Reducing the need for transfusion in preterm infants: Is there a role for erythropoietin?

Small volume blood transfusions are very common occurrences on neonatal intensive care units. The smallest, sickest and most vulnerable infants require the greatest number of blood transfusions. This article outlines the issues raised by the use of blood transfusions and the evidence for the use of erythropoietin and other methods to minimise the number that are given.

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Keywords

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Key points

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1. There is no reliable test or method for determining when a preterm infant would benefit from a blood transfusion.
2. Guidelines based on those from the British Standards in Haematology Transfusion Task Force to limit the need for blood transfusions, should be available in every neonatal unit.
3. Erythropoietin has not been shown to significantly reduce the number of transfusions in small sick preterm infants who receive the greatest number of blood transfusions.
4. Effective nutrition with supplemented breast milk or specialised preterm formulas promoting good growth will assist in limiting the need for transfusion.

Preterm infants have a low blood volume and during the first few weeks of life many, especially those less than 1 kg at birth, will become anaemic and require multiple transfusions. Small volume top up packed red blood cell transfusions are one of the more frequent treatments given to preterm infants. However there has never been a clear definition of when a preterm infant becomes anaemic sufficient to benefit from a blood transfusion. Other than a change in skin colour, many top up blood transfusions do not produce any noticeable improvement in the well-being of the infant. Despite this, most neonatal units have their own individual guidelines using a number of trigger criteria which are based on local preference and practice rather than solid evidence.

Over the last two decades, with a greater understanding of, and concern over, the risks of transmission of infection from the use of human blood products, there has been a desire to reduce the need for repeated blood transfusions. Various techniques have been developed to minimise iatrogenic blood losses and donor exposure. The ability to manufacture the hormonal regulator of red cell production in the form of recombinant human erythropoietin meant that a new treatment for the anaemias of prematurity became a real possibility.

The development of anaemia in preterm infants

At most stages of life anaemia can be defined as a haemoglobin level below the 10th centile of the normal range, but this is not possible for the preterm infant as premature birth is not a normal physiological state. *In utero* the haemoglobin level rises as the pregnancy progresses so that a healthy infant born at term would be expected to have a haemoglobin level of around 17-18g/dL[1]. This arises due to an increased relative hypoxia *in utero* as term approaches leading to greater bone marrow production of red blood cells. Extremely preterm infants however are born with significantly lower haemoglobin levels such that at 23 weeks the level is typically between 13-14 g/dL (**TABLE 1**). After birth increased oxygen availability leads to a physiological fall in haemoglobin in both term and preterm infants over the first 6-12 weeks (**FIGURE 1**). In preterm infants this process is exaggerated by a number of factors resulting in the development of anaemia of prematurity. Over the first few weeks after birth, the haemoglobin of a preterm infant may fall to as low as 7g/dL without developing an adequate bone marrow response.

The major causes of the development of anaemia in preterm infants include

Gestation weeks	22-23	24-25	26-27	28-29	30-31	32-33	34-42
Haemoglobin	13.9 g/dL	14.1g /dL	15.6 g/dL	16.5 g/dL	17.5 g/dL	17.5 g/dL	17.4 g/dL
Number of infants	40	119	139	151	208	264	1,032

TABLE 1 Haemoglobin values at birth by gestation. Data from St Mary's Hospital, Manchester, UK.

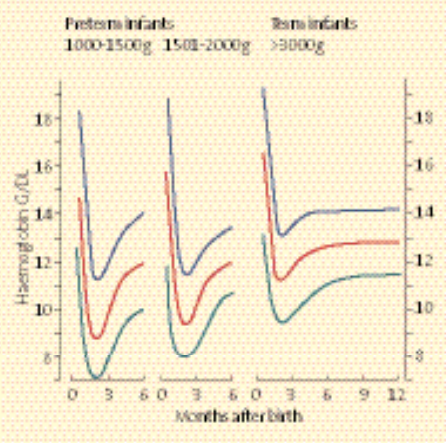

FIGURE 1 Haemoglobin changes after birth in preterm and term infants[2], showing the 90th, 50th and 10th centiles.

iatrogenic blood loss for laboratory tests, reduced red cell life expectancy, relatively poor nutrition and bone marrow dysfunction with low red cell production due to low levels of the natural regulating cytokine erythropoietin[3,4]. Early studies in preterm infants showed that erythropoietin is produced only at very low levels despite the development of a profound anaemia. Many preterm infants have an oxygen dependency due to respiratory disease and are generally considered to benefit from treatment of their developing anaemia. Determination of the haemoglobin level at which transfusion should be given has proved difficult. In the absence of an evidence base to guide blood transfusion policy development, a number of both local and national pragmatic transfusion guidelines have been proposed. Recently the British Standards in Haematology Transfusion Task Force have provided some recommendations for blood transfusions for preterm infants[5,6] (**TABLE 2**).

Studies have shown that the vast majority of all transfusions given to preterm infants were given in the first few weeks to those whose birth weight was less than 1000g or were less than 27 weeks' gestation at birth. Many of these infants received multiple blood transfusions. Infants between 1000g and 1500g birth weight may only require 1-2 transfusions on average, whereas infants less than 1000g may receive in excess of 10 transfusions (**FIGURE 2**).

Preventing preterm anaemia

One strategy to reduce the need for transfusion is to target the major causes of blood loss. It has long been recognised that the removal of blood for laboratory investigations including repeated blood gasses results in the rapid development of anaemia. It can be calculated that taking as little as 0.5 mL of blood from a 700g infant is equivalent to taking more than 50 mL of blood from an adult. A number of studies have shown that blood sampling volumes of 0.75-3.1 mL/kg per day are common[8,9]. Excessive phlebotomy losses have resulted in the guidance to transfuse after 10% of the blood volume has been taken. Over the last decade there has been significant development in the range and availability of reliable laboratory tests which can be performed on micro samples. With current equipment almost all routine investigations can now be done on a sample less than a 100µL. Many neonatal units have developed local guidelines to minimise excessive blood sampling.

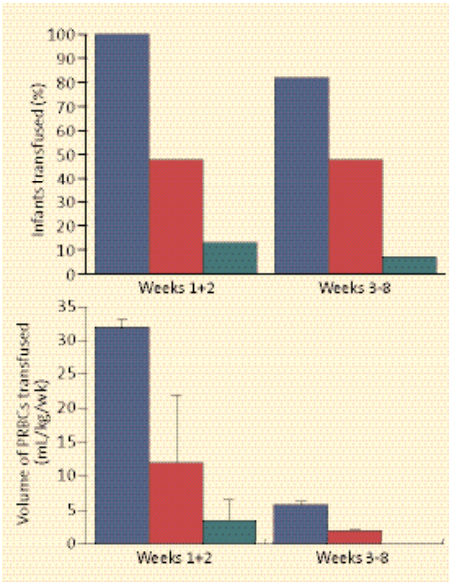

FIGURE 2 Packed red blood cell (PRBC) usage by gestation time after admission and gestation. Blue bars are 24-27 weeks; red bars are 28-32 weeks; green bars are 33-36 weeks.[7]

Criteria for packed red blood cell transfusion	Level
Anaemia in the first 24h	Hb <12 g/dL (Hct<0.36)
Cumulative blood loss in 1 week, receiving intensive care	10% blood volume
Neonate receiving intensive care	Hb <12 g/dL
Acute blood loss	10% blood volume
Chronic oxygen dependency	Hb <11 g/dL
Late anaemia, stable patient	Hb <7 g/dL

TABLE 2. Recommendations for when to transfuse premature infants published by the British Standards in Haematology Transfusion Task Force[5,6].

Risks of blood transfusions

Even with close attention to minimising iatrogenic blood losses, blood transfusions for preterm infants will still be required. Since 1982 when HIV infection was first recognised to be transmitted by human blood products there have been significant concerns around the high levels of donor exposure associated with the large number of blood transfusions required for preterm infants. Whilst it must be recognised that the risks with current blood bank practices are extremely small, there are a number of viral and other infections, in particularly cytomegalovirus (CMV), hepatitis B and C and more recently concerns over prion particle transmission, that have led to stringent controls on the use of blood products for newborn infants. The use of multiple packs from a single donation significantly limits the donor exposure and is now standard practice for all neonatal top up blood transfusions. The British Standards in Haematology Transfusion Task Force[5,6] has defined the requirements for the supply of packed red cells for preterm infant transfusions. The recommendations include:

- All blood components should be leucocyte depleted and cytomegalovirus seronegative
- All donors must have given one donation in past two years and be negative for all mandatory microbiological markers including cytomegalovirus
- Multiple aliquots taken from a single source should be used for repeated transfusions.

Whilst the standards of blood product screening and preparation are extremely high, and the consequent risks of viral transmission are low, the desire to eliminate the need for transfusion continues.

The role of erythropoietin

In 1988 commercially available human erythropoietin became available using recombinant technology[10] and early trials were undertaken to try to prevent the development of anaemia and the need for transfusion.

The first studies published in the early

FIGURE 3 Standard small transfusion red cell pack.

1990s[11-13] used erythropoietin doses of 25-100 U/kg given three times each week subcutaneously. These doses were considered to be safe. Although the early studies confirmed a reticulocyte response there was little evidence of a clinically significant reduction in the numbers of transfusions needed. Further studies were then undertaken using significantly higher doses up to 1400 U/kg of erythropoietin per week[14-16]. These studies suggested that there may be an effect on the reduction of transfusion in preterm infants especially if the infants were supplemented with iron. However many of these studies involved very small numbers of infants and conclusive evidence of a clinically significant reduction in blood transfusions remained to be clarified. A number of large, many of them multicentre, studies using a range of doses and frequencies of administration of erythropoietin were then undertaken but disappointingly these also failed to show any clinically significant reduction in the number of blood transfusions in the group of extremely low birthweight infants who receive the majority of transfusions (**TABLE 3**).

In light of the disappointing results Soubasi et al[23] further investigated the effect of erythropoietin on the need for blood transfusion in infants who were or were not ventilated. In his study 16 uncomplicated premature infants (birthweight 1227g, gestation 29.9 weeks) who did not require ventilation were compared with 28 infants (birthweight 1170g, gestation 29.9 weeks) who received artificial ventilation. Each group was divided into a control and treatment group, the latter received 150 U/kg erythropoietin (**TABLE 4**). The study showed a reduction in the need for blood transfusion with use of erythropoietin only in the uncomplicated group (**TABLE 5**). Overall this has little effect on the use of blood transfusion in preterm infants.

Finally the impact of frequency of dosing was investigated by Brown et al[24]. who reported the effect of giving the same weekly dose of erythropoietin in either 2 larger or 5 smaller but more frequent doses. He showed that more frequent smaller doses stimulated erythropoiesis to a greater degree than the less frequent bigger doses. However, again this study did not demonstrate a clinically significant reduction in blood transfusions, in the group of extremely low birthweight infants who receive the majority of transfusions.

Methods of assessing when blood transfusions are required

With the failure of erythropoietin to produce a clinically significant reduction in blood transfusions in preterm infants and the lack of a clear understanding of when preterm infants benefit from transfusion, there was a need to try to develop systems to give some clarity as to when blood transfusions would be of benefit. It is known that frequent transfusion with adult haemoglobin (HbA) increases oxygen delivery to the tissues thereby suppressing the infant's own red cell production resulting in a lower haemoglobin level.

The rationale for a top up blood transfusion is to enable improvement of tissue oxygen delivery. The factors which affect oxygen delivery, include the haemoglobin level, the type of haemoglobin, the red cell concentration of 2,3-diphosphoglycerate (2,3DGP), and the infant's cardiorespiratory status. However at present, other than the haemoglobin level, our ability to determine these accurately is very limited. Clinical features which might indicate poor tissue oxygenation such as pallor, tachycardia, tachypnoea, apnoea and poor feeding as indicators of sub optimal tissue oxygen delivery have been shown to be unreliable[25]. Laboratory measures such as haemoglobin level, haematocrit[25] or whole blood lactate are also poor predictors of tissue oxygen adequacy[26, 27].

Wardle et al[28] investigated the use of near infrared spectroscopy to measure peripheral fractional oxygen extraction (FOE) in infants less than 1500g as a measure of adequate tissue oxygen delivery. An arbitrary FOE value of > 0.47 was used. There was a trend to reduced transfusions in those with a measured FOE but this was not significant. This technique requires further research to determine whether it can be used as a reliable and effective clinical indicator of the need for blood transfusion.

Optimising nutrition to reduce the need for transfusion

It has been known for 20 years that the haemoglobin concentration in preterm infants is related to the adequacy of preterm nutrition. Rönnholm et al[29] showed that the haemoglobin level was significantly improved with increased protein intake in preterm infants fed breast milk. Supplementary vitamins and iron have also been shown to limit the development of anaemia of prematurity. Effective nutrition with supplemented breast milk or specialised preterm formulas promoting good growth of the infant should be achieved whenever possible.

Study	Population			Dose	Transfusions	
		Treated	Controls	U/Kg/week	Treated	Controls
Obladen et al[17]	28-32 weeks	43	50	70 v 0	23 (53%)	29 (58%)
Maier et al[18]	750-1499g	120	121	750 v 0	66 (55%)	86 (72%)
Maier et al[19]	500-900g	91	93	1500 v 750	63 (68%)	62 (68%)
Meyer et al[20]	28-32 weeks	40	40	600 v 0	7 (18%)	21 (52%)
Ohls et al[21]	401-1000g	87	85	1200 v 0	73 (84%)	74 (87%)
	1000-1250g	59	59	1200 v 0	22 (37%)	27 (46%)
Soubasi et al[22]	<1500g	24	29	300 v 0	7 (29%)	16 (55%)
	<1500g	22	29	750 v 0	4 (18%)	

TABLE 3 Summary of larger trials of high dose erythropoietin on the transfusion needs of preterm infants.

	Uncomplicated neonates		Complicated neonates	
	EPO	CON	EPO	CON
No of patients	9	7	16	12
Haematocrit	0.29 ± 0.03	0.27 ± 0.05	0.31 ± 0.06	0.28 ± 0.09
Hb (g/L)	91 ± 10	86 ± 15	99 ± 21	89 ± 26
Reticulocyte count	0.076 ± 0.016	0.054 ± 0.036	0.043 ± 0.026	0.025 ± 0.017
Leukocytes (× 10^9/L)	9.4 ± 0.3	11.6 ± 2.6	12.3 ± 6.1	10.6 ± 4.9
Platelets (× 10^9/L)	419 ± 155	33.4 ± 85.6	257 ± 186	259 ± 120
Serum EPO (U/L)	11.3 ± 14.3	5.13 ± 5.2	11.1 ± 11.8	8.9 ± 6.9
Weight (g)	1685 ± 167	1806 ± 172	1379 ± 354	1399 ± 308
TPN (d)	11.0 ± 6.2	9.4 ± 4.9	31.5 ± 18.7	35.9 ± 11.3

Values are expressed as mean ± SD. TPN, total parenteral nutrition.

TABLE 4. Characteristics of infants at the end of erythropoietin (EPO) treatment v controls (CON)[23].

Summary

Clinically significant anaemia in preterm infants has yet to be accurately measured or defined and its aetiology is multifactorial. It is well understood that the anaemia of prematurity is caused partly by low levels of endogenous erythropoietin. However extremely low birthweight infants who tend to be the sickest infants receiving the greatest level of intensive care and the largest number of blood transfusions are also the infants who do not respond even to very large or frequent doses of erythropoietin. It is only in larger preterm infants with an uncomplicated course that treatment with erythropoietin results in a significant reduction in the number of blood transfusions. Erythropoietin has little clinical impact in reducing the overall number of blood transfusions received by preterm infants in general.

There are no clinically useful measures of the level of circulating haemoglobin at which transfusion would be of benefit. This has led to a pragmatic transfusion policy supported by the British Standards in Haematology Transfusion Task Force with higher haemoglobin levels triggering blood transfusion in infants requiring added oxygen, ventilation or in those with clinical symptoms. Whilst specially prepared neonatal blood transfusions in the UK are remarkably safe it remains important to recognise the inherent risks. There remains a requirement to optimise nutritional care, minimise iatrogenic phlebotomy losses and when transfusion is needed, to use specially prepared multiple aliquots from a single donor in order to limit exposure to possible infective risks associated with transfusion whenever possible.

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BLOOD BALANCE DATA DURING EPO TREATMENT	Uncomplicated neonates		Complicated neonates	
	EPO	CON	EPO	CON
No of patients	9	7	16	12
Phlebotomies (mL)	20.7 ± 3.4	21.2 ± 3.2	66.3 ± 18.3	64.4 ± 18.5
Transfusions (mL)	5.5± 1.1†	26.4 ± 15.1	83.3 ± 35	84.75 ± 45.1

Values are expressed as mean ± SD. † $p < 0.01$ *vs* uncomplicated CON neonates.

TABLE 5. Numbers of transfusions received by infants receiving erythropoietin (EPO) treatment versus controls (CON)[23].