Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1349434

Anatolian Curr Med J. 2024;6(1):11-16

Association between red blood cell transfusion and mortality in critically ill children: a single-center pediatric intensive care experience

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Cite this article as: Durak C, Şahin C. Association between red blood cell transfusion and mortality in critically ill children: a single-center pediatric intensive care experience. *Anatolian Curr Med J.* 2024;6(1):11-16.

Received: 24.08.2023 ◆ **Accepted**: 23.11.2023 ◆ **Published**: 15.01.2024

ABSTRACT

Aims: Our study aimed to evaluate the association of erythrocyte transfusion with mortality and morbidity in critically ill children and to emphasize the importance of the risk it carries.

Methods: A retrospective evaluation of 524 pediatric patients aged 1 month to 18 years who had been admitted between February 2022 to March 2023 at Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, were performed. Children with hemoglobinopathies, and chronic anemia (defined as the presence of anemia for more than 6 weeks) were excluded. Demographic data, clinical variables, and outcome data were analyzed.

Results: The median age was 36.5 (1.0-272.0) months, and 56.1% of the patients were male. The median duration of a pediatric intensive care unit stay was 5 (1-114) days. Respiratory diseases (44.7%) were the most common reasons for admission to the pediatric intensive care unit, followed by, neurological diseases (12.8%)and sepsis (11.3%). Mortality rate was 5.7%. The median baseline hemoglobin level upon admission was 10.5 g/dl (3.2-18.8). Severe anemia (hemoglobin < 7 g/dl was present in 6.1% of all patients. One hundred and sixteen (22.1%) patients were transfused; 61 (11.6%) were transfused only once. A total of 292 packed red blood cells transfusions were administered. Transfused patients required prolonged hospital stays, support for inotropic agents, invasive mechanical ventilation, and extracorporeal treatment and had an excessive mortality rate ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$).

Conclusion: Clinicians should consider that the administration of packed red blood cells transfusions in critically ill patients may have the potential to both raise mortality and provide life-saving benefits during their pediatric intensive care unit stay. As with any treatment with potential side effects, it is essential to reduce the use of unnecessary blood products.

Keywords: Critical care, erythrocyte transfusion, mortality, pediatrics

INTRODUCTION

Anemia is prevalent among critically ill pediatric patients at the time of admission and throughout their pediatric intensive care unit (PICU) stay, and these patients may have a lower tolerance for anemia. Transfusion of packed red blood cells (PRBCs) is widespread, occurring in 74% of PICU patients.[1]

PRBC transfusions may be medically required and even life-saving in certain situations, such as severe anemia, and active blood loss.[2] The sole method for promptly treating severe anemia is through the administration of PRBC transfusions. The primary objective of PRBC transfusion is to elevate the hemoglobin (Hb) concentration, with the aim of enhancing both oxygen supply and oxygen consumption.[3,4]

Nevertheless, red blood cell (RBC) storage can impair the capacity to supply oxygen over time. Observational studies have indicated a heightened mortality risk among critically ill patients who received PRBC transfusions.[5] PRBC infusions carry a multitude of risks, encompassing infections, immunosuppression, transfusion reactions, fluid overload, and medical errors.[2] Hence, in light of the potential risks and elevated mortality rates linked to transfusions, healthcare professionals must exercise cautious discernment when assessing the requirement for PRBC transfusion.

Our study aimed to evaluate the association of erythrocyte transfusion with mortality and morbidity in critically ill children and to emphasize the importance of the risk it carries.

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METHODS

A retrospective cohort study was performed in the PICU at Şehit Prof. Dr. İlhan Varank Training and Research Hospital, University of Health Science, throughout February 2022 to March 2023. Healthcare provision for children aged from 1 month to 18 years is provided in our PICU, which is equipped with 12 beds, 12 ventilators, 5 Prismaflex™ hemofiltration machines (Baxter, USA), and 9 isolation rooms.

The study was conducted in accordance with the Declaration of Helsinki. The study's protocol was approved by Ethics Committee of Şehit Prof. Dr. İlhan Varank Training and Research Hospital (Date: 17.02.23 Decision No: E-46059653-050.99-209549220), and all study-related anonymized data are available upon reasonable request.

Demographic data (age, gender), clinical variables (diagnosis at the admission, Pediatric Risk of Mortality III score, length of PICU stay, requirement of invasive mechanical ventilation, inotropic agents, extracorporeal therapy, requirement of PRBC transfusion, number of PRBC transfusions, and outcome data (alive/expired) of 524 patients were collected. Pediatric Risk of Mortality III (PRISM III) scores corresponding to the first 24 hours of hospitalization were calculated according to the equation described by Pollack et al.6 PRBC transfusion is classified as none, 1 time, and ≥2 times. Children with hemoglobinopathies, and chronic anemia (defined as the presence of anemia for more than 6 weeks) were excluded. Our unit did not have a transfusion guideline. The decision to transfuse a patient was made by the attending clinician. Routinely, the quantity per erythrocyte transfusion amounts to 15 ml/kg.

Statistical Package for the Social Sciences (IBM Corp SPSS Statistics for Windows, Version 20.0. Armonk, NY) was used for statistical analyses. Numbers, frequencies [%], ratios, medians, and ranges were used in the descriptive statistics of the data. Continuous variables were tested for normal distribution by Kolmogorov-Smirnov or Shapiro-Wilk test. For analysis of continuous data, a t-test or Mann–Whitney U test was performed to detect differences between the groups, depending on the distribution. Relationships between categorical variables were analyzed by the Chi-square test. When Chi-square assumptions were not met, Fisher's exact test was used. A one-way analysis of variance (ANOVA) test is used for three or more groups of data, to gain information about the relationship between the dependent and independent variables.

RESULTS

The study included 524 patients who met the research criteria out of the total number of patients admitted to our PICU. The median age was 36.5 (1-272) months. The majority of the patients were male (56.1%). The most frequent diagnoses of admission to the PICU were respiratory diseases (44.7%), such as pneumonia and asthma attacks, followed by neurological diseases, such as epilepsy and encephalitis (12.8%), and sepsis (11.3%). The median length of stay in the PICU was 5 days, ranging from 1 to 114 days, and the median PRISM III score was 2 (0-40). The mortality rate was 5.7% (**Table 1**).

Table 1. Clinical characteristics of patients admitted to pediatric intensive care unit

Gender, n (%)	
Male	294 (56.1)
Female	230 (43.9)
Age (month), median (min-max)	36.5 (1.0-272.0)
Etiologies of admission, n (%)	
Respiratory diseases	234 (44.7%)
Neurological diseases	67 (12.8%)
Sepsis	59 (11.3%)
Intoxication	44 (8.4%)
Trauma	37 (7.1%)
Endocrinological diseases	24 (4.6%)
Acute renal failure	12 (2.3%)
Postoperative admissions	10 (1.9%)
Cardiological diseases	9 (1.7%)
Hematology-oncological diseases	7 (1.3%)
Others	21 (4%)
PRISM III score	2 (0-40)
Length of stay (day), median (min-max)	5 (1-114)
Requirement of IMV, n (%)	142 (27.2%)
Length of stay on IMV (day), median (min-max)	6 (1-102)
Requirement of CRRT, n (%)	41 (7.8%)
Requirement of inotropic agents, n (%)	69 (13.2%)
Requirement of TPE, n (%)	49 (9.4%)
Mortality, n (%)	30 (5.7%)

CRRT : Continuous renal replacement therapy, IMV : Invasive mechanical ventilation, PRISM III : Pediatric Risk of Mortality, TPE : Therapeutic plasma exchange

A total of 142 patients (27.2%) required invasive mechanical ventilation (IMV), with a median duration of 6 (1-102) days. Inotropic drugs were used in 69 patients (13.2%). While therapeutic plasma exchange (TPE) was performed on 49 patients (9.4%), continuous renal replacement therapy (CRRT) was performed on 41 patients (7.8%) (**Table 1**).

The median baseline hemoglobin level upon PICU admission was 10.5 g/dl (3.2-18.8). Severe anemia (Hb <7 g/dl) was present in 6.1% of all patients. One hundred and sixteen (22.1%) patients were transfused; 61 (11.6%) were transfused only once. A total of 292 PRBC transfusions were administered (**Table 2**).

Table 2. Hemoglobin values and transfusion requirements of patients admitted to the pediatric intensive care unit	
Hemoglobin (g/dl) at admission	10.5 (3.2-18.8)
Hemoglobin ranges	
≥8 g/dl	454 (86.6%)
7-8 g/dl	38 (7.3%)
≤7 g/dl	32 (6.1%)
PRBC transfusion	
None	408 (77.9%)
One time	61 (%11.6)
≥2 times	55 (10.5%)
Total PRBC transfusion count	292

PRBC: Packed red blood cell

Differences in demographic and clinical variables between patients who received one or more PRBC transfusions and those who were not transfused were examined. Between the three groups, there were statistically significant differences in age and gender (p=0.031 p=0.022). Upon comparing the etiology, it was noted that patients hospitalized for sepsis, hemato-oncological diseases, acute renal failure, and cardiological disorders had a much greater requirement for red blood cell transfusion (p<0,001). We found a significantly higher median PRISM III score in transfused patients, indicating that they were more critically ill (p<0.001) (**Table 3**).

Baseline hemoglobin levels were found to be statistically lower among people who required multiple transfusions (p<0.001). Transfused patients also required prolonged stays in the PICU and had a greater need for inotropic agents, IMV, and extracorporeal treatment(p<0.001, p<0.001, p<0.001, p<0.001). We observed an excessive mortality rate, especially among children who received multiple transfusions (p<0.001) (**Table 4, 5**).

Table 3. Comparison of PRBC transfusion requirements and clinical characteristics of patients				
	PRBC transfusion			
	None	**One time**	**≥2 times**	**p**
Gender/ Male, n(%)	237 (80.6%)	32 (10.8%)	25 (8.5%)	0.022
Age (month), median (min-max)	38 (1-272)	25 (1-214)	48 (1.33-20-08)	0.031
Etiologies of admission				<0.001
Respiratory diseases	206 (88.0%)	19 (8.1%)	9 (3.8%)	
Neurological diseases	58 (86.6%)	6 (9.0%)	3 (4.5%)	
Sepsis	20 (33.9%)	19 (32.2%)	20 (33.9%)	
Intoxication	43 (97.7%)	1 (2.3%)	0 (0%)	
Trauma	25 (67.6%)	5 (13.5%)	7 (18.9%)	
Endocrinological diseases	24 (100%)	0 (0%)	0 (0%)	
Acute renal failure	2 (16.7%)	4 (33.3%)	6 (50.0%)	
Postoperative admissions	8 (80%)	2 (20%)	0 (0%)	
Cardiological diseases	5 (55.6%)	1(11.1%)	3 (33.3%)	
Hematology-oncological diseases	1 (14.3%)	2 (28.6%)	4 (57.1%)	
Others	15 (71.4%)	4 (19.0%)	2 (9.5%)	
PRISM III score, median (min-max)	2 (0-30)	7 (0-40)	11 (0-39)	<0.001
Length of stay, median (min-max)	4 (1-62)	7.5 (1-77)	19 (1-114)	<0.001
Mortality, n (%)	8 (%26.7)	7 (23.3%)	15 (50.0%)	<0.001
Hemoglobin (g/dl) at admission	10.8 (6.5-18.8)	8.35(5.1-14.3)	8.9 (3.2-13.2)	<0.001
Hemoglobin ranges				<0.001
≥8 g/dl	386 (85.0%)	34 (7.5%)	34 (7.5%)	
7-8 g/dl	20 (52.6%)	11 (28.9%)	7 (18.4%)	
≤7 g/dl	1 (3.1%)	17 (53.1%)	14 (43.8%)	

PRISM III : Pediatric Risk of Mortality, PRBC: Packed red blood cell

Table 4. Comparison of PRBC transfusion requirements and supportive therapies, and outcomes of patients				
	PRBC transfusion			
	None	**One time**	**≥2 times**	**p**
Requirement of IMV, n (%)	66 (46.5%)	35 (24.6%)	41 (28.9%)	<0.001
Requirement of inotropic agents, n (%)	18 (26.1%)	16 (23.2%)	35 (50.7%)	<0.001
Requirement of CRRT, n (%)	10 (24.4%)	4 (9.8%)	27 (65.9%)	<0.001
Requirement of TPE, n (%)	12 (%24.5)	8 (16.3%)	29 (59.2%)	<0.001

CRRT : Continuous renal replacement therapy IMV : Invasive mechanical ventilation TPE : Therapeutic plasma Exchange PRBC: Packed red blood cell

Table 5. Comparison of hemoglobin levels and clinical characteristics of patients

	Hemoglobin (g/dl) at admission			
	≤7 g/dl	7-8 g/dl	≥8 g/dl	p
Gender/ Male, n(%)	12 (4.0%)	23 (7.8%)	259 (88.0%)	<0.001
Age (month), median (min-max)	37 (1-202)	12.5 (1-198)	39 (1-272)	0.001
Etiologies of admission				<0.001
Respiratory diseases	5 (2.1%)	23 (9.8%)	206 (88.0%)	
Neurological diseases	1 (1.5%)	2 (3.0%)	64 (95.5%)	
Sepsis	12 (20.3%)	3 (5.1%)	44 (74.6%)	
Intoxication	0 (0%)	0 (0%)	44 (100%)	
Trauma	3 (8.1%)	3 (8.1%)	31 (83.8%)	
Endocrinological diseases	0 (0%)	0 (0%)	24 (100%)	
Acute renal failure	6 (50.0%)	2 (16.7%)	4 (33.3%)	
Postoperative admissions	0 (0%)	0 (0%)	10 (100%)	
Cardiological diseases	0 (0%)	1(11.1%)	7 (77.8%)	
Hematology-oncological diseases	3 (42.9%)	2 (28.6%)	2 (28.6%)	
Others	2 (9.5%)	1 (4.8%)	18 (85.7%)	
PRISM III score, median (min-max)	9 (0-27)	2 (0-29)	2 (0-40)	<0.001
Length of stay, median (min-max)	7 (1-46)	5.5 (3-45)	4 (1-114)	0.018
Mortality, n (%)	6 (%20.0)	3 (10.0%)	21 (70.0%)	0.003
PRBC transfusion				<0.001
None	1 (0.2%)	20 (4.9%)	386 (94.8%)	
One time	17 (27.4%)	11 (17.7%)	34 (54.8%)	
≥2 times	14 (25.5%)	7 (12.7%)	34 (61.8%)	

PRISM III : Pediatric Risk of Mortality PRBC: Packed red blood cell

DISCUSSION

There are many causes of anemia in critically ill pediatric patients. First off, active bleeding and iatrogenic blood loss due to laboratory tests are frequent in the PICU. Patients receive a lot of intravenous fluids, which causes further hemodilation. In addition, critically ill patients are prone to anemia as a result of abnormal iron metabolism, nutritional deficiencies, decreased amount of erythropoietin, and inhibited bone marrow.[2] Due to these factors, numerous children will develop anemia at a certain point during their treatment in the intensive care unit.

A total of 22.1% of our patients received at least one PRBC transfusion. The median Hb values for patients who underwent one-time and numerous transfusions were 8.35 g/dl and 8.9 g/dl, respectively. These rates are consistent with retrospective studies in PICUs.[7-9] According to a study by Rafique et al.[13] PRBC were the most commonly incorrectly transfused blood product (20%). Confusion between the more recent restriction RBC transfusion strategy and the more established liberal RBC transfusion strategy is the most likely explanation for this.[10] Nevertheless, a definitive threshold for hemoglobin (Hb) levels that necessitate transfusion in severely ill patients has yet to be established. In 2019, the Pediatric Critical Care Transfusion and Anemia Expertise Initiative recommended transfusion of critically ill children with Hb below 5 g/dl and avoidance of transfusion in children above 7 g/dl if they are hemodynamically stable. In Hb values between 5-7 g/dl, they recommend deciding according to the patient's condition. However, it should be kept in mind that these patients are in critical condition and their oxygenation may be poor. Therefore, the decision should not be made based on the Hb value alone, and the clinical condition of the patient should also be evaluated, such as hemodynamics.[5]

The study revealed elevated transfusion rates among patients admitted for sepsis, hemato-oncological illnesses, and acute renal failure. However, Armano et al.8 demonstrated the requirement of PRBS transfusion in patients hospitalized for respiratory failure or elective surgery. The primary factor contributing to this difference can be attributed to the larger sample size of sepsis patients included in our research. Additionally, it is worth noting that cardiac surgery comprised the majority of elective procedures in the study conducted by Doctor et al.[8] On the other hand, in the study conducted by Muszynski et al.[11] in patients with sepsis, PRBC transfusion rates were shown to increase to 50%. The most frequent hospitalization diagnoses for patients requiring transfusions were respiratory failure, cardiac failure, and sepsis, according to a survey carried out in our nation.[12]

Our analysis identified several risk factors associated with PRBC transfusion, as evidenced by numerous previous studies. A higher PRISM III score, prolonged PICU stay, requirement of IMV, and extracorporeal treatments were found to be independently associated with a PRBC transfusion.[7,13,14] The likelihood of these risks is further amplified in cases involving several transfusions.

Interestingly, our study found no correlation between Hb levels below 7 g/dl and mortality. In contrast, mortality was more prevalent among patients with Hb levels above 8 g/dl. Upon careful examination of the data, it was observed that a total of 11 patients, constituting 36.7% of the non-survivors, were admitted to the PICU with a confirmed diagnosis of sepsis. Sepsis is one of the leading global causes of pediatric mortality. The potential explanation for the increased mortality observed in patients with hemoglobin (Hb) levels over 8 g/dl, may be attributed to efforts aimed at maintaining higher hemoglobin values which is intended to optimize tissue oxygenation.

While the presence of severe anemia can result in more adverse consequences, it is important to acknowledge that transfusions also have inherent dangers. Numerous studies have investigated the correlation between transfusions of PRBC and morbidity and mortality. The association between PRBC transfusion and mortality risk was investigated in a study conducted by Kneyber et al.[7] which included a sample of patients with anemia (Hb<9.6 g/dl) from PICU. The study revealed that children who received PRBC transfusion showed increased mortality, longer stays in PICU, and prolonged use of IMV, and inotropic agents. In another study, early transfusion within the first 2 days was found to be associated with mortality.[11] With mortality rates as high as 15%–30%, the main causes are hemolytic transfusion responses, acute lung injury from transfusions, and acute circulatory overload from transfusions.[15] However, pre-transfusion Hb level was not significantly associated with mortality.[7] In another study by Bateman et al.[17] it was found that PRBC transfusion was significantly associated with increased risk of mortality, cardiac arrest, nosocomial infections, and longer PICU stay and requirement of IMV, considering other factors such as age at presentation and severity of disease. Consistent with the literature, in our study, PRBC transfusions had a notable impact on death rates. Furthermore, this association was found to be more pronounced as the frequency of transfusions increased. Therefore, not only the benefits but also the risks of RBC transfusion should be considered when making the transfusion decision.

Study Limitations

The main limitation of our study was the inclusion of only one tertiary center. Research conducted across multiple centers has the potential to yield supplementary information. In addition, we could not provide complete data on transfusion-related complications. Multicenter studies on transfusion-related complications will provide insights to clinicians to determine the advantage/disadvantage ratio of PRBC transfusion and how much erythrocyte suspension should be given to which patient.

CONCLUSION

Clinicians should consider that the administration of PRBC transfusions in critically ill patients may have the potential to both raise mortality and provide life-saving benefits during their stay in PICU. As with any treatment with potential side effects, it is essential to reduce the use of unnecessary blood products.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ethical Committe of Şehit Prof. Dr. İlhan Varank Training and Research Hospital (Date:17.02.2023, Decision No: E-46059653-050.99-209549220).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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