Oxygen affinity of fetal and adult hemoglobin in action: shifting our understanding of red blood cell transfusions in neonates

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Oxygen affinity of fetal and adult hemoglobin in action: shifting our understanding of red blood cell transfusions in neonates

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Preterm infants commonly receive red blood cell (RBC) transfusions, yet much remains uncertain about the safety and effectiveness of these transfusions.[1] Most research efforts have focused on '*when*' to transfuse these infants, specifically which hemoglobin (Hb) thresholds should trigger a RBC transfusion. Two recent randomized trials comparing higher (liberal) versus lower (restrictive) transfusion thresholds found restrictive policies to be non-inferior to liberal ones.[2] However, little evidence is available regarding many aspects of neonatal transfusion care other than thresholds, such as '*how*' to transfuse (optimal transfusion volumes and transfusion rate) and in particular '*what*' to transfuse. RBC transfusions in neonates are performed using blood from adult donors. However, there is a developmental mismatch between RBCs from adult blood donors and those of preterm infants. Preterm infants carry predominantly fetal Hb (HbF), which has a higher oxygen affinity to facilitate oxygen transfer from the maternal circulation to the fetus in utero. When preterm infants receive multiple transfusions with adult RBCs, this causes progressive displacement of HbF by adult Hb (HbA). Increased oxygen delivery from HbA may result in a condition of hyperoxia at the cellular level, resulting in the overproduction of reactive oxygen species.[3] Several studies concluded that transfusions were associated with prematurity-related comorbidities such as retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), and bronchopulmonary dysplasia (BPD).[4] RBCs derived from umbilical cord blood (UCB) have therefore been suggested as a promising alternative as it contain primarily HbF instead of HbA. The first clinical studies are currently underway to evaluate their efficacy and safety.[5–7] However, much remains unknown about how adult RBCs affect neonatal oxygen affinity and what the optimal oxygen affinity of RBCs transfused to preterm infants is.

In this issue of the journal, Yazdanbaksh and colleagues studied the impact of adult RBC transfusion on fetal RBC oxygen affinity in an in vitro model.[8] They titrated stored adult-packed RBCs (pRBCs) into UCB samples of 19 preterm infants to measure the concentration-dependent change in p50. The p50 represents the partial pressure of oxygen (PaO_2, in mmHg) required to saturate 50% of Hb, with a lower p50 indicating a higher oxygen affinity. Interestingly, the authors found that the p50 of the titrations decreased as the proportion of adult pRBCs in the cord blood sample increased, indicating a left shift of the oxygen dissociation curve (ODC). This suggests that adult pRBCs contribute a higher oxygen affinity compared to the fetal RBCs in cord blood. Additionally, they assessed the effect of the biological age of adult pRBCs on fetal RBC oxygen affinity. Their findings showed that titrating old pRBCs into cord blood samples resulted in a lower p50 than titrations with young RBCs. This suggests that transfusing old pRBCs may have a stronger influence on oxygen binding. With this small proof-of-concept study, the authors provided new insights into our understanding of the impact of adult pRBCs on fetal Hb-oxygen affinity. Importantly, these findings appear to contradict the hypothesis that, due to the naturally lower oxygen affinity of HbA, transfusing adult RBCs would shift the ODC to the right, resulting in a higher p50 and reduced oxygen affinity.

While adult RBCs naturally have a lower oxygen affinity compared to fetal RBCs, this may be different for packed RBCs. During storage, pRBCs age and undergo various structural and biochemical changes known as storage lesions, impacting their functionality and viability. Over time, pRBCs gradually become less deformable, smaller, and more spherical. Additionally, levels of 2,3-diphosphoglycerate (2,3-DPG) decrease rapidly during storage. This decrease results in a leftward shift in the ODC, leading to an increased oxygen affinity of the pRBCs, and consequently, a decreased ability to deliver oxygen to tissues. Following this, the authors hypothesized that transfusion of adult pRBCs to preterm infants would shift the infants ODC even further to the left, resulting in less oxygen being available to the tissues, regardless of prior oxygen saturation.

To our knowledge, only one study from De Halleux et al. has previously assessed the effect of RBC transfusion on the ODC in preterm infants in vivo. In this small study in eleven extremely preterm infants the authors found that the mean (SD) p50 increased from 18.5 (±0.8) mmHg before to transfusion to 21.0 (±1.0) mmHg after transfusion of pRBC (on average 20 ml/kg), indicating a decrease of hemoglobin oxygen affinity.[9] These in vivo findings contrast with the in vitro findings of Yazdanbaksh et al., and the reasons for this are not clear. Yazdanbaksh et al. used pRBCs that were short-stored (less than 7 days), whereas the storage age of the transfusions studied by De Halleux et al. is not known. The latter study included infants with a lower gestational age, who were all intubated after birth, with mild to moderate respiratory distress syndrome requiring oxygen support. Additionally, the mean p50 among infants prior to transfusion in the De Halleux et al. study was much lower than observed in the UCB samples used by Yazdanbaksh et al. (18.5 ± 0.8 mmHg versus 25.20 ± 1.94 mmHg).

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If the hypothesis of Yazdanbaksh and colleagues holds – that transfusion of adult pRBCs to preterm infants results in a further leftward shift of the ODC – this effect may be expected to be more pronounced in transfusion of pRBCs with an older storage age compared to short-stored pRBCs. However, the largest available randomized controlled trial on this topic, comparing short-stored (≤7 days) RBCs with standard-issue RBCs (up to 42 days) in 377 preterm infants, found no difference in the incidence of major neonatal morbidities, including NEC and ROP, between the groups. This was despite the short-stored group receiving pRBCs with a median storage age of 5.1 days compared to 14.6 days in the standard-issue group.[10]

In conclusion, this innovative study by Yazdanbaksh et al. adds to our understanding of how adult RBC transfusion affects the oxygen affinity of fetal RBCs in vitro. Yet, much remains unknown about the oxygen affinity of neonatal RBCs in the context of RBC transfusion. Further research, both in vivo and in vitro, is essential to elucidate the mechanisms of both benefit and potential harm associated with RBC transfusion in preterm neonates. This is particularly important given the high transfusion rates in preterm infants and the potential long-term effects of considerable oxygen shifts. Neonates form a distinct group of transfusion recipients who likely benefit from blood components tailored to their specific physiologic needs, especially when it comes to oxygen affinity. We should always keep in mind that neonates are not small adults.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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