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COMMENT

Transfusions and neurodevelopmental outcomes in extremely low gestation neonates: to transfuse or not to transfuse, that is the question…

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Owing to the advances in neonatal care, the survival rate of preterm neonates has highly increased in the past decades, but survivors are at risk for a number of adverse outcomes. Preterm ill neonates hospitalized in the neonatal intensive care unit (NICU) often face cardiopulmonary instability, apnea, and desaturation episodes.

Within this framework, red blood cell (RBC) transfusions are administered to optimize oxygen delivery to tissues. Consequently, RBC transfusions play an important role in the management of preterm infants and >40% of neonates with a gestational age (GA) <32 weeks, 56% of neonates with a GA <30 weeks, and 90% of extremely low birth weight (<1000 g) infants receive at least one transfusion during their hospitalization in the NICU.[1–3] Nevertheless, it is still not clear which hemoglobin threshold for transfusion is most suitable for term and preterm infants. In fact, there is a wide variability of transfusion practices across NICUs, as some use a liberal approach and others a restrictive approach.[4] This lack of consensus on optimal transfusion strategy reflects the lack of clear evidence of benefit and harm.

In fact, although benefits of transfusions in this high-risk population are immediate and undeniable, transfusions carry also some risks. In literature, a number of studies have investigated the association between transfusions and adverse effects such as necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), and impaired neurodevelopmental outcome, but no clear evidence to support a protective or a negative effect of RBC transfusion could be demonstrated.

In their study, Vu et al.[5] investigated the impact of transfusions on neurodevelopmental outcome. They used the cohort of preterm neonates that were enrolled in the PENUT (Preterm Erythropoietin Neuroprotection Trial) trial[6] (936 infants 24–27 weeks GA, which were randomized to erythropoietin (EPO) 1000 U/kg or placebo every 48 h for six doses) and evaluated the association between BSID-III (Bayley Scales of Infant Development third edition) scores and the number and volume of RBC transfusions. In their analysis, transfusions were associated with worse neurodevelopmental outcomes.

In the NICU, RBC transfusions are administered in order to optimize oxygen delivery to tissues and enhance the cardiorespiratory function. Nevertheless, data supporting this statement are controversial. On the one hand, some authors have demonstrated that RBC transfusions are associated with a reduction in episodes of apnea or bradycardia,[7] but on the other hand, other studies did not show any benefit of RBC transfusion on the rate of apnea/bradycardia episodes[8] or level of respiratory support.[9] Likewise, some studies reported an association between RBC transfusion and NEC[10] and the term TRAGI has been used to indicate a transfusion-related acute gut injury,[11] possibly related to an inflammatory reaction combined with oxidative stress and gut immaturity. In reverse, other studies demonstrated a protective effect of RBC transfusions against NEC.[12] Besides, the safety of feeding during RBC transfusion is also a concern for the risk of developing NEC, and once again reports are contradictory, as some describe an association between NEC predisposition and feeding while transfusing,[13] while others show no benefit of withholding feeds during transfusion.[14]

RBC transfusions seem to expose preterm neonates to a higher risk of developing ROP[15] and IVH,[16] even though other studies have reported less IVH in neonates randomized to a liberal rather than a restrictive RBC transfusion strategy.[7] TRALI (transfusion-related acute lung injury) is believed to be largely underrecognized as is difficult to diagnose in preterm neonates, because diagnostic criteria are respiratory distress, cyanosis, and hypotension, which may all be present in ill preterm infants; nevertheless, increasing cases have been reported.[17] Other than short-term complications, RBC transfusions can cause long-term complications, such as neurodevelopmental delay. McCoy et al.[18] and Napoulos et al.[19] demonstrated that neurological outcomes were better in neonates allocated to a restrictive versus a liberal RBC transfusion strategy. Always referring to the neurological outcome, the effect of the administration of EPO has been evaluated by several studies. Early administration of EPO has been associated with a small reduction in the rate of RBC transfusions and with a neuroprotective effect,[20] whereas the PENUT trial did not confirm a neuroprotective effect of EPO, evaluated at 2 years of age. Nevertheless, a post hoc analysis showed a reduction in the rate and in the volume of transfusions in the EPO group compared to the control group.[21] Even late EPO administration was associated with a reduction in the amount of RBC transfusions, although it did not show a reduction in adverse clinical effects.[22] Although EPO seems to be a safe and effective treatment in reducing the amount of RBC transfusions, its routine use cannot be recommended in preterm infants because of its limited benefits and the increased risk of developing ROP.

Since a number of authors, including Vu et al.[5] demonstrated that transfusions may contribute to the poor neurodevelopmental outcome, it is recommended to implement strategies to reduce the need for RCB transfusions in preterm infants.

Several strategies can be suggested for this purpose. One recent method proposed to effectively reduce the need for transfusions is delayed cord clamping after birth, delaying the clamping of the

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cord to 180 s when possible.[23] Another strategy is to reduce phlebotomies, for this purpose it is possible to use blood cord samples rather than sampling from the neonate for the first assays performed on admission. It is also imperative to use noninvasive monitoring for parameters like oxygen saturation, CO_2, and bilirubin levels. Furthermore, caregivers should limit blood sampling to the minimum required for safe clinical care. Point of care testing is another way to limit phlebotomies, as it requires usually a very small amount of blood and yields immediate results.[24] Nevertheless, this strategy requires support from the institution's biochemistry laboratory.

Whereas late iron supplementation in preterm infants was not associated with a decrease in the amount of RBC transfusions, early enteral iron supplementation (1–3 mg/kg/day from 1 month until 6–12 months of age) was associated with a decreased rate of transfusions.[25]

In keeping with the results of Vu et al.[5] two recent trials have studied the effect of transfusion thresholds on the neurocognitive outcome of preterm infants. The ETTNO (Extremely Low-Birth-Weight Infants) trial[26] concluded that restrictive guidelines resulted in fewer transfusions, lower costs, and similar neurodevelopmental outcomes. The TOP (Transfusion of Prematures) trail (NCT01702805) is still ongoing, but will hopefully give new responses to the question. Confirmation that restrictive strategies are safe in neonates should guide the decision to transfuse a patient, putting into balance the potential risks and benefits of RBC transfusions. Efforts of caregivers should focus on adopting all the needed strategies to minimize blood loss and the need for transfusions in extremely preterm infants.

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