Critical haemoglobin thresholds in premature infants

Blood transfusion is an integral part of neonatal intensive care. Unfortunately, transfusion practice is often based on expert opinion and anecdote rather than scientific evidence. Historically, blood transfusions have been used as therapy for anaemia and bradycardia, poor feeding, poor weight gain, and pallor. Although many studies have examined these outcomes, few are methodologically sound, many lack sufficient power, and most contribute little to the discussion.

Theoretically, red blood cell transfusion is used to avoid the pathological state in which oxygen demand is greater than supply. As such, the principal outcome of any study of transfusion practice would need to incorporate measures of end organ hypoxia, specifically ischaemic brain injury, chronic lung disease, retinopathy of prematurity, and death. At the present time there are no methodologically sound prospective trials of transfusion practice that include long term neurodevelopmental outcome, the end result of brain hypoxia. This is in part because of the complexities of the dynamic balance between systemic oxygen transport (SOT) and oxygen consumption (VO2) (see fig 1).

In order to understand the concept of a critical haemoglobin threshold, if one exists, it is necessary to examine the balance between SOT and demand or VO2.

Oxygen is used by the electron transport chain within the mitochondria for oxidative phosphorylation. Its supply depends on many factors, in particular the distance between the capillary and the cell, the diffusion characteristics, and the oxygen pressure gradient between the capillary and the cell. This pressure gradient depends on regional blood flow, oxygen transport, and the characteristics of the haemoglobin–oxygen dissociation curve (HODC).

Systemic oxygen transport
SOT is cardiac output multiplied by arterial oxygen content. The arterial oxygen content is determined by the haemoglobin concentration, oxygen carrying capacity, oxygen saturation, and PaO2:

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[Hb] \times \text{SaO}_2 \times 1.36 + \text{PaO}_2 \times 0.0031
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with 1.36 ml of oxygen dissolved in 100 ml of blood and 0.0031 being the solubility coefficient of blood.

Cardiac output
Cardiac output (CO) is one of the principal contributors to systemic oxygen delivery. The critical mixed venous oxygen saturation (MvO2) at which oxygen demand is supply limited is higher for stagnant than for anaemic or hypoxic hypoxia. This is in part because other compensatory mechanisms such as increases in fractional oxygen extraction (FOE) and redistribution of flow away from low consumption organs are dependent on the maintenance of CO. Compared with adults, CO as a proportion of weight is high in newborns. Single ventricular output is 400 ml/kg/min compared with 100 ml/kg/min in adults.

Newborn infants operate with relatively fast heart rates and have limited capabilities to respond to increases in both preload and afterload. In a small non-blind, non-randomised study of “acceptably resuscitated” postcardiac surgery children, adrenaline infusion (0.05 to 0.3 µg/kg/min) increased both SOT (from 19.9 (5.0) to 25.9 (6.1) ml/min/kg post treatment) and VO2 (from 4.3 (0.8) to 5.5 (1.2) ml/min/kg post treatment); however, an increase in preload with packed red blood cell transfusion (10–15 ml/kg) increased SOT (from 20.5 (6.4) to 26.2 (7.1) ml/min/kg post treatment) but not VO2 (from 4.5 (0.8) to 4.4 (0.8) ml/min/kg post treatment). As there was no increase in FOE, it is most likely that the increase in consumption represents increased cellular metabolism that mirrors normal exercise (endogenous catecholamines) rather than supply dependence.

Haemoglobin

AFFINITY
Haemoglobin affinity is described by the P50—that is, the PaO2 at which 50% of Hb is saturated. The P50 of fetal Hb (HbF) is low (high affinity) and to the left of HbA on the HODC. This favours oxygen scavenging from maternal Hb at the placenta. As the Hb changes from fetal to adult, the HODC shifts to the right, affinity falls, and P50 rises from approximately 19.4 (1.8) to 30.3 mm Hg. This change in affinity favours tissue unloading. In low birth weight infants (1001–500 g) Delivoria-Papadopoulos has shown that despite a significant fall in haemoglobin concentration from 151 (13) to 82 g/l over 10 weeks, oxygen unloading capacity increased from 1.0 to 2.1 ml/100 ml of blood. This was caused by the concomitant increase in 2,3-diphosphoglycerate with a resultant increase in P50 from 18 (1.8) to 24.0 mm Hg.
The HODC shifts to the right with increases in H+ ions (fall in pH), temperature, and pCO2 (Bohr effect). This, in combination with morphological changes in haemoglobin (from HbF to HbA), favours tissue oxygen delivery by increasing the oxygen gradient between the perfusing capillary and the utilising cell. A similar change in P50 would occur in the HbF to HbA shift that takes place in the liver, where the Hb is oxygenated. The shift to the right is reversible with changes in temperature, pH or CO2 levels.

Critical value

MVO2 provides an estimate of the oxygen supply–demand equilibrium. In the absence of a left to right shunt, the saturation in the right atrium is marginally higher than the pulmonary artery. It can be measured in premature infants using a central venous catheter, though the correct placement of the catheter is critical. In addition, the measurement of MVO2 in combination with a non-invasive measure of cardiac output (echocardiogram) may be useful in neonatal intensive care. It may also offer clues as to the most appropriate therapy for hypoxia and hypotension.

Conclusion

Hypovolaemic anaemia, as would occur in haemorrhagic shock, is poorly tolerated and requires a high critical threshold, though exactly how high is not clear. Isovolaemic anaemia, including euvaloemic anaemia of prematurity, is better tolerated and allows a substantially lower critical threshold.

The overwhelming majority of infants less than 1000 g receive at least one transfusion, though most receive many more. Unfortunately, despite the widespread clinical use of transfusion thresholds, they are not based on evidence. It is clear that the dynamic balance between supply and demand is complicated, and a reliance on Hb threshold as a marker for oxygen restricted metabolism is naive at best. More research is necessary in order to unlock the fine balance between supply and demand, and it is imperative that this work be methodologically sound and include long term neurodevelopmental outcomes.

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