Erythrocyte transfusions and retinopathy of prematurity: plea for application of the two-phase theory

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Received: 21 November 2023 | Accepted: 15 December 2023

DOI: 10.1111/apa.17079

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

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Erythrocyte transfusions and retinopathy of prematurity: Plea for application of the two-phase theory

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Dear Editor,

With great interest we read the article by Glaser et al. regarding the risk of retinopathy of prematurity (ROP) in neonates with history of red blood cell (RBC) transfusions.[1] The authors reported increased odds of ROP in neonates who received more than two RBC units (aOR 1.2; 95% CI 1.0—1.3), while decreased odds of ROP were reported in neonates with less than two RBC units (aOR 0.7; 95% CI 0.6—0.7). This study provides important data in a large cohort ($n = 12\,565$). Unfortunately, similar to most studies reporting on this issue, data on timing of RBC administration were not available. We would appreciate the opportunity to discuss the effect of RBC transfusions when stratified for ROP phase I and II.

As previously described, ROP occurs in two phases: a vaso-obliterative and a vasoproliferative phase. Phase I, starting directly after birth, is characterised by hyperoxic exposure to the retina, which leads to retinal vessel growth arrest. As the authors have mentioned, RBC transfusions consist of adult haemoglobin, which has a lower affinity for oxygen compared with foetal haemoglobin. Most extremely preterm neonates receive RBC transfusions in the first postnatal weeks, which decrease foetal haemoglobin levels and, thus, increase oxygen availability to the retina and risk of ROP.[2] We speculate that RBC transfusions in phase I substantiate the increased ROP risk reported in this study.

Phase II, beginning around 32 weeks of postmenstrual age (PMA), is characterised by hypoxia of the developing retina, which stimulates abnormal retinal vessel growth. Anaemia in ROP phase II promotes the production of oxygen-related proangiogenic growth factors, which increases risk of ROP progression. When extremely preterm neonates with low haemoglobin levels in ROP phase II receive RBC transfusions, oxygen availability to the retina will theoretically increase and compensate retinal hypoxia. Hence, we believe that RBC transfusions in ROP phase II may have the opposite effect on phase I: decrease risk of ROP progression.

Data supporting the causal relationship between lower haemoglobin levels in ROP phase II and ROP progression are limited. One study by Uberos et al. ($n = 472$) reported an increased odds of ROP in neonates who received their first RBC transfusion < 32 weeks of PMA (aOR 2.2; 95% CI 1.1—4.4), but no association in neonates who received their first RBC transfusion ≥ 32 weeks PMA.[3] This study supports the idea that the effect of RBC transfusions differs when given in ROP phase I or II.

Hence, we advocate for future research investigating the effect of RBC transfusions on ROP to take the two-phase theory into account. Instead of solely focussing on the quantity of RBC transfusions, it is important to consider timing of administration as well. There is an urgent need for a randomised controlled trial specifically designed to compare liberal and restrictive transfusion policies

in ROP phase II with ROP progression as primary outcome. This is the only way to determine their potential causal relationship. Until then, we strongly encourage neonatologists to bear in mind the two-phase theory in clinical practice.

AUTHOR CONTRIBUTIONS

Salma El Emrani: Conceptualization; writing – original draft; writing – review and editing. **Lotte E. van der Meeren:** Conceptualization; writing – review and editing. **Enrico Lopriore:** Supervision; writing – review and editing; conceptualization. **Nicoline E. Schalij-Delfos:** Supervision; writing – review and editing; conceptualization.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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How to cite this article: El Emrani S, van der Meeren LE, Lopriore E, Schalij-Delfos NE. Erythrocyte transfusions and retinopathy of prematurity: Plea for application of the two-phase theory. Acta Paediatr. 2024;113:615–616. https://doi.org/10.1111/apa.17079