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Guest Editorial

Criteria for Transfusion of Red Blood Cells in the Critical Pediatric Patient: Take a Look at the Child, Not the Number

Arianne Ditzel Gaspar*, Jáder Pereira Almeida and Paulo Ramos David João

Pediatric Intensive Care Unite, Pequeno Príncipe Hospital, Brazil

***Corresponding Author**: Arianne Ditzel Gaspar, Pediatric Intensive Care Unite, Pequeno Príncipe Hospital, Brazil.

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Anemia is common in pediatric patients and transfusion of red blood cells can save lives in severely ill children, especially in hemorrhagic shock. We also know that the tolerance of anemia in this population has not yet been clarified, but the evidence in the two decades ago has suggested a careful analysis between benefits and adverse reactions, since red blood cell transfusion has been associated with increased rates of morbidity and mortality, and it is necessary to guarantee more appropriate decisions regarding its indication [1,2].

Historically, the cut-off point for hemoglobin ≤ 10 g/dL (hematocrit ≤ 30%) has been the rule for the indication of transfusion of red blood cells, but there is a lack of evidences to justify its indication, especially in pediatric patients. Some studies had shown an average of 5 units of red blood cells transfusion per critical patient, which is considered a high number [3]. The "liberal" treatment can result in millions of transfusions annually without a real benefit, overburdening the health system, especially in regions where resources are reduced [4].

But why is there such a tendency to transfuse red blood cell concentrate? We can justify through its physiological mechanisms: the main objective of red blood cell transfusion is to increase the supply of oxygen (DO_2) and consequently to enable greater tissue utilization of oxygen. DO_2 depends on hemoglobin concentration, cardiac output and arterial oxygen saturation. The increase in hemoglobin would enhance the ability to carry oxygen in the blood and optimize its supply. Finally, it would reduce anaerobic metabolism, decrease the risk of acid-base disorders and improve the functioning of the organs.

However, there are 3 pathophysiological mechanisms that suggest that red blood cell transfusion can result in deleterious effects for critically ill patients, despite allowing an increase in hemoglobin concentration: (1) 2 - 3 diphosphoglycerate is rapidly depleted and becomes undetectable one week after blood storage, taking 24 hours to restore its normal level after transfusion. Its depletion causes a deviation to the left of the hemoglobin dissociation curve, making it more similar to oxygen and reducing its tissue release; (2) adenosine triphosphate (ATP) is also depleted during storage, leading to deformity of the red blood cell membrane, which loses its integrity and is destroyed, causing obstruction of blood flow in the microcirculation; (3) the hemoglobin present in the red blood cell units reduces the production of nitric oxide, resulting in vasoconstriction of small vessels and a reduction in DO_2 [3].

In addition, we must consider other adverse events, such as transfusion-associated lung injury (TRALI), transfusion-associated circulatory overload (TACO) and transfusion-related immunosuppression (TRIM). These complications can occur in short or long term, being associated with a longer stay in the pediatric intensive care unit (ICU) and invasive mechanical ventilation [2]. Fever and transfusion-related allergies are common events, and can occur in up to 1% of cases, being related to the presence of leukocytes and donor plasma proteins in the stocked units, respectively. In addition, infections and transfusion-related hemolysis are additional risks, although there has been a large reduction in its incidence as a result of more sophisticated screening tests [4].

So, which is the most appropriate threshold for red blood cell transfusion in critical pediatric patients? Some studies in children, with a high level of evidence, can help us to answer this question. Lacroix., *et al.* in their multicenter randomized clinical trial comparing red

blood cell transfusion with restrictive threshold (Hb ≤ 7.0 g/dL) in relation to liberal threshold (Hb ≤ 9.5 g/dL) in 637 critically ill children, demonstrated that the restrictive strategy is as effective as the liberal strategy, in addition to reducing the number of transfusions without increasing the mortality rate, the length of stay in the intensive care unit (ICU) and adverse events [5]. Rouette., *et al.* in a multicenter randomized clinical trial evaluating pediatric patients undergoing surgical procedure, also did not observe an increase in the mortality rate and multiple organ dysfunction syndrome between the two groups, however an increase in the length of stay in the ICU was observed in the group with liberal transfusion [6].

Observational studies also showed benefits in relation to the use of restricted red blood cell transfusions. Bateman., *et al.* in a prospective multicenter cohort study evaluated 977 children, identified longer periods of mechanical ventilation and length of stay in the ICU, in addition to higher rates of infection, cardiorespiratory dysfunction and mortality in patients who received red blood cell units [7]. Valentine., *et al.* chose to compare transfusion in groups with Hb: 8 g/dl to Hb: 7 g/dl and in the second group there was a 10% reduction in transfusions without worsening results, including mortality [8]. Thus, we can realize a tendency to stricter criteria for transfusion of red blood cell units, both in clinical patients and in children in perioperative status.

It is necessary to emphasize the use of rigid methods, to guarantee the veracity of the studies, does not mean that rigidity must be used in clinical practice. The assessment of the patient's clinical-hemodynamic status should always be considered when indicating red blood cell transfusion. Therefore, if the serum hemoglobin level is at the limit for transfusion, it is more appropriate to reserve the blood component and use it in case of changes in the hemodynamic condition. This strategy is even used in more complex patients, such as children with congenital heart disease, without prejudice to the results [9].

Considering the current evidences, we believe that restrictive transfusion protocols are the future route for the management of critical pediatric patients. Even so, we realize that professionals have not adapted to this practice, perhaps due to the lack of pediatric guidelines to guide transfusions in children in recent decades. In this context, we suggest considering as a reference the consensus of recommendations for the practice of red blood cell transfusion in critically ill children published by the Pediatric Critical Care Transfusion and Anemia Expertise Initiative [2] (Table 1 and 2).

No hemorrhagic Shock	
Hb < 5g/dL	RBC transfusion
Hb 5-7g/dL	Clinical judgement
Hb > 7g/dL	If patient is hemodynamically stable, go to table 2.
	If patient is hemodynamically unstable, follow clinical judgment.
Hemorragic Shock	
RBC: Plasma: platelets 2:1:1 or 1:1:1 until bleeding is no longer life threatening	
Hb: Hemoglobin; RBC: Red Blood Cell Concentrate	

Table 1: *General criteria for red blood cell transfusion in critically ill pediatric patients. Adapted from Recommendations for Red Blood Cell Transfusion Practice in Critically ill children from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative (2018).*

General crticially ill	No transfusion
Post-operative	No transfusion
Respiratory failure (excluding severe PARDS)	No transfusion
Sepsis	No transfusion
Non-life threatening bleeding	No transfusion

Requiring renal replacement therapy	No transfusion	
Acute brain injury	Consider RBC if Hb 7 - 10 g/dL	
Oncologic diagnoses or undergoing hemato-poietic stem cell transplant	Consider RBC if Hb ≤ 7 - 8 g/dL	
Auto-immune hemolytic anemia	Clinical judgement	
Severe PARDS	Clinical judgement	
Cardiac Disease	Uncorrected congenital heart disease	Maintain Hb 7 - 9 g/dl de-pending cardiac reserve
	Biventricular repair	No transfusion
	Single ventricle, stage 1 palliation	No transfusion if Hb > 9 g/dL and adequate oxygenation
	Congenital or acquired myocardial dysfunction	Clinical judgement (no evi-dence that transfusion above 10 g/dl is beneficial)
PARDS: Pediatric Acute Respiratory Distress Syndrome.		

Table 2. *Red blood cell transfusion criteria in stable patients with hemoglobin ≥ 7 g/dL. Adapted from Recommendations for Red Blood Cell Transfusion Practice in Critically ill children from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative.*

Finally, the decision regarding the use of red blood cell concentrate should consider the patient's clinical and hemodynamic condition, prioritizing the child's treatment, not the number [10].

Conflict of Interest

There is no conflict of interest.

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