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REVIEW

Anaemia of prematurity: Pathophysiology and treatment

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ABSTRACT

Most infants with birth weight <1.0 kg are given multiple red blood cell (RBC) transfusions within the first few weeks of life. The anaemia of prematurity is caused by untimely birth occurring before placental iron transport and fetal erythropoiesis are complete, by phlebotomy blood losses taken for laboratory testing, by low plasma levels of erythropoietin due to both diminished production and accelerated catabolism, by rapid body growth and need for commensurate increase in red cell volume/mass, and by disorders causing RBC losses due to bleeding and/or hemolysis. RBC transfusions are the mainstay of therapy with recombinant human erythropoietin largely unused because it fails to substantially diminish RBC transfusion needs — despite exerting substantial erythropoietic effects on neonatal marrow.

1. Introduction

Preterm infants with birth weight <1.0 kg (commonly designated as *extremely low birth weight*, or ELBW, infants) have completed ≤29 weeks of gestation, and nearly all will need red blood cell (RBC) transfusions during the first weeks of life. Every week in the United States, approximately 10,000 infants are born prematurely (i.e., <37 weeks of gestation), with 600 (6%) of these preterm infants being ELBW.[1] Approximately 90% of ELBW neonates will receive at least one RBC transfusion.[2,3] Physiologic and nonphysiologic factors related to prematurity are responsible for the anaemia of prematurity and this high transfusion rate, with phlebotomy blood loss for laboratory testing as, perhaps, the biggest contributor.[4] Because of efforts to minimize the amounts of blood drawn from neonates for laboratory testing[5] and to transfuse more conservatively (i.e., to accept lower pretransfusion hematocrit values), the number of RBC transfusions given to preterm infants has dropped over the years.[2,6] At the University of Iowa Hospitals & Clinics, the mean value during years 2000 to 2005 of RBC transfusions given to each transfused ELBW infant was 5.4/infant, compared to 1.1/infant for premature infants with higher birth weights from 1001 to 1500 g.

2. Pathophysiology of the anaemia of prematurity

All neonates experience a decline in circulating RBCs during the first weeks of life. This decline results both from multiple physiological factors and, in sick preterm infants, from several additional factors — the major one being phlebotomy blood losses for laboratory testing. In healthy term infants, the nadir hemoglobin value rarely falls below 10 g/dL at an age of 10 to 12 weeks. Because this postnatal drop in hemoglobin level in term infants is well tolerated and requires no therapy, it is commonly referred to as the "physiological anaemia of infancy." In contrast, this decline is more rapid (i.e., nadir at 4–6 weeks of age) and the blood hemoglobin concentration falls to lower levels in infants born prematurely — to approximately 8 g/dL in infants with birth weights of 1.0 to 1.5 kg and to approximately 7 g/dL in infants with birth weights <1 kg. Consequently, because the pronounced decline in hemoglobin concentration that occurs in many ELBW infants is associated with abnormal clinical signs and need for allogeneic RBC transfusions, the "anaemia of prematurity" is not accepted to be a physiological and benign event.[7]

Physiological factors play a role in the pathogenesis of the anaemia of prematurity. Because ELBW infants are born before the 3rd trimester of gestation, they are deprived of most of the iron transported from the mother and a great deal of *in utero* fetal erythropoiesis. Extrauterine body growth is extremely rapid during the first months of life, and RBC production by neonatal marrow must increase commensurately. It is widely accepted that the circulating life span of neonatal RBCs in the bloodstream is shorter than that of adult RBCs due to several developmental differences in metabolic and membrane characteristics of neonatal RBCs compared to RBCs from adults. However, this is difficult to measure accurately because studies of transfused autologous (neonatal or placental) RBCs labeled with biotin or radioactive chromium may underestimate RBC survival in the infant's bloodstream for technical reasons.[8] In healthy adults — where body size is stable so that blood and RBC volumes are constant (i.e., not increasing with growth), when no RBC transfusions are given, and when large volumes of blood (RBCs) are not being taken for laboratory studies — the gradual disappearance of transfused labeled RBCs, caused by dilution with RBCs produced by the bone marrow, accurately reflects RBC survival in the bloodstream. In contrast, one or more of these confounding factors (i.e.,

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growth and increasing blood volume, RBC transfusions, phlebotomy RBC losses) exists in infants — particularly, sick preterms — to introduce errors into the calculations performed when determining RBC survival.

A key reason that the hemoglobin nadir is lower in preterm than in term infants is the former group's diminished plasma erythropoietin (EPO) level in response to anaemia.[9] Although anaemia provokes EPO production in premature infants, the plasma levels achieved in anemic infants, at any given hematocrit value, are lower than those observed in comparably anemic older persons.[10] Erythroid progenitor cells of newborn infants are quite responsive to EPO *in vitro* — a finding suggesting that inadequate production EPO is, at least, one major cause of neonatal anaemia, *not* marrow unresponsiveness.[11]

All of the mechanisms responsible for the low plasma EPO levels, as seen in preterm neonates, are only partially defined and, likely, they are multiple. One mechanism is that the primary site of EPO production in preterm infants is in the liver, rather than kidney.[12] This dependency on hepatic EPO is important because the liver is less sensitive to anaemia and tissue hypoxia — hence, there is a relatively sluggish EPO response (i.e., diminished production) to the infant's falling hematocrit (HCT) level. The timing of the switch from liver to kidney as the primary site for EPO production is set at conception and is not accelerated to compensate for preterm birth. Viewed from a teleological perspective, decreased hepatic production of EPO under *in utero* conditions of relative tissue hypoxia may offer an advantage to the fetus. If this were not the case, normal levels of fetal hypoxia *in utero* could trigger high levels of EPO production and lead to extreme erythrocytosis and consequent hyperviscosity. Following birth, however, diminished EPO responsiveness to tissue hypoxia is disadvantageous to the infant and leads to anaemia because it impairs compensation for low HCT levels caused by rapid growth, RBC losses due to phlebotomy, clinical bleeding, hemolysis, etc.

Diminished EPO production cannot entirely explain low plasma EPO levels in anemic infants because extraordinarily high plasma levels of EPO have been reported in some fetuses and infants.[13,14] Moreover, macrophages from human cord blood produce normal quantities of EPO messenger RNA and protein.[15] Thus, additional mechanisms beyond low production must contribute to diminished EPO plasma levels. For example, plasma levels of EPO are influenced by rapid metabolism (clearance) as well as by production. Data in human infants[16] have demonstrated low plasma EPO levels due to increased plasma clearance, increased volume of distribution, more rapid fractional elimination, and shorter mean plasma residence times — when compared to values in adults. Thus, accelerated catabolism compounds the problem of diminished EPO production, so that the low plasma EPO levels are a *combined effect* of decreased synthesis plus increased metabolism.

Phlebotomy blood losses play a key role in the anaemia of prematurity and in the need for RBC transfusions — particularly, during the first few weeks of life. The modern practice of neonatology requires critically ill neonates to be monitored closely with serial laboratory studies such as blood gases, electrolytes, blood counts and cultures. Small preterm infants are the most critically ill, require the most frequent blood sampling, and suffer the greatest proportional loss of RBCs because their circulating RBC volumes are smallest. In the past, the mean volume of blood removed for sampling has been reported to range from 0.8 to 3.1 mL/kg per day during the first few weeks of life for preterm infants requiring intensive care.[17] Promising "in-line" devices that withdraw blood, measure multiple analytes and then reinfuse most of the sampled blood have been reported.[18,19] They have decreased the need for RBC transfusions. However, until these devices are proven more extensively to be feasible, cost-effective, clinically efficacious and safe, replacement of blood losses due to phlebotomy will remain a key factor responsible for RBC transfusions given to critically ill neonates — particularly, transfusions given during the first four weeks of life. Meanwhile, it is critical to limit testing to only those tests absolutely needed for optimal care and to avoid overdraw (i.e., taking more infant blood than actually needed).[5]

3. RBC transfusions to treat the anaemia of prematurity

Guidelines for transfusing RBCs to preterm neonates are controversial, and practices vary greatly.[20–24] This lack of a universal approach stems from limited knowledge of the cellular and molecular biology of erythropoiesis during the perinatal period, an incomplete understanding of infant physiological/adaptive responses to anaemia, and contrary/controversial transfusion practice guidelines as based on results of randomized clinical trials and expert opinions. Generally, RBC transfusions are given to maintain a level of blood hemoglobin or HCT believed to be optimal for each neonate's clinical condition. Guidelines for RBC transfusions, judged to be reasonable by most neonatologists to treat the anaemia of prematurity, are listed by Table 1. These guidelines are very general, and it is important that terms such as "severe" and "symptomatic" be defined to fit local transfusion practices/policies. Importantly, guidelines are not mandates for RBC transfusions that must be followed; they simply suggest situations when an RBC transfusion would be judged to be reasonable/acceptable.

An important controversy that is still unresolved is the wisdom — or lack, thereof — of prescribing RBC transfusions to neonates using restrictive (RES) guidelines (i.e., permitting relatively low pretransfusion HCT values before giving an RBC transfusion) vs liberal (LIB) guidelines (i.e., relatively high pretransfusion HCT values). Two randomized, controlled trials have been published and, although many of their results agree, they disagree in one extremely important way — specifically, whether preterm infants are at increased risk of brain injury when given RBC transfusions per RES guidelines.[25,26] In both trials, preterm infants were randomly allocated to receive all small-volume RBC transfusions per either RES or LIB guidelines — with guidelines based on a combination of the pretransfusion HCT or hemoglobin level, age of the neonate, and clinical condition (i.e., need for ventilation, oxygen, etc.) at the time each transfusion was given.

Both studies found that neonates in the RES group received fewer RBC transfusions, without an increase in mortality or in morbidity as assessed by several clinical outcomes. However, one critical discrepancy was present. Bell et al.[25] found increases in apnea, severe intraventricular bleeding and brain leukomalacia in infants transfused per RES guidelines, whereas, Kirpalani et al.[26] found no differences in serious outcomes between infants in the RES vs LIB groups. However, rates of serious outcomes were fairly high in both groups of the Kirpalani study — perhaps, due to the extreme prematurity of the infants.[26] Although it is tempting to speculate that the higher blood HCT levels, in some way, protected the LIB group infants of Bell et al., it must be noted that the poor neurological outcome reported by Bell et al. was a *post hoc* composite endpoint.[25] Although the combination of severe apnea, intraventricular bleeding and brain leukomalacia was statistically significantly more frequent in RES infants, the trial was not designed to study this endpoint *a priori*. Thus, the finding cannot be accepted as proven at this time, nor has a cause-and-effect relationship between RBC transfusion practices and neurological damage been established.

It is important to note that a follow-up study of infants enrolled in the trial of Kirpalani et al.[26] was completed when the infants reached the age of 18–24 months.[27] There was no statistically significant difference found between RES and LIB groups when assessed by the primary outcome, stated *a priori*, as a composite of either death or survival with one or more findings of cognitive delay (Bayley II MDI <70), cerebral palsy, blindness or deafness. However, in a *post hoc* analysis using a higher Bayley II MDI score of <85, subjects in the RES group did significantly worse — suggesting some agreement with the finding of Bell et al.[25] that RBC transfusions given per RES guidelines