bjh commentary

# Allogeneic cord blood transfusions for *extremely* preterm neonates: an *extremely* promising proof of concept

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Prevention is always better than cure, and this also goes for anaemia in preterm neonates. Prevention of neonatal anaemia can partly be achieved by strategies including delayed cord clamping and reduction of blood loss by limiting laboratory investigations and using micro-blood testing. Despite the implementation of these measures in the past decades, neonatologists can still not do without the use of red blood cell (RBC) transfusions. Nearly all extremely preterm neonates (i.e. born before 28 weeks of gestation) receive at least one RBC transfusion in the first weeks of life due to severe anaemia.[1,2] On average they require three to four transfusions until discharge, but it is not unusual for a neonate born at 23–24 weeks of gestation to receive up to 10 transfusions. These patterns of use of RBC transfusions are seen despite general recommendations for restrictive transfusion policies.[2]

Although RBC transfusions are generally considered to be safe, complications might be under-recognised in the preterm neonatal population due to concomitant severe morbidity. Recent studies in preterm neonates suggested an association between RBC transfusions and various complications including transfusion-associated necrotising enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity (ROP) and also increased mortality.[2] Whether the association between the RBC transfusions and these complications also reflects causality is to date unclear.[3]

Indeed, the underlying pathophysiological link between RBC transfusions and these severe complications is not known. Some authors have postulated that this could be due to the characteristics and type of the blood component, in addition to the uncertain implications of transfusing a product collected from adult donors.[4] A standard RBC product contains predominantly adult haemoglobin (HbA), whereas (preterm) neonates have a predominance of fetal Hb (HbF) at birth. After birth, HbF gradually declines and finally disappears by 1–2 years of age. Importantly, HbA ($\alpha 2\beta 2$) and HbF ($\alpha 2\gamma 2$) have very distinct characteristics, as HbF has a greater affinity for oxygen compared to HbA, a crucial and beneficial characteristic in the fetal period. Thanks to the greater oxygen affinity, the oxygen-haemoglobin dissociation curve is shifted to the left, enabling fetuses to subtract oxygen from the maternal circulation into the placental (and fetal) circulation. The greater oxygen affinity of HbF is partly related to lower levels of 2,3 diphosphoglycerate, a glycolysis product that enhances the ability of RBCs to release oxygen near tissues that need it most. Predominance of HbF in preterm neonates therefore complicates the unloading of oxygen to the tissues. In turn, increase of HbA in preterm neonates with blood transfusions will automatically increase the oxygen availability to these tissues and end-organs. In the case of the retina, this sudden increase in HbA and higher oxygen delivery could contribute to the development of ROP and blindness.[5]

A physiological (and most logical) alternative to avoid this transfusion-induced unphysiological increase of HbA in preterm neonates would be to use placental blood (which contains predominantly HbF) as a source of RBCs. The use of placental blood, also termed as umbilical cord blood (UCB) as it is harvested by drawing blood from the cord after birth, was first described almost a century ago.[6] Unfortunately, it never got enough attention, until a few decades ago when renewed interest in use of placental blood was described. Several studies evaluated the possibility of using autologous blood transfusion for extremely preterm neonates by harvesting UCB at birth from their own placenta and processing

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this to an autologous RBC product for own use.[4,7] However, as shown by researchers at our centre, harvesting and processing UCB from preterm placentas is technically very challenging with as a principal limitation the low volume of blood collected from the small preterm placentas.[4,7] A placenta from a preterm neonate with a birth weight of 1 kg often yielded <15 ml of blood, whereas extremely preterm neonates need up to 45–60 ml (three to four transfusions at 15 ml/kg) of RBC transfusions until discharge. Therefore, only up to one-third of the needed blood could be derived from autologous UCB.[8]

In this present issue, Bianchi *et al.*[8] discuss the effects and advantages of the logical alternative: namely allogeneic UCB, drawn from placentas from term neonates to transfuse preterm neonates. Term placentas allow the collection of a much larger volume of blood around, on average 80–100 ml, which could (in theory) fulfil the transfusion needs of an extremely preterm neonate. This Italian research group has extensive experience with allogeneic UCB transfusion, and were the first to suggest its use in 2015.[9] In the present study, the authors evaluated the use of UCB in very preterm neonates (<30 weeks of gestation) as an alternative to the traditional blood component processed from adult donors. The choice of the product in this non-randomised study was based on availability of ABO- and Rh-matched cord blood units: if available, preterm neonates received UCB instead of adult blood. The authors measured the HbF percentage until 36 weeks post-menstrual age and, unsurprisingly, found that neonates transfused with UCB maintained high HbF percentages as compared to those transfused with adult blood experiencing a significant drop in HbF. Because the study was not designed to assess clinical effects, the authors could not reliably assess if higher HbF percentages also reduced the occurrence and severity of diseases such as ROP.

A number of important issues follow-on from the reported elegant and promising strategy to use allogeneic UCB for preterm neonates. There were challenges in providing sufficient UCB. Despite their experience with this strategy, only a minority (two of nine) of the transfused neonates in this study received 'UCB-blood-only' due to lack of availability of matched UCB. As rightly commented by the authors, an extensive collaboration between cord blood banks is required in order to implement an optimal and efficient allogeneic UCB strategy that does not interfere with the other use of UCB, namely as haematopoietic stem cell source. Other issues that need further work, relate to allogeneic blood appropriate typing, and serological/polymerase chain reaction testing but because of the semi-aseptic acquisition method of UCB probably also additional negativity of microbial cultures. Finally, the influence of storage conditions should be validated.

All the latter issues need to be tackled before safe and robust use of allogeneic UCB becomes possible and with it randomised controlled trials (RCTs) that will provide the true 'proof of the pudding'. Evidently, such RCTs should show that allogeneic UCBs as compared to 'standard of care' blood components from adult donors indeed reduce transfusion-associated morbidity and mortality. In this respect, this study shows that allogeneic UCB transfusions in extremely preterm neonates is a feasible and promising proof of concept that deserves further pursuit.

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