

NEONATES AND BLOOD TRANSFUSIONS

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Abstract

This article tries to revise the rationale behind PRBC transfusions, summarize studies evaluating the efficacy of restrictive transfusion guidelines and provide methods and suggested guidelines for reducing the number of transfusions. We considered that the need of transfusion should be individualized for each clinical case. We propose a different approach for neonatal transfusion based on postnatal age, clinical status, respiratory disease, need for oxygen for sick or normal growing preterm babies.

Key words: anemia, transfusion, neonates, preterm

Introduction

Hospitalised neonates, especially preterm infants in the NICUs, receive the highest amount of blood transfusions of any hospitalised patient group. During the first 2 weeks of life when blood loss is frequent, approximately 50% of ELBW preterms (birth weight under 1000 g) will receive their first transfusion. By the end of hospitalization, more than 80% of ELBW will receive at least one transfusion. Although the number of transfusions received by preterms remains significant, it has decreased in the last 20 years, mainly because restrictive transfusion guidelines have been instituted. Although blood product transfusions have been an integral part in the treatment of newborns hospitalised in NICUs, transfusion guidelines remain controversial because most of them are extrapolated from adult guidelines or based on small studies with limited statistical significance.

Indications for red cell transfusions

The main purpose of a red cell transfusion is to increase the oxygen delivery to the tissues. Oxygen delivery (DO₂) can be quantified as the product of cardiac output (CO) and arterial oxygen content (CaO₂):

$$CO(\text{dl}/\text{min}) \times \text{CaO}_2(\text{ml}/\text{dl}) = \text{DO}_2(\text{ml}/\text{min})$$

Arterial oxygen content is determined by the hemoglobin concentration, the arterial blood oxygen saturation (%), the oxygen carrying capacity of hemoglobin (ml/g x g/dl, Hgb), and the solubility of oxygen in plasma (in ml/dl): $\text{CaO}_2 = (\text{SaO}_2 \times 1,34 \times \{\text{Hgb}\}) + (0,0031 \times \text{PaO}_2)$

Improving cardiac output, hemoglobin concentration, or arterial oxygen saturation increases oxygen delivery to

tissues. If the cardiac output and oxygen saturation are both optimised, the only way to deliver more oxygen to tissues is to increase hemoglobin concentrations by increasing the erythrocyte count. In young, healthy adults the critical limit below which oxygen release is equal to oxygen consumption is less than 7,3 ml oxygen/kg/min(1,2). Under this value, any decrease in oxygen delivery means a decrease in oxygen consumption and tissue hypoxia. The ratio of oxygen consumption to oxygen delivery is known as the oxygen extraction ratio and generally ranges from 0,15 to 0,33, meaning that the body consumes 15-33% of the oxygen delivered. When the extraction ratio reaches or exceeds 0,4, organ and cellular functions begin to deteriorate (3). Neonates have the added disadvantages of high values of fetal hemoglobin, low concentrations of 2,3DPG, and an accelerated weight-gain curve. Despite these characteristics, newborns have an increased capacity to compensate a gradual decrease in hemoglobin. For example, neonates born with hemoglobin concentrations less than 4g/dl as a result of chronic and severe maternal hemorrhage can appear to be well compensated for this value, and oxygen delivery appears to be adequate, in that the infant has a normal heart rate, normal perfusion and no metabolic acidosis (4). Anemia occurs when the number of erythrocytes cannot meet tissue oxygen demands, the current treatment of anemia being a red cell transfusion. The difficulty comes in distinguishing between anemic newborns that require immediate transfusions of red cell and newborns with a low hematocrit. They mainly refer to rates of decrease, rather than „threshold” hemoglobin values. Neonates with significant acute blood loss require the immediate replacement of lost blood volumes but may or may not require a PRC transfusion. The newborn with a hemoglobin of 10g/dl following volume expansion may have an adequate release of oxygen to tissues and may only require iron supplementation to restore iron deposits lost during blood loss. In order to determine the blood volume that has been lost during an acute hemorrhage, the following formula can be used (5):

$$\text{PRC volume to be transfused} = 1.6 \times W \times (\text{desired hematocrit} - \text{patient's hematocrit})$$

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Therefore, a full term newborn weighting 3 kg with an acute drop in hematocrit at birth to 20% will need 120 ml PRBCs to achieve a desired hematocrit to 45%. It's very important to determine if the hematocrit fall is acute or chronic. A newborn with twin-to-twin transfusion syndrome or with chronic materno-fetal hemorrhage may be well compensated at birth, even if the hematocrit is below 20%. All neonates undergo a natural adaptation to extrauterine life that allows them to compensate for a gradual decrease in hematocrit. Immediately after birth increased oxygenation results in systemic oxygen delivery that far exceeds the tissues' demand for oxygen. Transfusions affect the newborns' erythropoiesis and the decision to transfuse must not be based solely on hemoglobin levels. For newborns with exchange transfusions or multiple transfusions, both the EPO levels and reticulocyte count are low at any hemoglobin value. It's known that oxygen release is low at newborns because of the higher affinity of fetal hemoglobin. In fact, a leftward shift in the hemoglobin-oxygen dissociation curve due to high level of fetal hemoglobin can maintain a better oxygen delivery during episodes of severe hypoxemia (6,7).

Blood product transfusions represent a high risk for transmitting infectious diseases, especially CMV, bacterial contamination, possible immunosuppressive effect, alloimmunization related to erythrocyte, thrombocyte and leucocyte antigens, as well as host rejection associated with significant long term comorbidity (8,9). For these reasons, an important role is played by erythropoietin in lowering transfusions in anemia of prematurity. Still, the long-term safety of erythropoietin, efficacy and cost have not been well established in this context.

PRBC transfusion guidelines are more conservative now than in the past, and volume/volume replacement of phlebotomy blood loss is less used. Micro-sampling devices that use infinitesimal quantities of blood, in-line blood

sampling and clinical monitoring are used. If small volume blood transfusions are required, it is necessary to reduce the exposure to multiple donors. Transfusion therapy must be individualized to every preterm, based on clinical status and institutional transfusion resources. Any guide has set acceptable clinical circumstances for transfusion conditions but not absolute in terms of indications. When considering a transfusion in a preterm infant with a low hematocrit (in the absence of acute hemorrhage), the clinician should first determine whether the infant needs an immediate increase in oxygen delivery. If the answer is **yes**, the treatment is to transfuse PRBC. If the infant's hematocrit is greater than 25% and further flebotomy losses are estimated to be minimal, a volume of 15 ml/kg can be administered. All other infants receive 20 ml/kg. If there is no evidence that suggests an immediate increase of oxygen delivery to the tissues, then treatment with red cell growth factors such as erythropoietin, nutritive substrate, iron therapy, folate, and vitamin E might be considered (Fig. 1).

The infant should be monitored for signs of anemia because the process stimulating erythropoiesis requires at least a week to increase reticulocyte count, and it's possible that hemoglobin level won't rise significantly during this period (10).

All neonates undergo a natural adaptation to extrauterine life that allows them to compensate for a gradual decrease in hematocrit. Immediately after birth increased oxygenation results in systemic oxygen delivery that far exceeds the tissues' demand for oxygen. The increased need for transfusions in preterms is mainly owed to: multiple blood drawing for diagnostic testing that reduces the relative blood volume, postnatal anemia as a result of cardiovascular compromise, limited or delayed bone marrow response to different situations of hematologic stress.

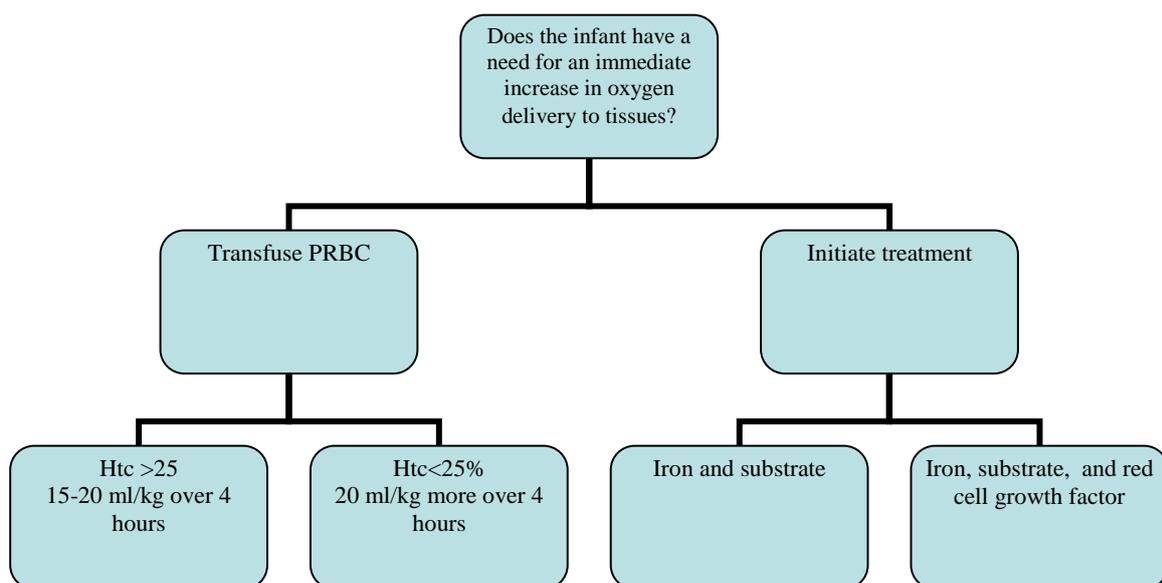


Fig.1. An approach to neonatal transfusions.

Suggestions for reducing transfusions in ELBW preterms

When a premature birth is expected (<32 weeks GA), an action plan to reduce the number of transfusions can be created. The plan consists of a few measures like: delayed clamping of the umbilical cord, administering erythrocyte growth factor and iron therapy, judicious laboratory testing that uses micro-sampling and restrictive transfusion policies (11)

- Discuss delayed cord clamping with the obstetrician and document the plan in the mother’s chart. After birth the newborn should be placed below the placenta while the umbilical cord is intact for 30-45 seconds (16)
- Initiate rHuEPO treatment during the first day of life. It can be administered either as s.c 400U/kg injection or I.V. 200U/kg in a protein-containing solution (D5% solution with 2% aminoacids), to run over 4-24h (17-19)
- Administer parenteral iron, 3mg/kg once a week or 0,5mg/kg/day(added to TPN or administered IV over 4-6 h) until the infant is tolerating adequate volume feedings, then administer oral iron at 6mg/kg/day

- Use micro sampling in laboratory testing to reduce phlebotomy volumes. Order blood tests judiciously
- Replace central line asw soon as possible
- Monitor daily losses due to phlebotomy
- Report the lowest hemoglobin or hematocrit value that can be tolerated, for a variety of clinical scenarios, and age in days, for example (20-21):
 - Newborn with 100% FiO2, significant ventilatory support, vasopressors, metabolic acidosis
 - Newborn under minimal CPAP ventilatory support
 - Newborn with enteral feeding that requires oxygen
 - Newborn with enteral feeding, adequate growth, no need for oxygen supplementation
- Adapt these scenarios to the postnatal age of the neonate (under 2 weeks, 2-4 weeks, older than 4 weeks) (Table 1)

Table 1. Blood tests for ELBW.

<p>ELBW < 1000g</p>	<p>ELBW 1000-1250g</p>	<p>ELBW > 1250g</p>
<ul style="list-style-type: none"> •CBC (0,3ml) •Blood cultures (1ml) •Blood type and Rh (0,5ml) •AGS at birth (0,25ml) 	<ul style="list-style-type: none"> •Electrolytes, blood glucose, calcemia – micro sampling or ABG (0,25ml) •Bilirubinemia only in early OAB/Rh incompatibility jaundice (1ml) •C reactive protein only if infectious risk is present or signs of infection (1ml) 	<ul style="list-style-type: none"> •CBC, reticulocyte count, sideremia •Blood cultures (in case of clinical signs of infection) •C reactive protein (in case of clinical signs of infection) •Complete chemistry panel if the neonate is in TPN •If not: micro sampling

- The hematocrit must be determined at birth or at the NICU. Blood drawn must be venous or arterial, never capillary. Another hematocrit determination will be made only under special circumstances
- Transfusions must be considered only if an acute >10% blood loss is apparent, asociated with signs of low oxygen release, or significant hemohrrage over 20% total blood volume
- Transfusions must be considered if there is an immediate need to increase oxygen availability to tissues. The main goal of PRC transfusions is to increase this availability
- Improving CO, hemoglobin concentration or arterial blood O2 saturation all increase O2

- availability to tissues. If CO and oxygen saturation are optimised, the only way to release more oxygen to the tissues is to increase hemoglobin concentration by increasing red cell mass.
- While treating a low hematocrit preterm(without acute hemohrrage) we must ask ourseleves if an immediate increase in oxygen availability is needed:
 - If the answer is YES, treatment consists in PRBC transfusions
 - If the answer is NO, treatment with EGF and nutritive substrate plus added iron, folic acid and vitamin E must be taken into consideration. The newborn must be monitored closely for signs of anemia because it takes at least a week for the

erythropoiesis to significantly increase the reticulocyte count, and hemoglobin concentration may not increase during that time

- Newborns must be transfused with 10-20ml/kg PRBC, less if Htc>29%. A 20ml/kg volume can be used if an important phlebotomy is anticipated in ELBW preterms.
- For newborns that receive erythropoiein the rate of hemoglobin/hematocrit decrease, reticulocyte count, postnatal age and the need for oxygen must be taken into consideration
- Central measuring of Hgb/Htc are preferred; alternatively, capillary blood measurements can be taken after adequate warming of the heel.

Transfusions must be taken into consideration in the following circumstances

1. For newborns that require moderate or significant mechanical ventilation, defined as MAP>8 cm H2O and FiO2>40% in conventional ventilation, or MAP>14 and FiO2>40% in high frequency ventilation, transfusions must be taken into consideration if Htc<38% (Hb<12g/dl)
2. For newborns that require minimal ventilation, defined as MAP<8 cm H2O and/or FiO2<40% or

MAP<14 cm H2O and/or FiO2<40% HFV, transfusion must be taken into consideration if Htc<35% (Hb<10g/dl)

3. For newborns that only require oxygen therapy, transfusions can be considered if Htc<25% (Hb<7g/dl) and at least one of the following symptoms is present
 - a. >24 hours tachycardia(HR>180) or tachypnea (RF>60)
 - b. Oxygen needs doubled in the last 48hrs
 - c. Lactate>2,5mEq/l or metabolic acidosis(pH<7,20)
 - d. Weight gain <10g/kg/day in the last 4 days while receiving >120kcal/kg/day
 - e. Major surgery in the next 72 hours

4. For newborns without any symptoms, transfusions can be considered if Htc<20% (Hb<6g/dl) associated with an absolute reticulocyte count <100.000/microliter(2%)

We suggest lowering the need for transfusions by minimizing routine labs (flebotomy) and a more restrictive guideline. Maybe an alternative treatment (erythropoetin, nutritive substrate, iron therapy, folate and vitamin E) for anemia can be used initially, reducing to a minimum the need for blood product transfusion - (table 2).

Table 2. Anemia of prematurity – An approach.

Limiting Phlebotomy

Minimizing **routine** labs.

- Daily report of total phlebotomy
- in-line blood sampling for ABG,Na, K,Hct if BW<750 grams or you are expecting monitoring the above at least every 4 hours.

Handling PRBC

- Assign bag:
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 - *>750 grams will share a unit with up to 2 babies.
- PRBC should be irradiated, CMV negative and leucoreduced.

Erythropoetin

Start time/ Duration: Birth weight up to 750grams - by DOL 14 for 6 weeks. Birth weight 751-1250grams - by DOL 7 for 4 weeks.

Dose: 250-400 unit/kg/dose three times a week...M/W/F between 10-11am (in order to batch the doses). Start baby on the nearest dosing day base on the above criteria. May give IV (if on TPN) or SQ (if on full feed).

• Preparation:

- Subcutaneous: give undiluted (2000 unit/ml)
- IV: Dilute 2 ml (2000 unit/ml) with 8 ml normal saline to make a final concentration of 400 units/ml. DO NOT SHAKE. Dose will be diluted and GIVE IMMEDIATELY over 4 hours. IV infusion is compatible with TPN

• Iron and Vitamin E: Supplement during rHu – EPO treatment.

- If PO feeding volume ≤ 20ml/kg/day: Iron dextran IV 1mg/kg/day in TPN (amino acid concentration must be ≥2%)
- If PO feeding volume > 20ml/kg/day: PO Ferrous sulfate 3 mg/kg/day + vitamin E 5 IU/day.
- If all PO feeding : Ferrous sulfate 6 mg/kg/day + vitamin E 10 IU/day.

Conclusions

Blood product transfusions represent a high risk for transmitting infectious diseases, possible immunosuppressive effect, alloimmunization, as well as host rejection associated with significant long term comorbidity.

Transfusions should be reserved just for selected cases (newborns on mechanical ventilation, newborns on oxygen therapy that meet specific criteria, acute blood loss) with the immediate need to increase oxygen availability to tissues.

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