Journal of Perinatology (2019) 39:351–353
https://doi.org/10.1038/s41372-018-0306-5

EDITORIAL

To transfuse or not transfuse a premature infant: the new complex question

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Received: 28 November 2018 / Accepted: 10 December 2018 / Published online: 16 January 2019

Premature infants are a heavily transfused population [1]. Anemia is a frequently assigned diagnosis in these infants and is rooted in diverse biological factors including the physiological hypoactivity of the neonatal bone marrow exposed to increased ambient oxygen ex utero [2], insufficient erythropoietin production [3], phlebotomy losses [4], increased RBC turnover [5], rapid somatic growth, and nutritional issues such as iron deficiency [2, 6]. Both the problem, that is the occurrence of severe anemia during critical developmental epochs, and its remedy, represented by the red blood cell (RBC) transfusions, are recognized for potential harm [7, 8]. Additionally, optimum transfusion thresholds are uncertain [9], and remain subjects of continued debate [10, 11]. The care-providers' discomfort gets further accentuated because most transfusions are administered to maintain hemoglobin/hematocrit levels above predetermined, arbitrary thresholds, not to replace actual blood loss or treat symptoms clearly due to anemia.

In this month's issue of the *Journal of Perinatology*, Lust et al. [12]. report that very-low-birth-weight infants who received "early" RBC transfusions within 10 days after birth were more likely to develop severe retinopathy of prematurity (ROP) [adjusted odds ratio (OR) = 3.8, 95% confidence interval (CI), 1.8−8.1]. Severe ROP was defined as disease requiring laser ablation and/or treatment with bevacizumab per standard criteria (threshold disease: stage 3 ROP with plus disease in zones I/II; high-risk prethreshold disease: any stage ROP with plus disease in zone I, stage 3 with/without plus disease in zone I, or stage 2 or 3 with plus disease in zone II). In this cohort of 1635 infants and 4464 RBC transfusions, 31% (1405/4464) of the transfusions were administered within 10 days after birth. Severe ROP occurred in 115/602 (19.1%) early-transfused infants vs. 11/1034 (1.06%) remaining infants (OR 22, 95% CI, 11.7−41.1, $p < 0.001$). RBC transfusions given after postnatal day 10 were not associated with severe ROP (OR 0.539; 95% CI, 0.244−1.187).

The novel and important finding in this study is that RBC transfusions given during early neonatal period may affect the recipient differently than those given later. These observations are biologically plausible, as early introduction of adult hemoglobin can cause an inadvertent shift in the oxygen dissociation curve, increasing oxygen delivery to tissues that are still developing adaptive mechanisms to tolerate increased oxygen concentrations [13]. The endothelial toxicity of oxygen in the developing retina is well-known [14, 15], and lends credence to these findings. While in existing studies, the link between ROP and RBC transfusions was noted in some [16, 17], it was not evident in others [10, 18, 19]; these earlier studies did not focus on the timing of transfusion.

The possibility that early RBC transfusions were a surrogate marker for higher severity of illness remains unresolved. During the early neonatal period, RBC transfusions may be given not only for severe anemia but also for other indications such as acute blood loss, hypotension, hypovolemia, to improve the oxygen-carrying capacity in infants with respiratory failure, and in some centers, to replace phlebotomy losses [20]. In the present study, infants who received early transfusions were of younger gestational age and lower birth weight, had lower hemoglobins at birth, were more likely to have been exposed to chorioamnionitis, inotropes, and postnatal steroids, to undergo ductal ligation, and to have comorbidities such as necrotizing enterocolitis and bronchopulmonary dysplasia (BPD). Early-transfused infants were also more likely to receive multiple transfusions. The investigators report that the association between early transfusions and severe ROP remained identifiable even when controlling for gestational age and

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BPD. They also attempted to appraise the contribution of clinical illness by combining gestation, birth weight, postnatal steroid use, inotrope need, chorioamnionitis, PDA ligation, and BPD and controlling for this composite variable in regression analysis. However, the use of unweighted composite variables for statistical adjustment needs cautious interpretation [21].

The study has important strengths—the investigators evaluated a substantial sample size, and the single-center cohort allowed for consistency in RBC transfusion thresholds and criteria for evaluation and treatment of ROP. There are limitations of a retrospective study design, such as the possibility of bias and restricted access to information on supplemental oxygen/ventilation, storage age of transfused RBCs, detailed retinal findings (retinal hemorrhages, vascular tortuosity, etc.), and the timing of ROP surgery or bevacizumab administration. Having said this, the findings in this study are important and merit validation through secondary analysis of large existing datasets and perhaps a prospective, randomized study focused on the early neonatal period.

Unlike with RBC transfusions in convalescing premature infants, the opportunity for a clinician to withhold/defer transfusions while treating a critically ill and anemic younger premature infant on multi-modality life-support may be somewhat limited. The key may be in prevention of anemia. Unfortunately, many practice improvement steps that hold promise in reducing late transfusions, such as iron supplementation, streamlining of "surveillance" laboratory tests, and long-acting erythropoietin analogs, may not work within the first 10 days after birth. Having transfusion guidelines reduces the overall number of transfusions, but we must exercise caution before arbitrarily lowering transfusion thresholds for the sole goal of reducing transfusions. Further work is needed to establish safe thresholds to avoid unintended increase in adverse outcomes that may be related to decreased oxygen delivery to the brain, lungs, and intestine. To reduce early transfusions, emphasis should be placed on cord stripping/delayed clamping, use of placental blood for initial laboratory testing, carefully monitoring the total volume of blood drawn through central lines for pathology testing, and reducing specimen volume requirements by using point-of-care tests whenever possible and by advocating for infrastructure improvements in the hospital clinical laboratory [22]. It may also be time to re-evaluate autologous placental blood transfusions [23]. Some solutions seem visible within the line of sight, and we may be able to pick a few while awaiting further study on safe transfusion practices.

Acknowledgements This work was supported by NIH awards HL124078 and HL133022 (to AM).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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