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Comprehensive Analysis of Liberal and Restrictive Transfusion Strategies in Pediatric Intensive Care Unit

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ABSTRACT

Background: We prospectively compared restrictive and liberal transfusion strategies for critically ill children regarding hemodynamic and laboratory parameters.

Methods: A total of 180 children requiring packed red blood cells (PRBCs) were randomized into two groups: the liberal transfusion strategy group (transfusion trigger < 10 g/dL, Group 1) and the restrictive transfusion strategy group (transfusion trigger ≤ 7 g/dL, Group 2). Basal variables including venous/arterial hemoglobin, hematocrit and lactate levels; stroke volume; and cardiac output were recorded at the beginning and end of the transfusion. Oxygen saturation, noninvasive total hemoglobin, noninvasive total oxygen content, perfusion index (PI), heart rate and systolic and diastolic blood pressures were assessed via the Radical-7 Pulse co-oximeter (Masimo, Irvine, CA, USA) with the Root monitor, initially and at 4 h.

Results: In all, 160 children were eligible for final analysis. The baseline hemoglobin level for the PRBC transfusion was 7.38 ± 0.98 g/dL for all patients. At the end of the PRBC transfusion, cardiac output decreased by 9.9% in Group 1 and by 24% in Group 2 ($p < 0.001$); PI increased by 10% in Group 1 and by 45% in Group 2 ($p < 0.001$). Lactate decreased by 9.8% in Group 1 and by 31.68% in Group 2 ($p < 0.001$).

Conclusion: Restrictive blood transfusion strategy is better than liberal transfusion strategy with regard to the hemodynamic and laboratory values during the early period. PI also provides valuable information regarding the efficacy of PRBC transfusion in clinical practice.

KEYWORDS: children, erythrocyte transfusion liberal strategy, pediatric intensive care, restrictive strategy

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BACKGROUND

Critically ill children have a high incidence of anemia at the time of admission and during their pediatric intensive care unit (PICU) stay [1, 2]. The use of the packed red blood cell (PRBC) transfusion is common, with approximately 17–50% of all PICU patients receiving transfusions [1–5]. Based on hemoglobin, a transfusion threshold of ≤7 g/dL for hemoglobin is as safe as the more liberal a transfusion threshold of <10 g/dL for critically ill adults and children without hemodynamic instability in terms of RBC transfusion risks [2, 6–12]. However, little is known about the effects of RBC transfusion on oxygen delivery and utilization. Until recently, there has been no noninvasive study that has evaluated detailed information about hemodynamic and tissue oxygenation parameters such as cardiac output (CO), perfusion index (PI) and hemoglobin oxygen content for liberal and restricted transfusion strategies. These may provide an opportunity to develop patient-specific clinical assessments for PRBC transfusion. Therefore, we aimed to compare liberal and restrictive transfusion strategies regarding circulatory and laboratory parameters for critically ill children.

METHODS

Study design

This study was performed at a PICU between January 2014 and December 2015. It was funded by the Erciyes University Scientific Research Unit (registration number TSA-2014-5299). A total of 200 critically ill children between 1 month and 16 years of age who had expected PICU stay of more than 24 h were included in the study. After obtaining informed consent, 20 patients were excluded from the study. Exclusion criteria were as follows: severe respiratory failure (patients receiving more than 0.6 FiO_2, positive end expiratory pressure ≥ 10 cmH_2O or high-frequency oscillatory ventilation more than 12 h prior to transfusion), cyanotic congenital heart disease, hemodynamic instability (mean systemic arterial pressure <2SD of the normal mean for age or requirement of increase in cardiovascular support for at least 2 h before enrollment), hemolytic anemia and acute blood loss [2, 6]. The remaining patients (*n*: 180) were randomly assigned to liberal (transfusion trigger <10 g/dL, Group 1) or restrictive (trigger ≤7 g/dL, Group 2) transfusion strategy group. Randomization was provided by a coin toss. If one child received more than one transfusion during intensive care stay, the first transfusion was considered for the study. Enrolled patients received 10 mL/kg PRBC over 4 h. All PRBC units were prepared containing equal amounts of hemoglobin and hematocrit via ALYX ComPonent System (Baxter) Health Care to administer standard hemoglobin and hematocrit to patients during transfusion.

DATA COLLECTİON AND PROCEDURES

Procedures

A disposable optical finger sensor (Rainbow Butterfly, Revision K, Masimo Corporation, Irvine, CA, USA) was placed on the ring finger of the nondominant hand of each subject and connected to the Root Pulse co-oximeter (Masimo, Irvine, USA).

Data collection

Basal variables including venous/arterial hemoglobin, hematocrit and lactate levels; heart rate; systolic and diastolic blood pressure; CO; SPHb (total hemoglobin); SPOC (oxygen content); and PI were recorded both at the beginning (T0) and at the end (T4) of the transfusion. SPHb, SPOC and PI were assessed via the Radical-7 Pulse co-oximeter (Masimo, Irvine, CA, USA). Additionally, demographic data, PRISM III, PELOD, reason and the number of transfusion, length of mechanical ventilator and PICU stay and survival were recorded from the medical chart.

Cardiac output measurement

-Cardiologists who assessed the CO measurements were blinded to treatment allocations. Echocardiographic studies were performed with a GE-System equipped with 3 to 7 MHz for two-dimensional and color flow Doppler mapping by two experienced pediatric cardiologists. There was agreement between two pediatric cardiologists. CO was calculated by transthoracic echocardiography, using the left ventricular outflow tract (LVOT) Doppler method. The following equations were used:

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$$\text{Cardiac output} = \text{heart rate} \times \text{stroke volume};$$

$$\text{Stroke volume} = \text{LVOT area} \times \text{LVOT VTI or} = \text{Pi}\ (\text{LVOT diameter}/2)^2 \times \text{LVOT VTI}.$$

The LVOT diameter was measured in the parasternal long axis in the systole. The LVOT velocity time integral (VTI) provides information regarding blood velocity across the period across the systole and in units of centimeters (cm). The LVOT pulsed wave Doppler in either the apical long axis or the chamber view and the VTI can be traced out on the ultrasound machine or using digital software offline.

Data statistical analysis

This was a non-inferiority trial and analysis was conducted with the use of the per-protocol approach. The required sample size was 132 to detect increase of 10% in PI levels in the group treated according to the restrictive transfusion strategy with an overall two-sided $\alpha = 0.05$ and power of 90%. Considering the probability of subject attrition, we included 180 patients in our study. Statistical analysis was performed using SPSS version 22.0 (IBM, Armonk, NY). The normality of parametric data was analyzed by the Shapiro Wilk test. Numerical variables were expressed as mean ± SD or median. Comparisons between groups for data with a normal distribution were performed using Student's *t*-test, and the comparisons between groups for data that did not show a normal distribution were performed using the Mann–Whitney U test. Categorical variables were compared using the χ^2 test. The bivariate correlation tests were used to analyze the correlations. A two-sided $p < 0.05$ was considered statistically significant.

RESULTS

One patient (loss of data) in Group 1 and 19 patients (loss of data and inappropriate monitoring) in Group 2 were excluded from this study. One hundred sixty children met all of the eligibility criteria for final analysis (Fig. 1). The median ages were 36 months (24–84 months) for Group 1 and 72 months (38–84 months) for Group 2. The reasons for PRBC transfusion included the following: low hemoglobin ($n = 106$, 66.25%), respiratory failure ($n = 34$, 21.25%) and bone marrow suppression/coagulopathy ($n = 20$, 12.5%). Patient characteristics on admission and outcome are summarized in Table 1. Changes in hemodynamic and other laboratory parameters during PRBC transfusion are presented in Table 2. CO decreased by 9.9% in Group 1 and by 24% in Group 2 ($p < 0.001$); PI increased by 10% in Group 1 and 45% in Group 2 ($p < 0.001$). Lactate decreased by 9.8% in Group 1 and by 31.68% in Group 2 ($p < 0.001$). The correlation analyses between Δ% PI and Δ% CO and Δ% PI and Δ% lactate are presented in Table 3. The interaction of SPOC and SPHb measurements, SPOC and SPO_2 are presented in Table 4.

DISCUSSION

The discovery in recent years that adopting a lower transfusion trigger (Hb ≤ 7 g/dL) had no adverse consequences and the potential risks of RBC transfusions has become apparent in transfusion practice [2, 13–16]. However, it is unclear why PRBC transfusions are associated with worse outcomes for critically ill patients. To our knowledge, there are only a few studies that explain the impact of PRBC transfusion on hemodynamic parameters and tissue oxygenation in critically ill patients [17–21]. This is the first study which compares liberal and restrictive transfusion regimens in terms of hemodynamic effects and laboratory parameters in the PICU. A significant number of intensivists use PRBC to increase systemic delivery of oxygen (DO_2) in critically ill children [22]. Anemia decreases the ability of blood to deliver oxygen due to a lower hemoglobin level [23, 24]. Global DO_2 is dependent on CO and the oxygen content of arterial blood (CaO_2). CO, stroke volume and heart rate significantly decreased at the end of the transfusion in both groups. Similarly, systolic and diastolic blood pressure levels significantly increased in both groups, too. However, Δ% change of CO between baseline and after transfusion was higher in Group 2 than in Group 1. We thought that the inverse ratio between blood viscosity and flow velocity may cause a disproportional decrease in CO in Group 2. Hudson *et al.* reported an increase in CO, but it was not statistically significant in anemic preterm infants. They also reported that red cell volume may be a good indicator for determining benefits from transfusion [19]. Another transfusion study

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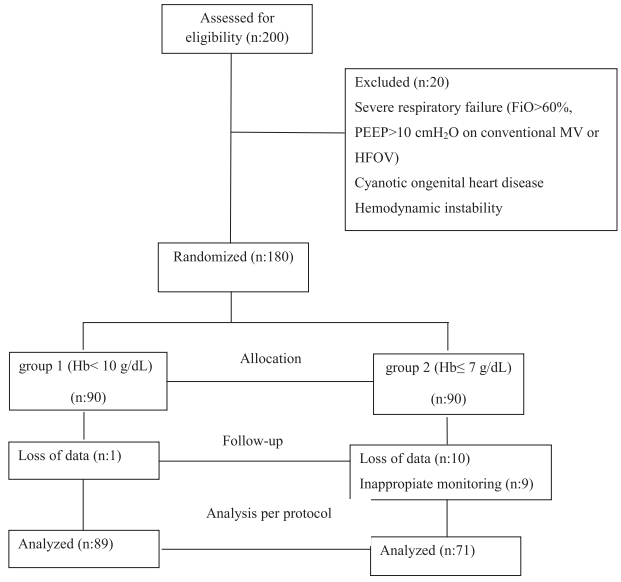


Fig. 1. Consort flow chart.

Table 1. Patient characteristics on admission and outcome in two groups

Variables	Group 1, *n* (%) 89 (55.6)	Group 2, *n* (%) 71 (44.4)	*p*
Sex, male, *n* (%)	41 (46.1)	36 (50.7)	0.560
Age, month	36 (24–84)	72 (36–84)	0.063
PRISM III	12 (6–16)	10 (6–13)	0.07
PELOD	11 (10–20)	10 (10–20)	0.09
Number of PRBC transfusions during PICU stay	2 (2–3)	1 (1–2)	<0.01
Mechanical ventilation, *n* (%)	50 (56.1)	32 (45)	<0.05
Mechanical ventilation days	15 (8–22)	13 (5–16)	<0.01
PICU length of stay days	13 (8–25)	10 (5–21)	<0.006
Admission diagnosis			
Respiratory, *n* (%)	30 (33.7)	28 (39.4)	
Cardiology, *n* (%)	12 (13.5)	10 (14.1)	
Infection, *n* (%)	15 (16.8)	12 (16.9)	0.125
Hematology, *n* (%)	32 (36)	21 (29.6)	
Mortality, *n* (%)	13 (14.6)	6 (8.4)	0.342

Data are expressed as *n* (%) or median (25%–75% percentile range). PRISM III: Pediatric Risk of Mortality III; PELOD: Pediatric Logistic Organ Dysfunction; PRBC: packed red blood cell; PICU: pediatric intensive care unit.

by Kanmaz *et al.* reported decreased CO by 9% but no change in PI for anemic preterm infants [24]. They explained that these findings were the result of the distribution of blood volume to supply oxygen to critical organs such as the brain, heart and kidneys. We used the PI to observe the efficiency of transfusion on tissue oxygenation, too. Lima *et al.* reported that low PI level was associated with decreased peripheral perfusion [25]. At the end of the transfusion, PI increased only in Group 2. Despite decreased CO in both groups, we only observed a statistically significant change in PI levels

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Table 2. Changes in hemodynamic and other laboratory parameters during transfusion

Variables	T0	T4	*p*	Δ%	*p*†
Hb (g/dL)	8.07±0.07	10.33±0.08	<0.01		
	6.53±0.07	**9.06±0.09**	**<0.01**		
Hct (%)	25±0.82	30.2±0.85	<0.01		
	21.2±0.3	**26.6±1.1**	**<0.01**		
SPHb (g/dL)	906±1,07	1 098±1,18	<0.01	14.6	=0.04
	798±1,08	**988±1,0**	**<0.01**	**18**	
SPOC (mL/dL)	11.83±0.19	14.63±0.16	<0.01	17.3	<0.05
	10.06±0.22	**12.9±0.18**	**<0.01**	**22.9**	
SPO_2 (%)	97.53±0.30	98.02±0.23	<0.01	2	<0.001
	96.0±0.35	**97.63±0.25**	**<0.01**	**10.4**	
PI (%)	1.55±0.06	1.68±0.82	0,120	10	<0.001
	1.32±0,07	**2.49±0.09**	**<0.01**	**45**	
Lactate (mmol/L)	1.65±0.09	1.54±0.08	0.018	9.8	<0.001
	1.79±0.10	**1.38±0.09**	**<0.001**	**31.68**	
HR (bpm)	125.45±1.95	115.14±1.81	<0.01	7	=0.02
	119.37±2.19	**104.65±2.04**	**<0.01**	**13**	
SV (mL)	29.36±2.04	25.81±1.63	<0.01	4.2	<0.001
	51.73±2.30	**38.87±1.83**	**<0.001**	**29.7**	
CO (L/min)	3.51±0.25	3.21±0.21	<0,01	9.9	<0.001
	6.08±0.28	**4.86±0.24**	**<0.01**	**24**	
SBP (mmHg)	91.19±1.25	96.63±1.29	<0.01	4.8	<0.05
	103.40±1.40	**106.18±1.45**	**<0.01**	**5.2**	
DBP (mmHg)	54.15±1.39	58.27±1.07	<0.01	3.5	<0.05
	64.76±1.55[a]	**66.60±1.20**	**=0.01**	**3.98**	

Bold indicates Group 2 data. Data are expressed as a mean ± standard deviation. *p* values show the comparison of T0 (initial) and T4 (end of the transfusion) values for two groups. *p*† values show the comparisons of two groups' Δ% change. All *p* values < 0.05 considered as statistically significant. Hb: hemoglobin; Hct: hematocrit; SPHb: noninvasive total hemoglobin; SPOC: noninvasive total oxygen content; SPO_2: oxygen saturation; PI: perfusion index; HR: heart rate; SV: stroke volume; CO: cardiac output; SBP: systolic blood pressure; DBP: diastolic blood pressure. Δ%: T0 (beginning of the transfusion) − T4 (end of the transfusion)/T0 (beginning of the transfusion).

Table 3. Correlations between Δ% PI and Δ% cardiac output, Δ% lactate for Group 1 and Group 2

	r	*p*
Δ% cardiac output	0.07	0.537
	−0.401	**<0.001**
Δ% lactate	−0.105	0.328
	−0.172	**0.152**

Bold indicates Group 2 data. Δ%: T0 (beginning of the transfusion) − T4 (end of the transfusion)/T0 (beginning of the transfusion).

Table 4. Correlations between Δ% SPOC and Δ% SPHb, Δ% SPO_2 for Group 1 and Group 2

	r	*p*
Δ% SPHb	0.745	<0.001
	0.689	**<0.001**
Δ% SPO_2	0.03	0.805
	0.023	**0.847**

Bold indicates Group 2 data. Δ%: T0 (beginning of the transfusion) − T4 (end of the transfusion)/T0 (beginning of the transfusion). *p* value < 0.05 considered as statistically significant. SPOC: noninvasive total oxygen content; SPHb: noninvasive total hemoglobin; SPO_2: oxygen saturation.

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in patients with Hb $\leq$ 7 g/dL. Significant changes in PI occurred by increasing CO by 24% at the end of the transfusion. In Group 2, we considered that blood flow velocity and viscosity may be attributed to a higher Δ% of PI. To our knowledge, this is the first study comparing the changes in hemodynamic and laboratory parameters including PI for two specific transfusion regimens in critically ill children.

Richard *et al.* reported that the SPOC measurement may provide an accurate measurement of the oxygen content of arterial blood (CaO_2) using SPHb [26]. In our study, SPOC levels increased in both groups compared with baseline values but % change of SPOC values (17.3% in Group 1 and 22.09% in Group 2, respectively) was significantly higher in Group 2. Although there was no correlation between Δ% SPOC and Δ% SPO_2 in the two groups, there was good correlation between Δ% SPHb and Δ% SPOC in the two groups. Considering these findings, the CaO_2 is determined by hemoglobin, SaO_2 and dissolved PaO_2 in blood, but the hemoglobin level has a much greater influence on CaO_2 [27].

In anemic patients, one of the laboratory parameters that reflects adequacy of tissue perfusion is blood lactate [27, 28]. The balance between oxygen delivery and consumption affects the serum lactate level. A study by Takahashi *et al.* reported that higher blood lactate may indicate decreased tissue perfusion and lactate clearance in anemic patients. According to the aforementioned results, serial venous blood lactate measurements may offer some valuable information to determine the optimal time for transfusion [28]. At the end of the transfusion, decreased serum lactate levels were detected for both groups but they were more prominent in Group 2. We also evaluated the relationship between blood lactate, PI and CO. There was no correlation between Δ% lactate and Δ% PI and/or between Δ% lactate and Δ% CO. Additionally, lactate is a very sensitive marker, and liver failure, hypocapnia, toxins, hyperglycemia and the use of catecholamines may contribute to this result [29, 30].

In agreement with the literature, the most common reason for transfusion in our study was low hemoglobin [1]. The baseline hemoglobin level for the PRBC transfusion was 7.38 $\pm$ 0.98 g/dL, which is just above the recommended level of 7 g/dL for all patients. When we analyzed the patients according to admission diagnosis and transfusion strategy groups, the most common problem was hematologic disease for the liberal transfusion strategy group and respiratory disease for the restrictive transfusion strategy group. However, 82 patients received PRBC during mechanical ventilation. Mean hemoglobin levels were higher in mechanically ventilated groups. It may be hypothesized that the improvement in oxygen delivery via PRBC transfusion may facilitate weaning from mechanical ventilation. Conversely, Hebert *et al.* showed that there is no evidence to support a decrease in mechanical ventilation days in the liberal strategy group [31]. Similar to these findings, mechanical ventilation days were longer in the liberal transfusion group in our study.

We also evaluated the relationship mortality and transfusion strategy. Nineteen patients died on follow-up. Thirteen of these patients were in the liberal transfusion strategy group and six patients were in the restrictive transfusion strategy group. There was no relationship between mortality and transfusion groups. Similar to our study, Holst *et al.* reported that when they compared the restrictive transfusion strategy with the liberal transfusion strategy, they found no differences with regard to the factors affecting overall morbidity [32].

Our study has some limitations. We compared the effects of the two transfusion regimens on hemodynamic and laboratory values during transfusion. As treatment is a dynamic process, we usually had to interfere with the management of the patients, such as vasoinotropic drugs, fluid management, mechanical ventilation settings and FiO_2, so it was not possible to assess longer-term monitoring and obtain detailed information regarding the two transfusion regimens for critically ill children.

This study supports our hypothesis that the restrictive transfusion strategy is better than the liberal transfusion strategy with regard to hemodynamic and laboratory parameters in the early period. To assess long-term outcomes of this strategy, further studies with larger groups of patients and prolonged monitoring are warranted. The PI also provides valuable information regarding the efficiency of PRBC transfusion in clinical practice.

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