



MINI REVIEW



Red blood cell transfusion in preterm neonates: a huge debate on tiny patients

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Abstract

Preterm infants are more liable to suffer from anemia, as 90% of extremely low birth weight infants receive red blood cell transfusion. When to receive red blood cell transfusion is not well defined until now, even the complications and hazards resulting from the transfusion of adult red blood cell into the premature circulation is still a matter of debate. In this review, fetal erythropoiesis and the unique pathophysiology of anemia of prematurity is discussed, different meta-analysis studies are presented regarding liberal (high hemoglobin threshold) or restrictive (low hemoglobin threshold) transfusion protocols, early or late transfusion preferences. To clarify the picture of this, everyday decision neonatologists need to take, whether or not to give this premature infant a red packed cell transfusion, which may affect the life of this infant indefinitely. Until now, no fixed guidelines are present regarding when to transfuse anemia and still dependent on expert opinion and center experience.

Keywords anemia; prematurity; transfusion

Introduction

Neonatal anemia, defined as a hemoglobin (Hb) or hematocrit (Hct) concentration of >2 standard deviations below the mean for postnatal age, is a major problem encountered in neonatal intensive care units (NICUs). Ninety percent of extremely low birth weight infants receiving at least one red blood cell (RBC) transfusion during their stay in the NICU [1]. A low Hb level at birth is considered as a risk factor for mortality [2].

Erythropoiesis in the fetus and newborn

Fetal erythropoiesis occurs sequentially during embryonic development in three different sites: yolk sac, liver, and bone marrow. Yolk-sac formation of RBCs is maximal between 2 and 10 weeks of gestation. Bone marrow production of RBCs begins at around week 18, and, by the 30th week of fetal life, bone marrow is the major erythropoietic organ [3].

At birth, in term newborns, almost all RBCs are produced in the bone marrow, although a low level of hepatic erythropoiesis persists through the first few days of life. An increasing role for erythropoietin (EPO) is observed during the hepatic and bone marrow phase of erythropoiesis, the liver being the most likely candidate for EPO production during fetal life

[4]. Fetal RBCs contain mainly fetal Hb which has higher oxygen affinity compared to adult Hb that is produced after birth. Hb, Hct, and RBC count increase throughout fetal life with a rate of RBC production during the latter part of fetal life that is fivefold that of a normal adult. Extremely large RBCs with an increased content of Hb are produced early in fetal life. The size and Hb content of these cells decrease throughout gestation, but the mean corpuscular hemoglobin concentration (MCHC) does not change significantly. Therefore, RBC indices and morphology at birth are different from the adult ones and gradually modify to reach childhood values several months after birth. The distinct features of newborn erythrocytes and their metabolism both in term and preterm infants must be taken into consideration when evaluating a neonate with anemia [5].

Reference hematologic values for term and preterm newborn have been published [6]. Due to population variation in RBC indices and variability of the norms in different automated machines, many centers determine normative values for their population and display reference values in their websites [7].

Etiopathology of anemia in preterm newborns

Several endogenous and exogenous factors contribute to the anemia of prematurity (AOP) [8]. Low plasma EPO levels in response to anemia due to decreased EPO production and accelerated EPO catabolism is the first factor in AOP. The postnatal decrease in EPO production translates into a 20% decrease in erythroid progenitor cells in the marrow. The mechanisms responsible for the diminished EPO output by preterm neonates are only partially defined. First mechanism is the fetus transitions from the hypoxic intrauterine environment to the oxygen-rich postnatal environment, EPO production is downregulated. Second mechanism of decreased EPO in preterm is that the primary site of EPO production in preterm infants is still in the liver, rather than the kidney. After birth, EPO production passes from the liver to the kidney. This transition occurs during the first 3-4 months past term birth. The timing of the switch from liver to kidney is set at conception and is not accelerated by preterm birth. This is an important contributor to the AOP because the liver is less sensitive to tissue hypoxia as a stimulus for EPO production than the kidney. The third known mechanism causing decreased EPO in preterm is that EPO clearance and volume of distribution is also high in neonates relative to adults, and this likely contributes to low circulating concentrations [9].

Increased growth rate compared to that of term infants is also an endogenous factor causing AOP. Exogenous factors contributing to the AOP include iatrogenic blood loss for frequent laboratory testing, iron deficiency, or other nutritional deficiencies, inflammation, infections, and chronic illness [9]. Physiological and non-physiological contributors of APO are shown in (Fig. 1) [10].

When is red blood cell transfusion (RBCT) indicated?

Anemia becomes symptomatic when there is an imbalance between oxygen delivery and consumption [11] which may not occur universally at the same Hb for every preterm infant. Symptoms of anemia (e.g., desaturations, bradycardias, increased oxygen requirement, and tachycardia) are non-specific and can be due to alternative causes including sepsis, evolving lung conditions (including worsening respiratory distress syndrome), or gastro-oesophageal reflux. Therefore, RBCT may not result in resolution of those clinical features [12].

Generally, RBCT are given to keep Hb levels above a certain threshold depending on the level of cardiorespiratory support required. Nearly half of RBCT given to ELBW infants are given during the first 2 weeks of life, when cardio-respiratory illness is most severe and laboratory

blood tests are greatest; weekly phlebotomy losses during this period average 10–30% of the total blood volume (10–25 mL/kg) [13].

RBCT are also given due to acute blood loss (e.g., fetomaternal hemorrhage or placental abruption) or due to clinical symptoms regardless of the Hb level, or to an infant breathing on their own in air, but with an Hb below a certain threshold, with the intention of improving their weight gain [14].

However, no universally used Hb threshold for RBCT has been defined [15], meaning that some infants are exposed to progressive anemia which may result in gut hypoxia and injury [16]. The decision for RBCT is made by clinicians based on their clinical judgement and national [17] or local guidelines. RBCT are administered when clinicians predict that the benefit will outweigh the risks. However, the reasons behind these judgements are not always evidence based and depend entirely on local guidance and the clinician's perception [18]. Other than clinical indicators, the only investigation to date that can give some insight into tissue oxygen sufficiency is Near Infrared Spectroscopy (NIRS) which can be used to determine the splanchnic cerebral oxygen ratio (SCOR). A recent study showed that infants with a low baseline SCOR (< 0.73) were more likely to improve after transfusion; thus, specifying premature infants who would

benefit from RBC transfusions [19]. However, this is not available and the dependency on clinical indicators, especially tachycardia and oxygen requirements, have still the upper hand.

Transfusion threshold: high threshold (liberal) versus low threshold (restrictive)

A Cochrane Review of four trials (2011) investigating low versus high thresholds for transfusion in the very low birth weight infant (difference of 2 g between transfusion thresholds) confirmed that there was no difference in survival, short term complications as well as long term complications including retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD) nor in neurological outcome between both groups. The Cochrane Review authors' overall recommendation is, therefore, not to exceed the higher levels of Hb used in these trials, and thus diminish the risks of over-transfusion, but not to allow the level of Hb to fall below the lower limits tested in these studies until further studies are completed (Table 1) [20].

Observations from post-hoc analyses in the Premature Infants in Need of Transfusion (PINT) study suggest poorer outcomes in neurodevelopment [21] and at hospital discharge [15] in the low threshold groups and make it difficult to reject a conclusion that the use of a high threshold may be beneficial.

More recently two meta-analysis [22, 23] studies confirmed that using restrictive red cell transfusion thresholds was associated with less donor exposure rates and lower mean number of transfusions. Restrictive thresholds were not associated with harm regarding mortality or overall morbidity and were associated with a reduced number of infections complicating transfusions.

In 2016, the British Committee for Standards in Hematology confirmed the restrictive red cell thresholds for very preterm babies. For older and term neonates there is no evidence for specific thresholds and transfusion decision should be clinically guided in keeping with the restrictive measures bearing in mind the increased Hemoglobin need with increasing oxygen requirement (Table 2) [24].

Despite these guidelines, stable growing premature babies, who are beyond two weeks of life and off supplemental oxygen, may still be quite comfortable with hemoglobin levels of 6.5–7 grams provided their iron level is maintained and they have an adequate reticulocyte response.

The level is not the indication. If they are exhibiting no symptoms and are gaining weight well, delaying transfusion is accepted [25].

Transfusion risks specific to preterm neonates

The preterm baby receiving multiple transfusions is not only exposed to multiple donors and to infection risk with blood borne viruses, but also exposed to preservatives used in blood products [26], volume overload and elevated plasma non-transferrin-bound iron [27] and RBCT leading to possible overloading of the liver with iron [28] in very low birth weight (VLBW) infants, the clinical implications of which is still unknown.

Bronchopulmonary dysplasia, Retinopathy of prematurity (ROP), and necrotizing enterocolitis (NEC) all likely involve oxidative damage to immature tissues. It has been postulated that transfusions of adult erythrocytes contribute to the risk of developing these morbidities, as a consequence of adult Hb releasing non-physiological quantities of oxygen to developing tissues. Previous studies reported two new potential risks of transfusions among VLBW neonates. The first is an association between “early” RBC transfusions and the subsequent occurrence of intraventricular hemorrhage [29, 30], although the underlying pathophysiological mechanism of this association remains to be demonstrated.

The second reported risk is an association between “late” RBC transfusions and the subsequent occurrence of NEC. In recent years, a positive correlation was found between receipt

of a blood transfusion and development of NEC within the following 48 hours [31].

The potential pathogenic mechanism(s) resulting in transfusion-associated NEC include the variables for which the transfusion was ordered (i.e. the Hct value of the patient at transfusion), immunologic mechanisms, and impaired biomechanical properties of the banked erythrocytes [30].

In a review in 2005, Agwu and Narchi found only low-quality evidence that blood transfusion was associated with the development of NEC in preterm infants [32]. Since then further studies, including a systematic review and meta-analysis, have provided additional supportive evidence [31,33]. However, significant controversy remains.

Conclusion

The decision of RBCT is a multifactorial expert needing opinion but may be the only treatment option when the preterm neonate reaches a critical oxygen point beyond their ability to cope. So, a judicious use of blood transfusions is recommended, by unit specific guidelines. One can limit donor exposure by using multiple small packs from a single donor to multi transfuse a preterm infant, thus reducing donor exposure.

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