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Why is it important to assess indications for red blood cell transfusion in premature infants?

Por que é importante analisar fatores associados à indicação de transfusões de hemácias em prematuros?

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Performing blood transfusions for premature infants is becoming an increasingly discussed and controversial topic. Interestingly, once a procedure that was routinely performed without much discussion when a premature infant was anemic or had severe blood loss, blood transfusion is now the focus of discussions regarding its indications, with conflicting concerns related to the harm resulting from excess or inadequate red blood cell transfusion.

Before discussing the risks and benefits of red blood cell transfusion, one must remember that anemia is common in the first few months of life in premature neonates, mainly due to the blood loss associated with multiple blood drawing during the first few weeks of life, during which critically ill premature infants require continuous monitoring for their respiratory, cardiovascular, infectious, metabolic, and nutritional status. Furthermore, the low rate of erythropoiesis associated with erythropoietin deficiency, which is characteristic of the initial adaptation to extrauterine life, causes premature neonates to become progressively more anemic during their hospitalization in the neonatal intensive care unit after the initial clinical stabilization.[1]

Thus, red blood cell transfusions are frequently necessary in neonatal units that care for premature infants. A study by the Brazilian Network on Neonatal Research (Rede Brasileira de Pesquisas Neonatais), in which 952 premature infants weighing between 400 and 1,499 g born in eight Brazilian university neonatal units between 2006 and 2007, showed that 532 infants (56%) received at least one blood transfusion. Of these patients, 335 (63%) received more than one transfusion during the hospital stay, and the mean number of transfusions per newborn ranged from 1.6±1.0 to 5.9±5.2 among the studied centers.[2] Another recent assessment of the data from this same research network, which included 4,238 premature infants with a mean gestational age of 29.9±2.9 weeks and weight of 1.084±275 g born in 16 units in eight Brazilian states from 2009 to 2011, indicated that 2,208 patients (52%) received at least one red blood cell transfusion, and the rate varied from 34 to 72% among the centers.[3]

Such variation among the centers may at least partially be attributed to using empiric, rather than evidence-based, guidelines for performing red blood cell transfusions, with protocols ranging from restrictive to liberal transfusion thresholds according to published international guidelines for indications for such transfusions.[4-6]

Restrictive criteria for blood product transfusion take procedure-related concerns into account. Traditionally, such concerns are due to the viral, bacterial, and prion infections related to the donor, but incidence of such infections has been progressively declining.[7] However, there has been a growing concern

Conflicts of interest: None.

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regarding increased mortality in transfused premature infants,[8] partially related to the immunomodulatory and proinflammatory effects of transfusions and the development of multiple organ failure.[9]

In this context, the association between necrotizing enterocolitis and red blood cell transfusion has been reported in the literature.[10,11] One hypothesis is that the release of free hemoglobin after red blood cell transfusion reduces the production of nitric oxide, a potent mesenteric vasodilator.[12,13] Additionally, red blood cell transfusion may lead to the activation of T-antigen variants or other antigens present on the surface of red blood cells, producing antibodies that may cause intravascular hemolysis. Such antibodies are also found in donor blood and have been frequently identified in children with sepsis and necrotizing enterocolitis, although their pathophysiological role in these diseases is not well characterized.[14,15] However, this association was described in experimental studies, and randomized, controlled studies are necessary for more robust conclusions.

In contrast, more liberal red blood cell transfusion criteria take into account the possible long-term effects of anemia, especially on growth and development, due to decreased tissue oxygen delivery. In a study that compared the long-term outcomes, premature infants were randomized to maintain high or low hemoglobin levels during the neonatal period. Neurodevelopment was assessed by Bayley II scales and delay was defined by mental index score <85 with a corrected age of 18 to 21 months. Developmental delay was more frequent in children who received transfusions under more restrictive criteria.[16] Other long-term studies that used psychological tests and functional brain imaging for 8- to 15-year-old patients favored more restrictive strategies for red blood cell transfusion during the neonatal period. One of these studies showed that premature infants transfused using liberal criteria performed poorly on tests of association, verbal fluency, visual memory, and reading compared to the infants transfused under restrictive criteria.[17] Corroborating these results, another study showed that several areas of the brain were smaller, especially the white matter and the subcortical nuclei, in the premature infants transfused using liberal criteria compared to restrictive criteria.[18] However, these studies had a significant loss of follow up after the neonatal period, compromising their external validity.[19]

In this context, Freitas and Franceschini bring their contribution to this issue of the Revista Brasileira de Terapia Intensiva.[20] The authors studied 254 premature infants born in one center in Minas Gerais State, Brazil, and 100 of these infants (39%) required at least one transfusion. A gestational age less than 32 weeks and the presence of neonatal sepsis were factors associated with transfusions in this group of premature infants. Other two studies of the Brazilian Network on Neonatal Research also evaluated factors associated to red blood cell transfusions in very low birth weight infants. The first one, which assessed 952 premature infants weighing between 400 and 1,499 g in eight Brazilian university neonatal units between 2006 and 2007, indicated that the factors related to transfusions, adjusted for the birth center, were: late-onset sepsis (OR=2.83, 95% CI 1.80-4.44), grade III/IV intraventricular hemorrhage (OR=9.42, 95% CI 3.32-26.75), resuscitation requiring intubation in the delivery room (OR=1.69, 95% CI 1.02-2.83), umbilical catheter use (OR=2.39, 95% CI 1.30-4.40), number of days on mechanical ventilation (OR=1.09, 95% CI 1.02-1.16), oxygen therapy (OR=1.05, 95% CI 1.03-1.07), and parenteral nutrition (OR=1.06, 95% CI: 1.03-1.10).[2] The second study assessed data from 4,238 premature infants born in 16 units in eight Brazilian states from 2009 to 2011 and showed that the factors associated with transfusions, adjusted for the birth center, were: low gestational age (OR=1.55; 95% CI 1.14-21.11), presence of apnea (OR=1.82; 95% CI 1.42-2.34), pulmonary hemorrhage (OR=2.18; 95% CI 1.39-3.43), use of oxygen for 28 days or more (OR=1.46; 95% CI 1.09-1.96), clinical sepsis (OR=3.37; 95% CI 2.63-4.33), necrotizing enterocolitis (OR=4.16; 95% CI 2.34-7.34), grade III/IV intraventricular hemorrhage (OR=1.74; 95% CI 1.10-2.77), retinopathy of prematurity (OR=1.36; 95% CI 1.00-1.86), mechanical ventilation (OR=2.62; 95% CI 1.98-3.47), umbilical catheterization (OR=2.03; 95% CI 1.45-2.285), parenteral nutrition (OR=3.17; 95% CI 1.84-5.43), vasoactive drugs (OR=1.74; 95% CI 1.21-2.50), and length of hospital stay >60 days (OR=4.90; 95% CI 3.67-6.54).[3] Therefore, regardless of using restrictive or liberal protocols for red blood cell transfusion, the studies together show that transfusion indications were associated with initial illness severity, which was highlighted by the presence of prematurity and associated morbidities, and by the prolonged need of life support measures such as oxygen, mechanical ventilation, central catheters, and parenteral nutrition. Furthermore, the diagnosis of late-onset sepsis on preterm newborn infants, which indicates their immunological immaturity and their unique susceptibility to infra-structure deficiencies of human and equipment resources in Neonatal Intensive Care Units, was associated with

clinical instability and the need for support, including the need for transfusion of blood products.

Thus, using evidence-based guidelines for red blood cell transfusion in premature infants is absolutely necessary. The major issue is that the evidence is controversial and does not allow for determining universal guidelines. Future studies must identify factors associated to the need for red blood cell transfusion in neonatal intensive care units and attempt to minimize these factors as well as phlebotomy losses in this susceptible population in order to rationalize the indications for such transfusions.

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