RESEARCH ARTICLE

Red blood cell transfusion in critically-ill children and its association with outcome

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Abstract

Objective: To determine the indications and threshold of haemoglobin levels for packed red blood cell transfusion and its association with outcomes in a paediatric intensive care setting.

Method: The retrospective study was conducted in the paediatric intensive care unit of the Aga Khan University Hospital, Karachi, and comprised medical records of all inpatients with age between 1 month and 16 years who received packed red blood cell transfusions between January and December 2017. Data was retrieved from the hospital database and was analyzed using SPSS 22.

Results: Of the 147 subjects with a mean age of 67.89±65.8 months, 76(51.7%) were males. Mean paediatric risk of mortality score was 11.72±7.86. Major admitting diagnosis included sepsis and multiorgan dysfunction 50(34%), respiratory diseases 26(17.7%) and haematology/oncology diseases 22(15%). The indications for transfusion was low haemoglobin in 90(61.2%) patients, shock 29(19.7%) and hypoxia 28(19%). Acute transfusion reaction was observed in 1(0.7%) patient; 120(82%) required mechanical ventilation; and 94(64%) required inotropic support. Of the total, 88(59.9%) patients survived. Paediatric risk of mortality score, need for inotropic support and mechanical ventilation were associated with mortality ($p<0.05$).

Conclusion: Packed red blood cell transfusion, which is frequently prescribed in intensive care settings, was not found to be associated with favourable outcome.

Keywords: RBC transfusions, Paediatric intensive care unit, Mechanical ventilation, Mortality. (JPMA 71: 1967; 2021)

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Introduction

The transfusion of packed red blood cells (pRBCs) remains a cornerstone in the management of many critically ill children admitted in the paediatric intensive care units (PICUs).[1] An approximate 15 and 85 million pRBC units are transfused annually in the United States and worldwide, respectively.[2,3] One explanation for the vast use of pRBC transfusion may be the prevalence of anaemia in patients admitted to the PICU. Anaemia has been found to be present in 36.7% to 74% children admitted in PICUs; 15% of them requiring pRBC transfusion.[2,3] Furthermore, the causes of anaemia are multi-factorial and include overt or occult bleeding, iatrogenic bleeding, blood loss due to underlying disease or illness severity, and treatment causing bone marrow suppression.[2] These anaemic patients have been found to have higher paediatric risk of mortality (PRISM) score, longer length of hospital stay (LOS) and longer duration of mechanical ventilation compared to patients without anaemia.[2]

The decision to transfuse pRBCs is based on the patient's haemoglobin (Hb) levels, clinical status, age categories in terms of children, adolescents and infants as well as the clinician's expert opinion, common practice, and evidence extrapolated from literature.[4] Recent guidelines have suggested a threshold of 5gm/dl of Hb for pRBC transfusion, but the level of evidence is very low.[5]

However, the benefits of pRBC transfusions must be cautiously weighed against its risks.[6] There has been increasing evidence showing association of pRBC transfusion with increased mortality, longer PICU stay, longer duration of mechanical ventilation, increased risks of infections and transfusion reactions.[1,7] There have also been an increase in immune modulations, haemolysis, transfusion-related acute lung injury (TRALI), alterations in micro-circulations, allergic reactions and development of multi-organ dysfunctions (MODs) in these patients.[7,8] A study in 2007 showed that red blood transfusion in critically ill children is independently associated with increased mortality, prolonged duration of mechanical ventilation, infusions of vasoactive agents and PICU stay.[9] Higher mortality rates were found among patients with multiple transfusions.[9] Patients who received pRBC transfusion were 5 times more likely to die than patients who did not receive pRBC transfusions, and similar conclusions have been made by other studies.[10]

Hence, although pRBC transfusion is considered a

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potentially life-saving intervention with the aim of improving adequate oxygen delivery to vital organs in critically ill children, it is not a benign therapy.[11] Further prospective, randomised trials and retrospective studies as well recent Transfusion and Anaemia Expertise Initiative (TAXI) thereby suggest using a more conservative pRBC transfusion in most scenarios.[12] There has also been a lot of emphasis on haemovigilance and pRBC sparing strategies and goal-directed pRBC transfusion with the sole purpose of increase tissue oxygen delivery.

The current study was planned to determine indications for pRBC transfusion, and its association with outcomes in a paediatric intensive care setting.

Materials and Methods

The retrospective study was conducted in the PICU of the Aga Khan University Hospital (AKUH), Karachi, and comprised data from January to December 2017, after approval from the institutional ethics review committee. AKUH is a 700-bed tertiary care university hospital with laboratory and blood accredited with the College of American Pathologists (CAP) and supervised by transfusion medicine physicians. The practice of haemovigilance has been implemented a few years ago, using a threshold of Hb 7gm/dl for pRBC in critically ill stable, non-cyanotic patients.[13]

Data retrieved from the hospital database comprised records of all inpatients with age between 1 month and 16 years who received pRBC transfusions during the study period. Data was excluded for patients weighing <3kg, having postconceptionl age <40 weeks, and those admitted with acute bleeding/haemorrhagic shock.

The data was collected using a structured proforma which included patient demographics as well as clinical variables, like the reason for PICU admission, paediatric risk of mortality (PRISM) III score, multi-organ dysfunctions (MODs) on admission or during PICU stay, requirement for inotropic support/ mechanical ventilation, any surgical procedure(s), reason for packed cell volume (PCV) transfusion, number of PCV transfusion, volume of transfusion and storage age of RBC. Also noted were laboratory variables, like admission Hb, pre- and post-transfusion Hb, lactic acid, blood gas values, blood culture and sensitivity reports. Indication for pRBC transfusion was taken from physician notes. Central line-associated blood stream infection was defined as per the Center for Disease Control and prevention (CDC) guidelines.[14]

The primary outcome was indication of pRBC transfusion, pre- and post-transfusion Hb levels, length of mechanical ventilation and PICU stay, and mortality in this group.

Data was analysed using SPSS 22 and results were presented as mean with standard deviation and frequencies with percentages. P value was determined to assess the significance in groups using two sample t test for normally distributed data and Wilcoxon rank sum test for non-normal data. Univariate and multivariate logistic regression was performed to calculate odds ratio (OR) for outcome mortality with LOS, length of mechanical ventilation and with liberal, defined as pre-transfusion Hb >7gm/dl, and conservative RBC transfusion, defined as pre-transfusion Hb <7gm/dl) group. P<0.05 was considered statistically significant. Variables that were found to be significant at 0.25 level of significance were considered for multivariate analysis using stepwise forward model selection method.

Table-1: Demographic and clinical data (n=147).

Variables		n/mean ((%)/ SD/Median with IQR)
Mean Age (months)		67.89± 65.80
Gender	Female	71 (48.3%)
	Male	76 (51.7%)
PRISM III Median(IQR)		10(9)
Diagnostic Category	Sepsis / Infection	50 (34.0%)
	Respiratory Illnesses	26 (17.7%)
	Haematological/Oncological Diseases	22 (15.0%)
	Neurological Illnesses	13 (8.8%)
	Cardiovascular	10 (6.8%)
	Miscellaneous	26 (17.7)
Indication of transfusion	Low Haemoglobin	90 (61.2%)
	Shock	29 (19.7%)
	Hypoxia	28 (19.0%)
Storage age of Red Blood Cells	1-15 days	114 (77.6%)
	16-30 days	26 (17.7%)
	31-45 days	7 (4.8%)
Admission Haemoglobin (gm/dl)		9.27 ±2.18
Pre-transfusion Haemoglobin (1st transfusion) (gm/dl)		7.83±1.61
Pre-transfusion Haemoglobin (2nd transfusion) (gm/dl)		7.98±1.90
Pre-transfusion Haemoglobin (3nd transfusion) (gm/dl)		7.77±0.98
Pre-transfusion haemoglobin	<7 mg/dl	38 (25.9%)
	> 7mg/dl	109 (74.1%)
Post-transfusion Haemoglobin (1st transfusion) (gm/dl)		10.71±1.98
Post-transfusion Haemoglobin (2nd transfusion) (gm/dl)		10.29±1.93
Post-transfusion Haemoglobin (3nd transfusion) (gm/dl)		10.2±1.78
Outcome (survived)	Yes	88 (59.9%)
	No	59 (40.1%)
Length of stay(days) Median(IQR)		6 (8)
Length of mechanical ventilation (days) Median(IQR)		5 (6)

n=frequency; SD=Standard Deviation

Table-2: Comparative data between patients who survived and those who expired (n=147).

Variables		Expired	Survived	OR (CI)	*p*-value	adjusted OR(CI)	*p*-value
Age (months)		64.22±65.83	70.35±66.04	0.99(0.99,1.00)	0.579		
Gender	Male	51 (58.0%)	25 (42.4%)	1.87 (0.96,3.65)	0.065		
	Female	37 (42.0%)	34 (57.6%)				
Indication	Low Haemoglobin	55 (62.5%)	35 (59.3%)	0.87(0.44,1.71)	0.698		
	Shock.	16 (18.2%)	13 (22.0%)	-------	-----		
	Hypoxia	17 (19.3%)	11 (18.6%)	0.79(0.27-2.28)	0.672		
Storage Age of Red Blood Cells	1-15 Days	65 (73.9%)	49 (83.1%)	0.815(0.43,1.52)	0.524		
	16-30 Days	20 (22.7%)	6 (10.2%)	0.225(0.038-1.29)			
	31–45 Days	3 (3.4%)	4 (6.8%)				
PRISM III Median(IQR)		13(12)	9(7)	1.10 (1.04,1.15)	0.000		
Inotropic support	yes	43 (49.4%)	51 (86.4%)	0.15(0.06,0.36)	0.000	0.22(0.08,0.60)	0.003
	No	44 (50.6%)	8 (13.6%)				
Mechanical Ventilation	yes	65 (74.7%)	55 (93.2%)	0.21(0.06, 0.66)	0.007		
	no	22 (25.3%)	4 (6.8%)				
Length of mechanical Ventilation		7.50±7.24	5.14±5.77	1.05(1.00, 1.11)	0.039	1.28(0.99,1.66)	0.053
MODS at admission	yes	6 (6.8%)	29 (49.2%)	0.07(0.02,0.20)	0.000	0.12(0.04,0.38)	0.000
	no	82 (93.2%)	30 (50.8%)				
LOS (Mean)		8.66±8.11	8.23±8.107	1.00 (0.96,1.04)	0.756		

OR: Odds ratio; CI: Confidence interval; PRISM: Paediatric risk of mortality; MODS: Multi-organ dysfunctions; LOS: Length of hospital stay.

Results

During the study period, 600 patients were admitted in PICU, with 210(35%) receiving pRBC transfusion. Of them, 63(30%) did not meet the inclusion criteria and data related to them was excluded. The final sample comprised data of 147(70%) patients. The overall mean age was 67.89±65.8 months and 76(51.7%) of the patients were males. Mean PRISM score was 11.72±7.86. Admitting diagnosis included sepsis and MODs, respiratory diseases, haematology/ oncology diseases, neurological illnesses and miscellaneous conditions, while indications for transfusion included low Hb, shock and hypoxia (Table 1).

Amongst the 147 transfusions, 114(77.6%) were aged <15 days, 26(17.7%) were aged 16-30 days, and 7(4.8%) were aged 31-45 days. There was 1(0.7%) case of immediate transfusion reaction. Further, 84(57.1%) patients received one transfusion, 37(25.2%) received two transfusions and 24(16.3%) received three transfusions, while

Table-3: Comparison between pre-transfusion haemoglobin lesser or greater than 7 mg/dl (n=147).

		Haemoglobin <7 mg/dl	Haemoglobin > 7mg/dl	*p*-value
Age (Mean±SD)		87.81±64.39	60.94±65.145	0.0297
Gender	Male	17 (44.7%)	59 (54.1%)	0.320
	Female	21 (55.3%)	50 (45.9%)	
Diagnosis	Neurological Illness	5 (13.2%)	8 (7.3%)	0.073
	Cardiovascular diseases	4 (10.5%)	6 (5.5%)	
	Respiratory diseases	1 (2.6%)	25 (22.9%)	
	Gastrointestinal diseases	3 (7.9%)	5 (4.6%)	
	Renal diseases	1 (2.6%)	0 (0.0%)	
	Sepsis and infection related MODS	11 (28.9%)	39 (35.8%)	
	Post-operative	5 (13.2%)	11 (10.1%)	
	Haematological and oncological disease	8 (21.1%)	14 (12.8%)	
Indication of transfusion	Low Haemoglobin	22 (57.9%)	68 (62.4%)	0.200
	Hypoxia	5 (13.2%)	23 (21.1%)	
	Shock	11 (28.9%)	18 (16.5%)	
Transfusion Reaction	Yes	0 (0.0%)	1 (0.9%)	0.550
	No	38 (100.0%)	108 (99.1%)	
Age of RBCS	1-15 days	29 (76.3%)	85 (78.0%)	0.970
	16-30 days	7 (18.4%)	19 (17.4%)	
	31-45 days	2 (5.3%)	5 (4.6%)	
MODS	Yes	12 (31.6%)	23 (21.1%)	0.190
	No	26 (68.4%)	86 (78.9%)	
PRISM; Median(IQR)		10(7)	9(9)	0.973
Survived	Yes	27 (71.1%)	61 (56.0%)	0.100
	No	11 (28.9%)	48 (44.0%)	
Inotropic support	Yes	20 (52.6%)	74 (68.5%)	0.079
	No	18 (47.4%)	34 (31.5%)	
Surgery	Yes	18 (47.4%)	47 (43.1%)	0.650
	No	20 (52.6%)	62 (56.9%)	
Mechanical ventilation	Yes	27 (71.1%)	93 (86.1%)	0.037
	No	11 (28.9%)	15 (13.9%)	
Hospital Length of stay (Mean)		6.55±6.85	9.05±8.40	0.1006

SD: Standard deviation; RBCS: Red blood cells; PRISM: Paediatric risk of mortality; MODS: Multi-organ dysfunctions; LOS: Length of hospital stay.

1(0.7%) patient each received four and five transfusions. Of the total, 88(59.9%) patients survived; 48(57.1%) from among those receiving one transfusion; 27(73%) among those who received two transfusions and 13(54.2%) survived from among those who received three transfusions. There were no survivors from among those who underwent four and five transfusions. Mean mixed venous oxygen saturation, done in 82(55.8%) patients before pRBC transfusion, was 58.1±14.7% and post-transfusion, done in 25(17%) patients. was 61.2±16.2%. Overall, 94(64%) patients required inotropic support and 120(82%) required mechanical ventilation with mean length of mechanical ventilation was 6.11±6.5 days.

The mean length of stay in the PICU was 8.4±8.087days. Mean values for PRISM score, length of mechanical ventilation and PICU stay among the survivors were significantly different compared to those who expired (Table 2).

Comparison was also done on the basis of pre-transfusion Hb level below or over the 7mg/dl cut-off (Table 3)

Discussion

Mean Hb threshold for pRBC transfusion in patients during the current one-year audit was 7.87gm/dl, which is according to global recommendations and the AKUH protocol.[13] However, recent transfusion guidelines recommend even lower threshold of 5gm/dl Hb in stable PICU patients.[5] As such, there is room for improvement in this aspect. Previous studies also suggested that transfusing pRBCs at lower Hb threshold is better or at least not worse than transfusing pRBCs at higher thresholds.[15-17] Anaemia was the most common indication for blood transfusion in the current study, which is in accordance with literature.[4] The incidence of anaemia observed in the current study, however, was significantly higher (55.9%) than the other studies.[2,18,19] However, it is of note that these studies were done in developed countries and there is no known comparative data from developing countries. Anaemia in PICU patients is multi-factorial, resulting from underlying illness, pre-existing iron deficiency, frequent laboratory testing etc.[2] The post-transfusion Hb level was around 10gm/dl which shows adequate increase and practice of enough minimum volume of transfusion to just bring Hb levels by 2gm/dl above the pre-transfusion levels.[13] Another important thing to note is that in a small number of patients (25/147; 17%) post-transfusion mixed venous saturation mean values only improved from 58% to 61%. This means that probably the patients were either in shock or tissue oxygen delivery did not improve much with pRBC transfusion. This is very important point to consider while prescribing pRBC transfusion in PICU as the aim of pRBC transfusion is to improve arterial oxygen content and tissue oxygen delivery.

RBC storage is another important point to consider while transfusing pRBCs as this has also been associated with worse outcomes.[20] A study showed that pRBC storage of >14 days was associated with prolonged LOS and development of MODs.[20] In a recent randomised controlled trial (RCT), there was no difference in outcomes between patients transfused fresh versus standard stored pRBCs.[21] In our study more than two-thirds of patients received pRBC storage life of 15 days or less and we did not find any association of storage life of RBCs with adverse outcomes.

Overall, patients had a mortality of 40% which is a considerably high incidence compared to earlier studies.[9,15,17,19] The patients who did not survive had a higher overall PRISM score compared to the survivors. These findings can also be extrapolated from another study in a similar setting which concluded that critically ill children with high PRISM score are also at a higher risk of developing TRALI.[22]

One study showed mortality was independently associated with the number of transfusions.[9] In 2004, a study concluded that the number of RBC units transfused to intensive care patients with anaemia was an independent predictor of a poor outcome.[19] However, the current study did not show such an association. Transfusion reaction was also found to be rare (0.7%) among the patients and hence, it could not be concluded if there was a direct relationship between transfusion reactions and mortality.

Furthermore, patients in the current study had an increased length of mechanical ventilation and increased hospital stay. Similar finding was reported by another study in which RBC transfusion was independently associated with longer duration of mechanical ventilation in paediatric patients with acute respiratory syndrome.[17] Patients who were transfused with a restrictive strategy had similar or better outcomes and requirement of inotropes as those with liberal transfusion strategies which has also been shown by previous studies.[15,16]

The current study has certain limitations, including retrospective nature with limited number at a single centre without any control group. Another important aspect that the study did not look at was wastage of blood products and cost implications of excessive or unnecessary pRBC transfusions. Quite often, more pRBC units are provided than required, and the leftover is discarded which can be easily prevented by ordering accurate volume of blood. Despite the limitations, the current study has highlighted

some important practice trends in RBC transfusion in AKUH PICU. We continue to work more collaboratively with our haemovigilance team to decrease threshold of pRBC transfusion and use it judiciously in number as well in volume. We also strongly suggest that hospital systems and physicians work with blood bank and make a haemovigilance team to make the use of blood and blood products safe, rationale and judicious. It will be a cost-effective strategy since it will save cost as well as adverse effects of blood products, and make it available for more patients.

Conclusion

Transfusion of pRBC, which is frequently prescribed in PICU settings, was not found to be associated with favourable outcome. It is commonly prescribed with a threshold higher than the recommended Hb levels. Haemovigilance can be of great help in restricting unnecessary use of pRBC in PICUs.

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References

1. Secher EL, Stensballe J, Afshari A. Transfusion in critically ill children: an ongoing dilemma. Acta Anaesthesiol Scand 2013; 57: 684-91.
2. Bateman ST, Lacroix J, Boven K, Forbes P, Barton R, Thomas NJ, 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.
3. Desmet L, Lacroix J. Transfusion in pediatrics. Crit Care Clin 2004; 20: 299-311.
4. Chang TT. Transfusion therapy in critically ill children. Pediatr Neonatol 2008; 49: 5-12.
5. Valentine SL, Bembea MM, Muszynski JA, Cholette JM, Doctor A, Spinella PC, et al. Consensus Recommendations for RBC Transfusion Practice in Critically Ill Children From the Pediatric Critical Care Transfusion and Anemia Expertise Initiative. Pediatr Crit Care Med 2018; 19: 884-98.
6. Demaret P, Tucci M, Ducruet T, Trottier H, Lacroix J. Red blood cell transfusion in critically ill children (CME). Transfusion 2014; 54: 365-75.
7. Istaphanous GK, Wheeler DS, Lisco SJ, Shander A. Red blood cell transfusion in critically ill children: a narrative review. Pediatr Crit Care Med 2011; 12: 174-83.
8. Goodman AM, Pollack MM, Patel KM, Luban NL. Pediatric red blood cell transfusions increase resource use. J Pediatr 2003; 142: 123-7.
9. Kneyber MC, Hersi MI, Twisk JW, Markhorst DG, Plotz FB. Red blood cell transfusion in critically ill children is independently associated with increased mortality. Intensive Care Med 2007; 33: 1414-22.
10. Tyrrell CT, Bateman ST. Critically ill children: to transfuse or not to transfuse packed red blood cells, that is the question. Pediatr Crit Care Med 2012; 13: 204-9.
11. Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. Crit Care Med 2008; 36: 2667-74.
12. Parker RI. Transfusion in critically ill children: indications, risks, and challenges. Crit Care Med 2014; 42: 675-90.
13. New HV, Berryman J, Bolton-Maggs PH, Cantwell C, Chalmers EA, Davies T, et al. Guidelines on transfusion for fetuses, neonates and older children. Br J Haematol 2016; 175: 784-828.
14. National Healthcare Safety Network CfDC. Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central Line Associated Bloodstream Infection). [Online] 2021 [cited 2021 March 3]. Available from: URL: https://www.cdc.gov/nhsn/pdfs/pscmanual/4psc_clabscurrent.pdf.
15. Radebe PBS, Jeena PM. Red blood cell concentrate transfusion strategies utilised at a tertiary-level paediatric intensive care unit: A descriptive study on impact and cost. S Afr J Child Health 2018; 12: 164-9.
16. Akyildiz B, Ulgen Tekerek N, Pamukcu O, Dursun A, Karakukcu M, et al. Comprehensive Analysis of Liberal and Restrictive Transfusion Strategies in Pediatric Intensive Care Unit. J Trop Pediatr 2018; 64: 118-25.
17. Zubrow ME, Thomas NJ, Friedman DF, Yehya N. RBC Transfusions Are Associated With Prolonged Mechanical Ventilation in Pediatric Acute Respiratory Distress Syndrome. Pediatr Crit Care Med 2018; 19: e88-e96.
18. Habib MA, Black K, Soofi SB, Hussain I, Bhatti Z, Bhutta ZA, et al. Prevalence and Predictors of Iron Deficiency Anemia in Children under Five Years of Age in Pakistan, A Secondary Analysis of National Nutrition Survey Data 2011-2012. PLoS One 2016; 11(: e0155051.
19. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Abraham E, et al. The CRIT Study: Anemia and blood transfusion in the critically ill--current clinical practice in the United States. Crit Care Med 2004; 32: 39-52.
20. Karam O, Tucci M, Bateman ST, Ducruet T, Spinella PC, Randolph AG, et al. Association between length of storage of red blood cell units and outcome of critically ill children: a prospective observational study. Crit Care 2010; 14: R57.
21. Spinella PC, Tucci M, Fergusson DA, Lacroix J, Hebert PC, Leteurtre S, et al. Effect of Fresh vs Standard-issue Red Blood Cell Transfusions on Multiple Organ Dysfunction Syndrome in Critically Ill Pediatric Patients: A Randomized Clinical Trial. JAMA 2019; 322: 2179-90.
22. Jamil MT, Dhanani Z, Abbas Q, Jurair H, Mahar FK, Haque A. Transfusion-Related Acute Lung Injury In A Paediatric Intensive Care Unit Of Pakistan. J Ayub Med Coll Abbottabad 2017; 29: 702-5.