

Red blood cell transfusions in newborn infants: Revised guidelines



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In general, health care professionals taking care of high risk infants in neonatal intensive care units have become more restrictive in their use of red blood cell transfusion over the past 10 years. The present statement is intended for those caring for high risk newborn infants (preterm to one month of age). The objectives of this statement are to provide guidelines to reduce the incidence of anemia in preterm and term infants, to identify strategies to decrease the need for red blood cell transfusions and to limit donor exposure in this population. Recommendations for red blood cell transfusions are included.

Key Words: *Anemia; Blood transfusion; Erythrocytes; Erythropoietin; Infant; Newborn; Phlebotomy*

While indications to transfuse term infants with red blood cells (RBCs) have not changed during the past decade, clinical indications for RBC transfusions in extremely low birthweight and very low birthweight infants have become more restrictive (1-3). The increasing awareness of the risks associated with transfusions and parental apprehension have influenced these changes (1-3). Several reports indicate a decline in the number of RBC transfusions per neonate, and the number of donor exposures per neonate, particularly among infants older than 26 weeks of age (4-7).

RBC transfusion in preterm or sick term infants is essential in the management of their clinical conditions to prevent the effects of anemia (8). Blood loss in these infants may be either acute or chronic, and anemia may be, in part, iatrogenically related to frequent blood sampling. However, strategies for the prevention and treatment of anemia are available.

Transfusion practices for high risk infants differ widely among neonatal intensive care units (1-7). These practices vary as a function of birth weight, gestational age and sever-

ity of illness. The identification of infants at greater risk for multiple transfusions has been shown to reduce exposure to donor blood (9), and prophylactic measures can reduce the incidence of significant anemia.

The objectives of this review are to provide guidelines for RBC transfusions in newborn infants aimed at reducing exposure to RBC transfusions and preventing clinical occurrence of anemia in growing newborn infants. The goals are to reduce donor exposures and RBC transfusions in infants.

To develop these guidelines, the literature was reviewed from 1976 to 2001 using the electronic library MEDLINE, The Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Register. Our review included studies in English and French, and articles in other languages when an abstract was provided in English or French. The following key words were used: infant, newborn, blood transfusion, anemia, phlebotomy, erythrocytes and erythropoietin. Retrieved articles included randomized controlled trials, population-based studies, epidemiological studies and observational reports.

PREVENTION AND TREATMENT OF ANEMIA

Anemia in infants can be classified as physiological or non-physiological. In physiological anemia observed in infants born at term, the hemoglobin concentration declines between eight and 12 weeks of life, remains stable for several weeks and then increases progressively. Physiological anemia often presents without signs, and there is no need for RBC transfusions. In contrast, anemia of prematurity develops earlier (ie, at four to 12 weeks of life) (10-12). Preterm infants with anemia may present with clinical signs such as tachycardia.

In sick preterm infants, anemia of prematurity can be accentuated by nonphysiological anemia, characterized by a decreasing hematocrit, reticulocytopenia, bone marrow hypoplasia, and endogenous erythropoietin concentrations that are inappropriately low relative to the degree of anemia. The most common cause of nonphysiological anemia is blood loss, which may be acute or chronic. A common and potentially avoidable cause of postnatal blood loss is iatro-

genic as a result of frequent blood sampling (phlebotomy) in sick preterm infants.

To prevent and reduce the severity of anemia, and to reduce donor exposure or the risks associated with RBC transfusions, strategies to consider may include:

- delayed clamping of the umbilical cord;
- restricting blood sampling;
- using recombinant human erythropoietin to stimulate erythropoiesis;
- using iron supplementation or vitamins to minimize the severity of anemia;
- using appropriately collected and stored multipack RBC units;
- using appropriately screened and handled RBCs from regular or designated donors; and
- collecting and transfusing umbilical cord blood (autologous blood transfusion).

HOW TO REDUCE THE NEED FOR RBC TRANSFUSIONS

Delayed umbilical cord clamping

In several randomized controlled trials, delayed umbilical cord clamping compared with early umbilical cord clamping (the exact timing varied between trials) reduced the need for transfusion without increasing adverse outcomes (13).

Restricting blood loss

A preventive strategy of reducing blood loss represents an important step for limiting the severity of anemia (4). Decreasing unnecessary repeated blood sampling is crucial for preventing the depletion of circulating RBCs. Returning the dead space volume after sampling an arterial catheter is also useful. Microtechnique laboratory procedures further decrease the amount of blood drawn for laboratory tests. Finally, the development of noninvasive monitoring methods allows for a reduction of repeated analysis for blood gases and other laboratory tests (14).

Recombinant human erythropoietin

Intrauterine fetal production of erythropoietin occurs only in the liver. In extrauterine life, the primary site of erythropoietin production is the kidney. The switch in erythropoietin production site is probably determined genetically in a manner similar to hemoglobin production switching from fetal to adult type (10-12). Endogenous erythropoietin concentrations are low in preterm and term infants. The responses to hypoxia are reduced in infants because of decreased sensitivity of the liver oxygen sensors. Immature renal oxygen sensors also may play a role (15).

Erythropoietin deficiency is a major cause of anemia of prematurity. Erythropoietin therapy for anemia of prematurity may be effective and very promising, particularly for

stable preterm infants whose bone marrow is able to respond to treatment, and for at risk infants with large phlebotomy losses. Some data suggest that restrictive guidelines for RBC transfusions may have the same effect as the administration of erythropoietin in preterm infants (16). Several review articles (17-21) and randomized controlled trials (22-32) have been published where the potential benefits, safety and cost effectiveness (33-36) of human erythropoietin administration have been examined. Several studies have demonstrated beneficial effects, but in association with conservative transfusion criteria, the minimization of phlebotomy losses and early iron administration (37). When considering the administration of erythropoietin, be aware that the preparation contains human albumin.

In summary, erythropoietin administration may reduce RBC transfusions in high risk infants. The importance of this impact is not yet known. However, erythropoietin administration does not change the need for RBC transfusions in the first two weeks of life, particularly in sick preterm infants (38,39). A meta-analysis of controlled clinical trials studying the efficacy of erythropoietin in reducing RBC transfusions was recently published (40). While many benefits in high quality studies using conservative RBC transfusion criteria were noted, the authors also reported an extreme variation in the findings and they concluded that erythropoietin therapy should not be a standard treatment for anemia of prematurity (40).

Further investigations are needed regarding the optimal dose, the timing, the overall nutritional support that is required during erythropoietin treatment, and the potential toxic effects associated with erythropoietin administration in preterm infants (41). Clear guidelines for the use of erythropoietin to prevent neonatal anemia are not available.

Vitamin and mineral supplementation

Several studies have reported the problem of inadequate iron intake with or without erythropoietin treatment (22,24,42-45). Although the optimal dose of iron is not known, based on a previous statement by the Canadian Paediatric Society's Nutrition Committee (46), preterm infants need a supplement of 4.0 to 4.5 mg/kg of dietary iron to prevent late anemia.

It is generally accepted that 25 IU of vitamin E be administered to the preterm infant to prevent hemolytic anemia (47). Appropriate intake of folate and vitamin B₁₂ must also be part of the nutritional support of high risk newborn infants (47).

WHAT TYPE OF RBCs SHOULD BE USED?

Preservative for storage of blood

In the past, increases in extracellular potassium, a fall in pH levels and a decline in RBC 2,3-diphosphoglycerate during RBC storage were of concern to physicians caring for sick newborns. The duration of storage is also a concern because RBCs stored for extended periods may worsen the toxicity by increasing further the extracellular potassium. In 1993,

the preservative used for the storage of RBCs was changed from citrate, phosphate, dextrose and adenine to adenine-saline (AS-3) anticoagulant and/or preservative. AS-3 solutions may be used safely for small-volume RBC transfusion in high risk newborn infants (48). The increase in the storage period allows an increase in the availability of blood, which limits donor exposure. After five days, the serum potassium is substantially elevated, and the units should be used only for slow, small-volume, 'top-up' transfusions. Rapid and large-volume transfusions should use blood that is less than five days old.

Irradiated blood

If the blood is obtained from first- or second-degree relatives, it should be irradiated (14,49) to prevent graft-versus-host disease, which may otherwise occur (54). Leucocyte-reduction filters do not safely prevent graft-versus-host disease and are not an alternative method (50). Unless an infant had a previous in utero transfusion or a directed blood donation has been used from a relative, small volume RBC transfusions do not need to be irradiated (49,51). Because of the risk of potassium leakage, RBCs should be transfused within 24 h of irradiation if hyperkalemia represents a clinical risk. Extra washing may be necessary. Irradiation is recommended for RBC units to be administered to fetuses receiving intrauterine transfusions, selected immunocompromised infants, newborn infants receiving blood from a relative, and infants who have previously received an in utero transfusion (52).

Infectious screening of donated blood

Each unit of donated blood is analyzed for the following tests: presence of antibody to HIV-1 and HIV-2, hepatitis C virus, human T-lymphotrophic virus (HTLV)-I and HTLV-II, presence of hepatitis B surface antigen and HIV-1 p24 antigen. Moreover, blood is screened for syphilis and cytomegalovirus (CMV) antibodies (52).

In spite of the low incidence of morbidity due to transfusion-transmitted CMV infection in the neonatal population, most guidelines recommend the provision of CMV-negative blood components for low birthweight infants (53,54). It is uncertain whether leukodepletion is adequate for the prevention of CMV, such that CMV antibody positive units could be given to preterm infants.

Leukodepletion

High efficiency leukodepletion filters are used routinely across Canada. There are no proven benefits for newborn infants, but there are probably no disadvantages to the use of leukodepleted RBCs (55).

RBC transfusions by unrelated or directed donors

To reduce exposure to multiple donors, the most important approach is the use of multipack collection systems so that multiple RBC transfusions from the same random or designated donor can be given to the same baby over an extended period of time. With AS-3 preservative, RBCs can be stored for at

least four weeks and transfused safely to newborn infants.

Since the 1992 Canadian Paediatric Society guidelines for transfusion of erythrocytes were published (53), a large number of neonatal intensive care units have developed a program of directed blood donation. This occurred at the same time as parental apprehension developed following concerns regarding blood-transmitted infections (CMV, HIV) (1,2).

Given the safeguards of current blood banking processing, directed donations probably do not provide a safer approach than random donations. A small randomized controlled trial of parental-directed donation documented the feasibility of this approach, although many mothers (15 of 23) were ineligible to donate blood because of anemia, ABO blood grouping incompatibility, fever or infection, or other medical problems (56). In that study 100% of the infants in the parental donation group had a single donor compared with 69% in the unrelated donor group. The risks of donation by mothers, whose blood potentially contains alloantibodies that may cross-react with infant blood cell antigens, require further investigation (57). Important issues specific to directed blood donation include:

- identifying a compatible donor in the family;
- a time delay in obtaining the compatible donor's blood (blood grouping and other tests) for transfusion;
- requirement for irradiation;
- lack of available blood in the blood bank at the time of transfusion (difficulty with storage);
- raising important ethical issues (eg, identifying positive HIV status within the family); and
- complying with parental wishes, potentially leading to reduced anxiety.

Autologous blood

A literature review of autologous blood transfusion for preterm infants is available (58). Initially, this was developed as an interesting means of avoiding allogeneic blood transfusion. However, this labour-intensive practice is not a standard approach. Bacterial contamination, incorrect identification and clotting issues are unresolved problems (41,58-61).

WHEN ARE RBC TRANSFUSIONS INDICATED?

Blood loss or shock

Around the time of birth, acute blood loss may occur in relationship to vasa previa, abruptio placenta, cord accidents, fetomaternal transfusion or other conditions. The resulting hypovolemic shock may necessitate emergency RBC transfusion. To maintain perfusion pressure, the circulating blood volume can be re-expanded by crystalloid solutions or colloids. However, a significant fall in hematocrit usually requires RBC transfusions (53). Emergency and high volume transfusions should involve the use of blood that is less than five days old.

TABLE 1
Recommendations for red blood cell (RBC) transfusions

RBC transfusions should be considered in newborn infants in the following specific clinical situations:

- Hypovolemic shock associated with acute blood loss
- Hematocrit between 30% and 35% or hemoglobin concentration between 100 g/L and 120 g/L in extreme illness conditions for which RBC transfusion may improve oxygen delivery to vital organs
- Hematocrit between 20% and 30% or hemoglobin concentration between 60 g/L and 100 g/L, and the infant is severely ill and/or on mechanical ventilation with compromised oxygen delivery
- Hematocrit falling (20% or less) or hemoglobin concentration (60 g/L or less) with a reticulocyte count of 100 to 150 $\cdot 10^9/L$ or less (suggesting low plasma concentration of erythropoietin), and if the following clinical signs are present: failure to thrive or no weight gain, tachycardia more than 180 breaths/min, respiratory signs including tachypnea and supplemental oxygen needs, and lethargy (12,51)

Transfusion to prevent severe anemia in high risk term or preterm infants

RBC transfusions in preterm infants have been suggested to decrease heart rate and cardiac output, improve growth parameters, decrease lactate levels, or decrease apneic episodes in stable infants (58). However, a decrease in heart rate and cardiac output is an expected physiological response to an increase in oxygen-carrying capacity and does not necessarily suggest any clinical benefit (62). The remaining suggested benefits have not been demonstrated in adequate studies. Furthermore, the adequacy of tissue oxygen delivery is difficult to determine clinically, and clinical signs such as apneic spells or irregular breathing, tachy-

cardia, poor suck and inadequate weight gain, lethargy, and increased lactate levels are not reliable manifestations of inadequate tissue oxygenation resulting from anemia. Furthermore, no studies show that RBC transfusions improve clinically important outcomes in stable high risk infants.

During the past few years, concerns about the lack of efficacy of RBC transfusions for treating anemia in high-risk infants have been confounded by high profile occurrences of transfusion-induced untoward effects. Transfusion reactions, graft-versus-host disease, toxic effects related to storage additives and anticoagulants, complications from the use of old RBCs, and infectious risks are among the potential complications of RBC transfusion in the newborn (14).

CONCLUSIONS

RBC transfusions will continue to be necessary in the care of high risk preterm and term infants. However, prevention of anemia, restriction of donor exposure and restriction of the number of RBC transfusions must be part of a comprehensive approach to high risk neonates. The present statement provides some modalities to prevent the occurrence of severe anemia in growing newborn infants and to limit the necessity of therapeutic interventions.

RBC transfusion protocols have rarely been subjected to randomized controlled trials and careful clinical investigation. The variations in practice among different neonatal units illustrate this lack of evidence (3,7). On the basis of unanswered questions in the current literature, the Committee makes these recommendations (Table 1), and is awaiting better evidence of efficacy and safety. Further investigation is required to clarify the future approach to these important clinical dilemmas. Ongoing clinical trials are presently examining these questions.

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The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate.

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