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REVIEW ARTICLE

Prevention of the anaemia of prematurity

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Abstract Despite recent advances in neonatal and perinatal medicine, extremely low birth weight infants (ELBW) are at high risk of developing anaemia of prematurity (AOP) requiring packed red blood cell (RBC) transfusions. The benefit of transfusing allogenic RBCs for AOP is a controversial issue, except for disturbances in tissue oxygenation. Although the role of erythropoietin (EPO) in the pathophysiology of AOP is well known, neither early nor late recombinant human EPO therapy alters the number or volume of RBC transfusions. It is also known that one-half of the feto-placental blood volume remains outside the newborn infant's circulation at 30 weeks of gestation if the umbilical cord is clamped immediately. Delayed cord clamping (DCC) and umbilical cord milking (UCM) are the main methods for enhancing placental transfusion. The basic principle of these approaches depends on providing high haemoglobin (Hb) levels to premature infants in the delivery room. The enhancement of placental transfusion clearly results in higher Hb levels at birth, reducing the need for RBC transfusions as well as creating a better haemodynamic status during the initial hours of life. To date, enhancement of placental transfusion in the delivery room by either DCC or UCM seems to be the best preventive measure for AOP. Yet, studies on the associated neurodevelopmental outcomes are insufficient to reach a conclusion. This review summarizes the pathophysiology, treatment and preventative strategies of anaemia of prematurity in light of the current literature.

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1. Introduction

Recent advances in perinatal and neonatal medicine and the broader use of antenatal steroids, exogenous surfactants, sophisticated incubators and ventilator support modalities have resulted in a remarkable increase in the survival of preterm infants. Despite these advances, extremely low birth weight (ELBW) preterm infants remain at significant risk for the most frequent life-threatening complications of prematurity, such as intraventricular haemorrhage (IVH), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP) and anaemia of prematurity (AOP) [1]. Preterm infants, particularly those with a birth weight less than 1500 g, are at high risk of requiring at least one, and often, multiple red blood cell (RBC) transfusions [2]. The mean number of transfusions in the two largest studies ranged from 3.3 to 5.7, depending on whether restrictive or liberal transfusion guidelines were used [3,4]. Nearly 50% of ELBW infants (or infants born at or before 29 weeks of gestation) receive their first transfusion during the first 2 weeks of age, and 80% receive at least one additional blood transfusion by the end of their hospitalization [5].

Although RBC transfusions are a critical part of neonatal intensive care unit (NICU) stays and can be life saving for premature infants with severe anaemia or haemorrhage, they also convey risks and are costly and not easy to utilize, especially in resource-limited settings [6]. Therefore, preventive strategies to start life with higher haemoglobin levels have become popular during the last few decades [7]. This article reviews preventive strategies for AOP, giving particular emphasis to the enhancement of placental transfusion in the delivery room.

2. Anaemia of prematurity

Anaemia of prematurity is a pathological condition unlike physiologic anaemia in newborns [8]. The pronounced decline in the haemoglobin (Hb) concentration that occurs in ELBW infants is usually associated with abnormal clinical signs and requires allogeneic RBC transfusions [8,9]. AOP is characterized by reduced endogenous erythropoietin (EPO), reduced RBC lifespan and hypo-regenerative bone marrow [7]. Non-physiologic factors related to prematurity, such as phlebotomy losses for laboratory evaluations and nosocomial infections resulting in oxidative haemolysis, also contribute to high transfusion preterm infants [10].

When tissue hypoxia occurs, the transcription and expression of EPO mRNA increases, followed by an increase in erythropoiesis. Hypoxia-induced EPO expression is controlled by an enhancer element called hypoxia inducible factor-1 (HIF-1). Induction of HIF-1 binding in hypoxic cells requires RNA and protein synthesis, as well as protein phosphorylation. Sustained hypoxia is required for increasing EPO production. EPO production occurs primarily in the liver before 30 weeks of gestation (and is produced primarily in the kidney thereafter), and hypoxia is a less effective isolated stimulus for EPO production and erythropoiesis. The switch in hypoxia responsiveness and in the site of EPO production may contribute to AOP [2]. Suboptimal erythropoiesis appears to be the result of the inadequate synthesis of EPO in response to hypoxia [11]. EPO deficiency is greater in smaller premature infants compared to less mature infants [12]. Iron, folate, vitamin B12, or vitamin E deficiencies can also contribute to inadequate erythropoiesis [11].

Traditionally, AOP has been treated with frequent packed RBC transfusions [13]. Among all age groups, the need for allogenic packed RBCs is common in newborns. Furthermore, preterm infants are among the most heavily transfused patient populations [3,4]. The goal of packed RBC transfusions in infants with AOP is to restore or maintain oxygen delivery without increasing oxygen consumption [11]. However, according to the UK Serious Hazards of Transfusion (SHOT) National Haemovigilance Scheme, an increased number of adverse events related to RBC transfusion occur in children compared to adults, more so in neonates [14]. There are recognized potential adverse associations related to RBC transfusions unique to neonates. For example, associations between RBC transfusions and NEC, IVH, and chronic lung disease (CLD) as well as mortality have also been described [15—22].

In recent years, most institutes have implemented more restrictive transfusion guidelines to reduce the number of transfusions and donor exposures [3,4]. Two larger RCTs (the Iowa and PINT trials) have examined the transfusion criteria in the ELBW population. Both trials compared restrictive with liberal transfusion criteria for clinically relevant outcomes. Both trials developed transfusion algorithms based on the need for oxygen and the level of respiratory support in conjunction with Hb or haematocrit (Hct) levels [3,4]. Both studies found that neonates in the restrictive group had fewer RBC transfusions, without an increase in mortality or morbidity. However, one critical discrepancy was present. Bell et al [3] described increases in apnoea, severe IVH and periventricular leukomalacia in infants transfused with restrictive guidelines, but the trial was not designed to study these end points. Although the rates of serious outcomes were fairly high in both groups of the Kirpalani et al [4] trial, they found no differences in the rates of serious outcomes between infants in the restrictive vs. liberal groups.

3. Preventive strategies for anaemia of prematurity

3.1. Recombinant human EPO

Prevention and treatment of AOP with recombinant human EPO (r-HuEPO) has been the subject of many randomized controlled studies for over 20 years among over 3000 infants [2]. Although the role of EPO in the pathophysiology of AOP is well known, neither early (2—14 days of life) nor late (2—3 weeks of life) r-HuEPO therapy, nor co-treatment with iron, vitamin B12 and folate, alters the number or volume of RBC transfusions [7]. The combination of early r-HuEPO and iron does not reduce the RBC transfusion requirements in infants below 1250 g of birth weight, although the reticulocyte counts and Hct values are higher in the treatment group [23]. The use of early r-HuEPO does not significantly reduce the use of one or more RBC transfusions or the number of RBC transfusions per infant compared with late r-HuEPO administration. The finding of a statistically