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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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. 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. 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:

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.

Keywords

anaemia of prematurity; erythropoietin; blood transfusions

Key points


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.

Table 1: Haemoglobin values at birth by gestation. Data from St Mary’s Hospital, Manchester, UK.

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

FIGURE 1  
Infant mortality and morbidity of prematurity

TABLE 1  
Haemoglobin values at birth by gestation. Data from St Mary’s Hospital, Manchester, UK.
i atrogenic 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. 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 (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 gases 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. 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.

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 Force5, 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 the 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 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...
administration of erythropoietin were then using a range of doses and frequencies of large, many of them multicentre, studies remained to be clarified. A number of significant reduction in blood transfusions however many of these studies involved doses up to 1400 U/kg of erythropoietin per week14-16. These studies suggested that then undertaken using significantly higher transfusions needed. Further studies were significant reduction in the numbers of studies confirmed a reticulocyte response.

With the failure of erythropoietin to produce a clinically significant reduction in blood transfusions in preterm infants, 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 (Hb A) 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 unreliable20. Laboratory measures such as haemoglobin level, haematocrit20 or whole blood lactate are also poor predictors of tissue oxygen adequacy21,22.

Wardle et al22 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.

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 (Hb A) increases oxygen delivery to the tissues thereby suppressing the infant’s own red cell production resulting in a lower haemoglobin level.

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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 al29 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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Dose</th>
<th>Transfusions</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treated</td>
</tr>
<tr>
<td>Obladen et al21</td>
<td>28-32 weeks</td>
<td>43 50</td>
<td>70 v 0</td>
</tr>
<tr>
<td>Maier et al23</td>
<td>750-1499g</td>
<td>120 121</td>
<td>750 v 0</td>
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<tr>
<td>Maier et al23</td>
<td>500-900g</td>
<td>91 93</td>
<td>1500 v 750</td>
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<tr>
<td>Meyer et al24</td>
<td>28-32 weeks</td>
<td>40 40</td>
<td>600 v 0</td>
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<tr>
<td>Ohls et al25</td>
<td>401-1000g</td>
<td>87 85</td>
<td>1200 v 0</td>
</tr>
<tr>
<td></td>
<td>1000-1250g</td>
<td>59 59</td>
<td>1200 v 0</td>
</tr>
<tr>
<td>Soubasi et al26</td>
<td>&lt;1500g</td>
<td>24 29</td>
<td>300 v 0</td>
</tr>
<tr>
<td></td>
<td>&lt;1500g</td>
<td>22 29</td>
<td>750 v 0</td>
</tr>
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</table>

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

FIGURE 3 Standard small transfusion red cell pack.
BLOOD TRANSFUSION

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.

References


TABLE 4. Characteristics of infants at the end of erythropoietin (EPO) treatment v controls (CON)12.

<table>
<thead>
<tr>
<th>Condition</th>
<th>EPO</th>
<th>CON</th>
<th>EPO</th>
<th>CON</th>
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</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>9</td>
<td>7</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Phlebotomies (mL)</td>
<td>20.7 ± 3.4</td>
<td>21.2 ± 3.2</td>
<td>66.3 ± 18.3</td>
<td>64.4 ± 18.5</td>
</tr>
<tr>
<td>Transfusions (mL)</td>
<td>5.5 ± 1.1†</td>
<td>26.4 ± 15.1</td>
<td>83.3 ± 35</td>
<td>84.75 ± 45.1</td>
</tr>
</tbody>
</table>

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)13.

<table>
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