001	<0.0001	<0.0001	0.0049	0.054

Packed red blood cell (PRBC) transfusion volume, events, and donor exposures varied significantly between centers whereas pretransfusion hemoglobin and hematocrit were more uniform. IQR indicates interquartile range.

DISCUSSION

In this large, multicenter cohort of neonates who underwent S1P, the majority (82%) received at least 1 postoperative PRBC transfusion. Transfusion practice varied between centers in the number and volume of transfusions given and number of donor exposures, though transfusion thresholds were relatively consistent. After adjusting for severity of illness, postoperative PRBC transfusion was significantly associated with longer ICU LOS and longer duration of mechanical ventilation. We identified no association between PRBC transfusion and death or infection.

To our knowledge, this is the only multicenter study focused on PRBC transfusion practice after S1P. The larger sample size achieved by this multicenter approach allowed us to study variability in transfusion practices and to adjust for severity of illness covariates while assessing for a relationship between PRBC transfusion and study outcomes. Additionally, pooling data from multiple centers adds to the generalizability of our study. Our study assessed not only PRBC transfusion volume but also donor exposures, as recommended by the Pediatric Critical Care Transfusion and Anemia Initiative.[26]

Table 4. Multivariable Regression Analysis of Risk Factors for Packed Red Blood Cell Transfusion

Effect	Odds Ratio	95% CI	*P* Value
Oxygen saturation	0.96	0.93, 1.00	0.02
Total cardiopulmonary bypass time	1.01	0.99, 1.02	0.46
Peak post-op lactate	1.03	0.92, 1.14	0.66
Circulatory arrest time	0.99	0.96, 1.03	0.73
Maximum vasoactive-inotropic score	1.01	0.95, 1.07	0.79
Chest tube drainage 2 d, mL/kg	1.05	1.02, 1.08	0.0003
Delayed sternal closure	6.74	1.89, 24.02	0.0033
Received whole blood intraoperatively	3.28	0.97, 11.09	0.06

The optimal transfusion threshold in neonates after S1P remains undefined. PRBC transfusion given to maintain a hemoglobin of 12.3 g/dL is reported to improve diastolic blood pressure, oxygen saturation, and cerebral near-infrared regional spectroscopy.[18] This is consistent with the transfusion thresholds found in our study. Polycythemia and higher hematocrit have been associated with longer hospitalization and early mortality in cyanotic neonates after S1P, though our data did not demonstrate such a relationship.[20,27] Additionally, no difference in lactate or markers of oxygen delivery were found in single ventricle subjects with Glenn or Fontan physiology randomized to restrictive (hemoglobin <9 g/dL) versus liberal (hemoglobin >13 g/dL) transfusion strategies.[17] The same was found in a heterogeneous group of infants undergoing heart surgery that included a small number of cyanotic, single ventricle subjects.[16] These trials suggest that lower transfusion thresholds may be safe, even in cyanotic infants with single ventricle physiology. Our findings support these conclusions.

We previously conducted a survey of pediatric critical care physicians and found significant variability in PRBC transfusion practice.[28] PRBC transfusion thresholds were driven by patient rather than practitioner or center-related variables. Our study identified oxygen saturation, delayed sternal closure, and chest tube output as the variables most predictive of PRBC transfusion, further indicating that PRBC transfusion is mainly driven by patient-related variables. However, the relatively uniform transfusion thresholds between centers also suggest center-specific practices may influence the incidence of relative anemia.

We found a significant association between postoperative PRBC transfusion and worse patient outcomes. Our findings support those previously reported in other critically ill pediatric subjects and suggest that limiting PRBC transfusion, even in cyanotic, single-ventricle neonates, may be prudent.[8,11,12,14,30] The proposed pathophysiology of PRBC transfusion is multifactorial. Stored PRBCs may develop "storage lesions," leading

Table 5. PRBC Transfusion Is Significantly Associated With Longer Duration of Mechanical Ventilation and Length of Intensive Care Unit Stay

	Overall	No Transfusion	One Transfusion	>1 Transfusion	*P* Value	*P* Value 1 vs >1 PRBC Transfusion (Adjusted)	*P* Value 0 vs 1 PRBC Transfusion (Adjusted)
	(N=396)	(N=73)	(N=111)	(N=212)	(Unadjusted)		
Length of mechanical ventilation, d	6 (3, 11)	3 (1, 5)	4 (3, 6)	9 (5, 16)	<0.0001	<0.0001	0.43
Length of intensive care unit stay	17 (11, 31)	9 (6, 19)	13 (8, 25)	21 (13, 38)	<0.0001	<0.0001	0.059
Infection (wound infection, sepsis)	34 (9%)	5 (7%)	9 (8%)	20 (9%)	0.79	1	1
Death	27 (7%)	2 (3%)	7 (6%)	18 (8%)	0.22	1	0.65

When comparing between strata, those receiving >1 transfusion during the study period had significantly longer intensive care unit length of stay and duration of mechanical ventilation. PRBC indicates packed red blood cell.

to impaired oxygen delivery, free radical release, and scavenging of endogenous nitric oxide.[31–32] It is unclear if the age of transfused blood products contributes significantly to transfusion complications, and we did not record the age of PRBCs used in this study. Though the risk of transfusion reaction or transmission of a communicable disease is thankfully extremely low, these complications occur disproportionately in children.[33] Transfusion-related immunomodulation and transfusion associated acute lung injury are well-recognized inflammatory complications of PRBC transfusion that carry significant morbidity and mortality and may be underrecognized in children.[8] These may be partially mitigated by modern leukoreduction techniques.[34] Finally, transfusions are associated with increased thrombotic complications in neonates undergoing cardiac surgery.[13,35]

This study has several limitations. The first is its retrospective design, which exposes it to bias from unmeasured severity of illness variables and selection bias affecting the decision to transfuse. Though we used a propensity score to adjust for subjects' severity of illness, it is impossible to fully account for all important covariates in critically ill subjects. There is likely a collinearity between severity of illness and transfusion requirement, which cannot be fully adjusted for. For example, intubated patients may require additional laboratory testing and progress to iatrogenic anemia requiring PRBC transfusion. Technical performance score was not included in our propensity score adjustment, though this may be an important variable.[36] Additionally, there were differences in the patient populations between sites (Table 1). This may partially explain the PRBC transfusion practice variability we observed. This variation also prevented us from using some known predictors of poor outcome, such as the presence of a genetic syndrome in our propensity score, as ascertainment appeared to vary between sites. Though we made an effort to standardize data collection between centers, the observed differences may also reflect variation in data collection. We could not reliably determine the indication for each PRBC transfusion, and thus, cannot comment on considerations involved in the decision to transfuse. We excluded subjects who required ECMO support during the early postoperative period. The decision to exclude these subjects was based on the hypothesis that PRBC transfusion may be protocolized in the setting of mechanical support. However, this may have biased our analysis by excluding the most critically ill subjects, and those with the highest transfusion burden. As the majority of subjects who died during the study period received postoperative ECMO, excluding these subjects may have caused us to underestimate any association between PRBC transfusion and death. We did not include intraoperative transfusions and postoperative transfusion of additional blood products in this

study. Such an analysis is planned. Finally, cerebral near-infrared regional spectroscopy data were not available from all participating centers. This has been used as a proxy of mixed venous oxygen saturation and would be helpful to assess for a physiologic difference in subjects who did and did not receive PRBC transfusions.

In conclusion, PRBC transfusion was independently associated with longer length of stay in a cardiac intensive care unit and longer duration of mechanical ventilation in this multicenter retrospective cohort. Further, the relationship was dose dependent, with subjects who received more than 1 PRBC transfusion doing worse than those exposed to only one. This retrospective study is, at most, hypothesis generating. However, because PRBC transfusion may carry risk, and lower transfusion thresholds than those we found may be tolerated even in cyanotic, single ventricle subjects, we underscore the need for a multicenter, randomized controlled trial to define the optimum transfusion threshold for this fragile population.

ARTICLE INFORMATION

Received November 14, 2019; accepted March 27, 2020.

Affiliations

From the Children's Hospital of Philadelphia, Philadelphia, PA (F.K.M., X.Z., D.F.F., H. Katcoff, P.H., J.B.); University of Iowa Stead Family Children's Hospital, Iowa City, IA (A.B., H. Kothari); University of Texas Southwestern Medical Center, Dallas, TX (P.Y., J.W.); Boston Children's Hospital, Boston, MA (J.K., S.v.d.B.); Texas Children's Hospital, Houston, TX (A.G.C., J.J.L.); University of Alabama at Birmingham, AL (S.B., K.H., J.H.).

Acknowledgments

We are grateful for the thoughtful feedback and contributions of Drs Chitra Ravishankar, Janet Kwiatkowski, and Robert Levy.

Sources of Funding

This work was supported in part by The Cardiac Center Research Core at The Children's Hospital of Philadelphia.

Disclosures

None.

REFERENCES

1. Proulx F, Joyal J, Mariscalco M, Leteurtre S, Leclerc F, Lacroix J. The pediatric multiple organ dysfunction syndrome. *Pediatr Crit Care Med*. 2009;10:12–22.
2. Leteurtre S, Martinot A, Duhamel A, Proulx F, Grandbastien B, Cotting J, Gottesman R, Joffe A, Pfenninger J, Hubert P, et al. Validation of the paediatric logistic organ dysfunction (PELOD) score: prospective, observational, multicentre study. *Lancet*. 2003;362:192–197.
3. Graciano A, Balko J, Rahn D, Ahmad N, Giroir B. The Pediatric Multiple Organ Dysfunction Score (P-MODS): development and validation of an objective scale to measure the severity of multiple organ dysfunction in critically ill children. *Crit Care Med*. 2005;33:1484–1491.
4. Watson R, Crow S, Hartman M, Lacroix J, Odetola F. Epidemiology and outcomes of pediatric multiple organ dysfunction syndrome (MODS). *Pediatr Crit Care Med*. 2018;18:1–27.
5. Wolf A, Humphry A. Limitations and vulnerabilities of the neonatal cardiovascular system: considerations for anesthetic management. *Paediatr Anaesth*. 2014;24:5–9.
6. Feinstein J, Benson D, Dubin A, Cohen M, Maxey D, Mahle W, Pahl E, Villafae J, Bhatt A, Peng L, et al. Hypoplastic left heart syndrome: current considerations and expectations. *J Am Coll Cardiol*. 2012;59:S1–S42.
7. Ohye R, Schonbeck J, Eghtesady P, Laussen P, Pizarro C, Shrader P, Frank D, Graham E, Hill K, Jacobs J, et al. Cause, timing, and location of death in the Single Ventricle Reconstruction trial. *J Thorac Cardiovasc Surg*. 2013;144:907–914.
8. Guzzetta N. Benefits and risks of red blood cell transfusion in pediatric patients undergoing cardiac surgery. *Paediatr Anaesth*. 2011;21:504–511.
9. Mazine A, Rached-D'Astous S, Ducruet T, Lacroix J, Poirier N. Blood transfusions after pediatric cardiac operations: a North American multicenter prospective study. *Ann Thorac Surg*. 2015;100:671–677.
10. Neunhoeffer F, Hofbeck M, Schuhmann M, Fuchs J, Schlensak C, Esslinger M, Gerbig I, Icheva V, Heimberg E, Kumpf M, et al. Cerebral oxygen metabolism before and after RBC transfusion in infants following major surgical procedures. *Pediatr Crit Care Med*. 2018;19:318–327.
11. Bateman ST, Lacroix J, Boven K, Forbes P, Barton R, Thomas N, Jacobs B, Markovitz B, Hanson J, Li H, et al. Anemia, blood loss, and blood transfusions in North American children in the intensive care unit. *Am J Respir Crit Care Med*. 2008;178:26–33.
12. Kneyber M, Grotenhuis F, Berger R, Ebels T, Burgerhof J, Albers M. Transfusion of leukocyte-depleted RBCs is independently associated with increased morbidity after pediatric cardiac surgery. *Pediatr Crit Care Med*. 2013;14:298–305.
13. Anderson B, Blancha V, Duchon J, Chai P, Kalfa D, Bacha E, Krishnamurthy G, Ratner V. The effects of postoperative hematocrit on shunt occlusion for neonates undergoing single ventricle palliation. *J Thorac Cardiovasc Surg*. 2017;153:947–955.
14. Lacroix J, Hébert P, Hutchison J, Hume H, Tucci M, Ducruet T, Gauvin F, Collet JP, Toledano B, Robillard P, et al. Transfusion strategies for patients in pediatric intensive care units. *N Engl J Med*. 2007;536:2213–2224.
15. Willems A, Harrington K, Lacroix J, Biarent D, Joffe A, Wensley D, Ducruet T, Hébert P, Tucci M. Comparison of two red-cell transfusion strategies after pediatric cardiac surgery: a subgroup analysis. *Crit Care Med*. 2010;38:649–656.
16. Cholette J, Swartz M, Rubenstein J, Henrichs K, Wang H, Powers K, Daugherty L, Alfieris G, Gensini F, Blumberg N. Outcomes using a conservative versus liberal red blood cell transfusion strategy in infants requiring cardiac operation. *Ann Thorac Surg*. 2017;103:206–215.
17. Cholette J, Rubenstein J, Alfieris G, Powers K, Eaton M, Lerner N. Children with single-ventricle physiology do not benefit from higher hemoglobin levels post cavopulmonary connection: results of a prospective, randomized, controlled trial of a restrictive versus liberal red-cell transfusion strategy. *Pediatr Crit Care Med*. 2011;12:39–45.
18. Kuo J, Maher K, Kirshbom P, Mahle W. Red blood cell transfusion for infants with single-ventricle physiology. *Pediatr Cardiol*. 2011;32:461–468.
19. Gupta P, King C, Benjamin L, Goodhart T, Robertson M, Gossett J, Pesek G, DasGupta R. Association of hematocrit and red blood cell transfusion with outcomes in infants undergoing Norwood operation. *Pediatr Cardiol*. 2015;36:1212–1218.
20. Blackwood J, Joffe A, Robertson C, Dinu I, Alton G, Penner K, Ross D, Rebeyka I. Association of hemoglobin and transfusion with outcome after operations for hypoplastic left heart. *Ann Thorac Surg*. 2010;89:1378–1384.
21. Tabbutt S, Ghanayem N, Ravishankar C, Tabbutt S, Sleeper L, Cooper D, Frank D, Lu M, Pizarro C, Frommelt P, et al. Risk factors for hospital morbidity and mortality after the Norwood procedure: a report from the Pediatric Heart Network Single Ventricle Reconstruction trial. *J Thorac Cardiovasc Surg*. 2012;144:882–895.
22. Gaynor J, Mahle W, Cohen M, Ittenbach R, Decampli W, Steven J, Nicolson S, Spray T. Risk factors for mortality after the Norwood procedure. *Eur J Cardiothorac Surg*. 2002;22:82–89.
23. Shamszad P, Gospin T, Hong B, Mckenzie E, Petit C. Impact of preoperative risk factors on outcomes after Norwood palliation for hypoplastic left heart syndrome. *J Thorac Cardiovasc Surg*. 2010;147:897–901.
24. Wernovsky G, Wypij D, Jonas R, Mayer J, Hanley F, Hickey P, Walsh A, Chang A, Castañeda A, Newburger J, et al. Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. *Circulation*. 1995;92:2226–2235.
25. Gaies M, Gurney J, Yen A, Napoli M, Gajarski R, Ohye R, Charpie J, Hirsch J. Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr Crit Care Med*. 2010;11:234–238.
26. Cholette J, Willems A, Valentine S, Bateman S, Schwartz S. Recommendations on RBC transfusion in infants and children with acquired

and congenital heart disease from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative. *Pediatr Crit Care Med*. 2018;19:S137–S148.
27. Siehr S, Zhongkai H, Bo J, Bruce L, Shin A. Exploring the role of polycythemia in patients with cyanosis after palliative congenital heart surgery. *Pediatr Crit Care Med*. 2016;17:216–222.
28. Badheka A., Yu P., Mille F, Durbin D., Elci O., & Blinder, J. Red cell transfusion practices after stage 1 palliation: A survey of practitioners from the Pediatric Cardiac Intensive Care Society. *Cardiology in the Young*, 2019;29:1452–1458.
29. Kneyber M, Hersi M, Twisk J, Markhorst D, Plötz F. Red blood cell transfusion in critically ill children is independently associated with increased mortality. *Intensive Care Med*. 2007;33:1414–1422.
30. Schechter A, Gladwin M. Hemoglobin and the paracrine and endocrine functions of nitric oxide. *N Engl J Med*. 2003;348:1483–1485.
31. Kor D, Van Buskirk C, Gajic O. Red blood cell storage lesion. *J Vet Emerg Crit Care*. 2009;9:187–199.
32. García-Roa M, Del Carmen Vicente-Ayuso M, Bobes A, Pedraza A, González-Fernández A, Martín M, Sáez I, Seghatchian J, Gutiérrez L. Red blood cell storage time & transfusion: current practice, concerns & future perspectives. *Blood Transfus*. 2017;15:222–231.
33. Morley S. Red blood cell transfusions in acute paediatrics. *Arch Dis Child Educ Pract Ed*. 2009;94:65–73.
34. Bilgin Y, van de Watering L, Brand A. Clinical effects of leucoreduction of blood transfusions. *Neth J Med*. 2011;69:441–450.
35. Faraoni D, Emani S, Halpin E, Bernier R, Emani S, Dinardo J, Ibla J. Relationship between transfusion of blood products and the incidence of thrombotic complications in neonates and infants undergoing cardiac surgery. *J Cardiothorac Vasc Anesth*. 2017;31:1943–1948.
36. Nathan M, Sleeper L, Ohye R, Frommelt P, Caldarone C, Tweddell J, Lu M, Pearson G, Gaynor W, Pizarro C. Technical performance score is associated with outcomes after the Norwood procedure. *J Thorac Cardiovasc Surg*. 2014;148:2209–2212.