Blood transfusion in the preterm infant

Simple, precise guidance on when to transfuse the preterm infant to correct or prevent anaemia has never been formulated. This is not surprising considering the complex processes concerned in transferring oxygen molecules from inspired gas to tissue cells, of which the oxygen carrying capacity of the blood is but a part. Nonetheless, anaemia can make a considerable contribution to tissue hypoxia (which is not apparent from measurements of arterial Po_2) and this fact is often insufficiently attended to in the face of obsession with pulmonary dysfunction and a teaching tradition which holds that a low haemoglobin concentration is 'normal' in preterm babies.

Respiratory adaptation problems

The blood which the fetus receives from the placenta has a Po_2 of approximately 4 to 5 kPa (30 to 37 mm Hg). Without the hypoxic defences inherent in the fetal circulatory plan, the existence of fetal haemoglobin, and the relative polycythaemia, oxygenation of vital fetal tissues would be barely adequate. Although teleology is perhaps too often invoked in support of physiological argument, it seems reasonable to speculate that the high haemoglobin value is evidence of the fetus invoking one of the classic defences against hypoxia.

Under normal circumstances there is a brisk and sustained increase in arterial Po_2 when the lung takes over as the organ of gas exchange; the polycythaemic adaptation is no longer needed and the haemoglobin value is allowed to fall as a result of considerably decreased erythrocyte production. In some infants, however, such as those with cyanotic heart disease,¹ who continue to experience hypoxia after birth, there is evidence that no such reduction in the oxygen carrying capacity of the blood is allowed to occur. What then of the preterm infant who experiences hypoxia as a result of respiratory distress syndrome or recurrent apnoea? Is there benefit in the maintenance of a high haemoglobin concentration in this situation?

Unfortunately the multiple problems accompanying preterm birth (among which I include encounters with the 'blood thirsty' neonatologist) frustrate the possibility of the baby exercising much endogenous control over his haemoglobin concentration and make it very difficult for us to gain insight into his adaptational intentions in this respect. A few

studies have described an inverse relation between the size of the red cell mass at birth and the incidence and severity of respiratory distress in preterm infants^{2,3} but research in this area is otherwise very sparse. Indeed, the work alluded to, which is sometimes quoted in support of a policy of maintaining a reasonably high haemoglobin value by transfusion, supplies about all that exists in the way of objective data; and even then it has not been shown convincingly that the size of the red cell mass or the haemoglobin concentration are influential factors in the outcome of respiratory distress rather than simply an association. In view of the large number of variables that affect the course of respiratory adaptation it would in fact be a difficult task to isolate the influence of haemoglobin concentration, although the question does warrant further scrutiny. There is the additional problem that anaemia should be designated in terms of the functional activity of haemoglobin and not just the amount of it⁴ but unfortunately knowledge of variables such as the shape and position of the oxygen dissociation curve is not readily available in current clinical practice.

Despite uncertainties it is the opinion of many neonatologists and several text books of neonatal intensive care that in babies requiring assisted ventilation or supplemental oxygen the haematocrit should be maintained above 45% (haemoglobin approximately 14 g) by transfusion. This advice, which is undoubtedly physiologically sound, is based predominantly on clinical observation and experience. It is recommended that it be actively implemented as an important part of supportive treatment for the sick infant. In very small babies frequent microhaematocrit determinations are needed to assess the changing situation and several transfusions may be necessary in the first week or two. Another approach is to replace the volume of blood removed for laboratory tests each time this reaches 10% of the circulating blood volume. The needle and syringe are, however, not the only cause of haemoglobin loss from the circulation.

The usual size of a single transfusion is 15 ml/kg bodyweight. This should be given slowly (5 ml/kg/hour) so that there is no acute effect on arterial pressure. The degree of haemoglobin increase produced by such a transfusion has a negligible effect on blood viscosity and the theoretical risk that the transfusion of adult haemoglobin may predispose to

retrolental fibroplasia does not seem to be borne out in practice.⁵

The use of exchange transfusion with adult blood to move the oxygen dissociation curve to the right has been advocated by some authorities.⁶ Although there is no room in this annotation for extensive discussion, it should be remarked that in sick babies in whom it is impossible to raise the partial pressure of oxygen in arterial blood above 5 or 6 kPa (37 or 45 mm Hg) the needs of tissue oxygenation may actually be better served by fetal haemoglobin.

'Early' anaemia of prematurity

There is now reasonable evidence that the fall in haemoglobin concentration seen in preterm babies that reaches a nadir between 4 and 8 weeks of age is quite often associated with clinical manifestations of hypoxia which can be reversed by blood transfusion.⁷ This implies that the erythropoietic response to hypoxia is sometimes inadequate and recent work suggests that it may be the production of erythropoietin by renal tissue which is deficient.⁸

Once again we have to recognise the difficulty of defining anaemia solely on the basis of the haemoglobin concentration. This is especially problematic in the newborn because of the considerable variability between individuals in the proportions of fetal and adult haemoglobin and the red cell diphosphoglycerate concentration, both of which exert a potent influence on delivery of oxygen to the tissues. The concept of 'available oxygen' as an age related feature proposed by Wardrop *et al*⁷ goes some way towards improving the definition of functional anaemia but does not, if we are to be precise for the individual baby, overcome the need for measurement of the Hb/O₂ affinity or some other equally inaccessible direct measurement such as mixed venous Po₂. So, for the time being we are limited to assessing the need for blood transfusion on clinical grounds and it may be difficult to improve on this in any really practical way. The signs of pallor, lethargy, poor feeding, tachypnoea, tachycardia, and poor weight gain are not precisely objective and certainly not specific to anaemic hypoxia but when looked for on a serial basis are valid clinical signs. What is needed is more general willingness to transfuse when suspicions of anaemia are aroused in preterm babies whose haemoglobin concentration is less than 10.5 g/dl. It is usually sufficient to raise the haemoglobin concentration by 3 or 4 g/dl which means transfusing very slowly 12 to 15 ml/kg of concentrated red cells (haematocrit value around 60%).

It is sometimes advocated that blood transfusion should be deferred in these circumstances if there is

a reticulocytosis (greater than 4%) suggestive of an erythropoietic response. When the symptoms of anaemia are mild this is a reasonable and theoretically sound approach as the reticulocyte count is generally a good indicator of an earlier erythropoietin stimulus.⁸ It must be said, however, that reticulocyte counts as performed for routine haematological reporting are unreliable because commonly an insufficient number of cells is looked at. The fear that raising the haemoglobin by transfusion may suppress endogenous erythropoiesis is not adequately substantiated and does not seem to be an important problem in practice.

Vitamin E deficiency may contribute to the early anaemia of prematurity and should be considered if the blood film is suggestive of haemolysis. When the ratio of Vitamin E to polyunsaturated fatty acids in the diet exceeds 0.6, however, which it virtually always does with breast milk or a preterm formula, and when iron supplementation is delayed until the age of 6 weeks deficiency seems to be rare.

Blood for transfusion

There is a belief that blood still warm from the donor has superior properties to that supplied from a blood bank but modern techniques of storage probably render this judgement more emotional than scientific. The low titres of alloantibodies found in the newborn and the requirement for only small volumes of blood have tempted some clinicians to by pass full compatibility testing and blood bank protocol. There is a risk, however, not yet evaluated systematically, that imperfectly matched transfusions received in the neonatal period may create difficulties in later life—for instance during pregnancy or when further blood transfusion is required. It is recommended therefore that standard procedures are followed and adapted only in the light of further information.

Citrate-phosphate-dextrose-adenine blood of less than 5 days old seems very satisfactory in terms of red cell life span and maintenance of diphosphoglycerate concentration, although further improvements in blood storage techniques are undoubtedly on the horizon. The blood used must of course be free from risk of hepatitis B transmission. Cytomegalovirus (CMV) infection acquired from blood transfusion has been reported as a considerable problem in some units,⁹ although incidence seems very variable between populations. In ideal circumstances blood for transfusion would be free from risk of CMV transmission but in most hospitals it is not possible to get suitable blood exclusively from CMV sero-negative donors. Since the likelihood of acquiring CMV infection from blood

transfusion increases with the number of donors to which the infant is exposed it is worth trying to use CMV sero-negative blood for the smallest and sickest infants, who are likely to need several transfusions over an extended period of time.

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