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CLINICAL RESEARCH UPDATE

TRANSFUSION

The whole is greater than the sum of its parts: Rethinking our approach to neonatal transfusion research

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Abstract

Many preterm infants are exposed to multiple transfusion types during their admission in the neonatal intensive care unit. Yet, evidence supporting current practice consists of several randomized controlled trials and observational studies focusing on a single transfusion product at the time. Rather than approaching transfusions as three distinct categories as currently done in the literature, there may be benefit by accounting for the interconnected nature of these practices. In this Clinical Research Focus article, we advocate for a broader perspective in future research on neonatal transfusion practices. By looking at the whole instead of its parts, we can gain a more comprehensive understanding of the impact of transfusion exposure, potential associated adverse effects, and their implications for neonatal care.

KEYWORDS

platelet transfusion, RBC transfusion, transfusion practices

Preterm infants frequently receive red blood cell (RBC), platelet, and plasma transfusions with the aim to optimize oxygen transport and prevent bleeding. We recently conducted a large cohort study describing neonatal transfusion practices in 1143 preterm infants across 64 neonatal intensive care units (NICU) in 22 European countries. We found that 34.6% (396/1143) of infants received RBC transfusions, 6.2% (71/1143) platelet transfusions, and 8.0% (92/1143) plasma transfusions.[1–3] The evidence supporting current practice consists of several randomized controlled trials and observational studies. All of these trials have focused on a single transfusion product at a time, even though these interventions are often given to the same patients within a limited time window, such as during the first week of life or around a critical episode in the later clinical course.

Therefore, we quantified the overlap in our cohort study and found that a considerable proportion of transfused infants were exposed to multiple types of transfusions (Figure 1). We found that 90% (64/71) of preterm infants who received platelets, 87% (80/92) of those who received plasma, and 28% (111/396) of those who

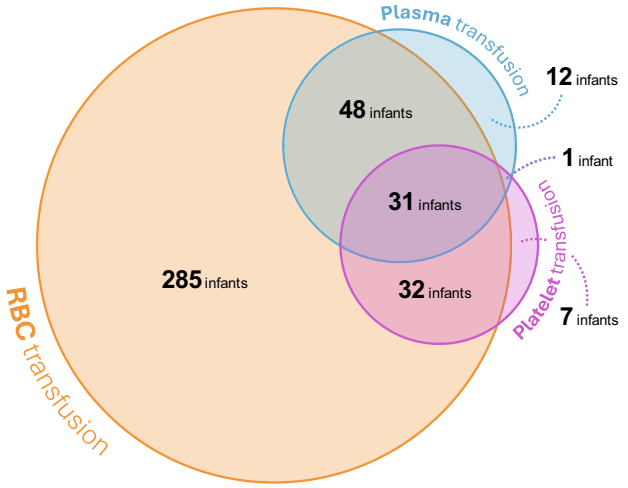

FIGURE 1 Venn diagram illustrating the overlap among transfused infants.

received RBCs were also exposed to at least one additional transfusion type. This substantial overlap may be clinically relevant and needs to be accounted for in neonatal transfusion research for three important reasons.

Firstly, different transfusion products can affect the same clinical outcomes. For example, RBC, platelet, and plasma transfusions are all biological agents, which all result in donor exposure and may carry potential risks such as alloimmunization, infectious disease transmission, allergic reactions, or immune responses. Moreover, all neonatal transfusions are derived from adult donor blood despite a "developmental mismatch" with neonatal RBCs, platelets, and plasma. This refers to differences in functional properties, cellular lifespan, and biochemical composition between neonatal and adult blood cells. The developmental mismatch has been suggested to trigger neonatal immune and inflammatory responses, although it is essential to better understand the biological consequences. Additionally, neonatal transfusions have been associated with inflammatory effects that may mediate neonatal complications such as retinopathy of prematurity, bronchopulmonary dysplasia, necrotizing enterocolitis, and intraventricular hemorrhage.[4] As transfused infants often receive more than one type of product, a meaningful analysis of these effects needs to consider of all three products. Otherwise, possible similarities in their effects on preterm infants may be overlooked.

Secondly, transfusion products have similar characteristics that justify a comprehensive approach. For example, a key evidence gap in neonatal transfusion research is optimal transfusion volumes and infusion rates. We observed striking variations in both transfusion volumes and durations across European countries, resulting in high infusion rates for many transfusions. This was hypothesized as one of the potential mechanisms of harm associated with a liberal platelet transfusion threshold in the PlaNET-2/MATISSE trial.[5] However, if true, this hypothesis most likely extends beyond platelet transfusions and may apply to RBC and plasma transfusions as well, underlining the potential benefit of a unified approach.

Thirdly, transfusion of different products within the same time window may interact with each other, which may affect clinical outcome.[6] For example, platelets are known to interact with a host of other cell types, including RBCs and plasma components. Sufficient red cell concentrations are needed to shift platelets to the periphery of the blood vessel, where they can perform their hemostatic functions.[7] These interactions could potentially have synergistic effects (sufficient red cells may optimize platelet functions) as well as detrimental effects (red cells can inhibit platelet aggregation through the release of functional equivalents of nitric oxide) and therefore need to be taken into account in neonatal research.

Given these considerations, we advocate for a broader perspective in future research on neonatal transfusion practices, since we found many infants are exposed to multiple transfusion types during their admission. Rather than approaching transfusions as three distinct categories, as currently done in the literature, there may be benefits by accounting for the interconnected nature of these practices. As a starting point, transfusion studies should record and report the use of other transfusion products in the study population, or statistical analyses could include interactions between different transfusion products. Moreover, studies assessing the effect of volume or transfusion rate should also provide volumes and rates of different products combined. Future studies, ideally advanced randomized controlled trial designs, could explore the effects of combinations of different transfusion products. In short, by looking at the whole instead of its parts, we can gain a more comprehensive understanding of the impact of transfusion exposure, potential associated adverse effects, and their implications for neonatal care.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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