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Recent advances in NICU platelet transfusions☆

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1. Platelet transfusions in neonates

Neonates, especially those born preterm, have a high incidence of thrombocytopenia, defined as a platelet count <150 × 10^9/L [1–3]. The incidence of thrombocytopenia increases with decreasing gestational age and birth weight, reaching ~70 % among extremely low birth weight (ELBW) neonates [4]. This same population is at the highest risk for intracranial hemorrhage, specifically intraventricular hemorrhage. Approximately 20–25 % of neonates born with a birth weight <1,500 g will develop an intraventricular hemorrhage during the first week of life, which can be associated with worse long-term neurodevelopmental outcomes. The platelet count below which the bleeding risk increases to the point of justifying a transfusion in the neonatal population has been unclear, resulting in the administration of prophylactic platelet transfusions to non-bleeding neonates at platelet count thresholds higher than those used in older children and adults. In a recent study of neonatal platelet transfusion practices in seven hospitals in the United States from 2013 to 2016, the median platelet count prior to transfusion was 71 × 10^9/L, which is much higher than the threshold of 10 × 10^9/L typically used in older populations [5]. This historic lack of data also led to substantial world-wide variability in neonatal transfusion practices [6], with one study finding that North American neonatologists gave ~2.3-fold more platelet transfusions compared to European colleagues, based on practice variability alone [7]. These liberal platelet transfusion practices assumed that increasing the platelet count would decrease the neonate's bleeding risk and improve outcomes. However, while a platelet transfusion will (at least transiently) increase the platelet count, the evidence available offers little support for this assumption. Thrombocytopenic neonates do have a higher incidence of intraventricular hemorrhage compared to non-thrombocytopenic neonates [1,8], but multiple studies have shown a poor correlation between the degree of thrombocytopenia and the incidence of bleeding [8–11]. Given this lack of correlation, it is not surprising that studies found no significant effect of platelet transfusions on the incidence of bleeding, at least when transfusions were given for moderate thrombocytopenia [8,12,13]. Taken together, these studies suggest that factors other than the platelet count may be more important determinants of the bleeding risk in preterm neonates.

In addition to not mitigating bleeding risk, several observational and retrospective studies found an association between platelet transfusions and neonatal morbidity and mortality [14–16]. However, this association was heavily confounded by illness severity, as the most critically ill infants are often the recipients of platelet transfusions. In 2019, the Randomized Trial of Platelet-Transfusion Thresholds in Neonates (PlaNeT-2) Trial, the largest platelet transfusion threshold trial conducted in this population, was published [17]. This study randomized 660 preterm infants (gestational age <34 weeks) to receive a platelet transfusion at a high platelet count threshold of 50 × 10^9/L or a low platelet count threshold of 25 × 10^9/L. Infants randomized to the high-threshold group had a significantly higher rate of major bleeding and/or death in the 28 days after randomization, the primary outcome of the trial. Among secondary outcomes, infants in the high-threshold group also had a higher incidence of bronchopulmonary dysplasia (BPD) compared to infants in the low threshold group [17].

Recently, the 2-year outcomes from infants in the PlaNeT-2 Trial were published. At this age, investigators assessed the incidence of death or neurodevelopmental impairment (defined as developmental delay, cerebral palsy, seizure disorder, and/or profound hearing or vision loss) using a combination of data sources, including doctors' notes, parental questionnaires and formal testing. Follow up data was available for 92 % of eligible participants and showed that infants randomized to the high threshold group had an increased incidence of death and/or poor neurodevelopmental outcome by 2 years of age compared to infants randomized to the low-threshold group [18]. More recently, a secondary analysis of data from the Preterm Erythropoietin Neuroprotection Trial (PENUT) investigated the association between exposure to platelet transfusions during the NICU hospitalization and neurodevelopmental outcomes at 2 years corrected age, measured using the Bayley Scales of Infant Development-Third Edition. Out of the 819 infants included in the analysis, 30 % received at least one platelet transfusion during their initial hospitalization. Similar to the findings of PlaNeT-2, infants exposed to one or more platelet transfusions had a statistically higher

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incidence of the primary outcome of death or severe neurodevelopmental impairment (NDI) at 2 years' corrected age, compared to non-transfused infants (Fig. 1) [19]. Analysis of the association between number of transfusions and the primary outcome found that, for each additional platelet transfusion exposure, the adjusted odds ratio of death of severe NDI was 1.25 (95 % CI, 1.07–1.45). Upon analysis of the specific components of NDI (motor, language, and cognition), infants who had received 1 or more transfusions had lower mean motor scores at 2 years' corrected age [19].

Together, the available data strongly suggest that liberal platelet transfusions can negatively impact the short- and long-term outcomes of preterm neonates. However, the mechanisms responsible for these harmful effects are just beginning to be elucidated.

2. Potential mechanisms mediating the harmful effects associated with platelet transfusions in neonates

2.1. Fast transfusion rates

Historically, platelet transfusions have been administered as fast as possible, frequently over 30 min or less. The reasons underlying this common practice, quite different from red blood cell transfusions, are unclear. In extremely preterm neonates, fluid boluses (also administered rapidly) have been associated with increased rates of intraventricular hemorrhage (IVH). Thus, it has been hypothesized that the rapid administration of platelets, particularly at a dose of 15 mL/kg as was done in the PlaNeT-2 trial, could have been a contributing factor to the increased incidence of major/severe bleeding observed in neonates assigned to the high threshold group in that trial [17]. To investigate whether platelets could be safely and effectively transfused at a slower rate (i.e. closer to red cell transfusions), a single center randomized trial compared the platelet increment observed in preterm neonates transfused over 2 h vs. over 30 min, and found no difference between the two groups [20]. While this was a small study, these findings support the safety and efficacy of transfusing platelets over 2 h, at least in extremely preterm infants during the highest risk period for IVH.

2.2. Developmental differences in platelet function

While neonates and adults have similar platelet counts and their platelets are structurally identical, there are significant developmental differences in regard to platelet function [21,22]. When activated by various agonists, platelets respond by changing the conformation of a key surface glycoprotein (GPIIb/IIIa) to a fibrinogen-binding form, and by translocating P-selectin from their alpha granules to the surface. The ability to bind fibrinogen is critical for the platelet's hemostatic functions, including aggregation, while the increased surface P-selectin allows platelets to directly interact with immune cells, including neutrophils and monocytes, which express the P-selectin receptor PSGL-1 on their membranes. Following stimulation, platelets from neonates exhibit significantly lower levels of fibrinogen binding and lower surface P-selectin expression compared to platelets from adults [21]. This, in turn, translates into lower levels of platelet aggregation and less binding to immune cells compared to adult platelets.

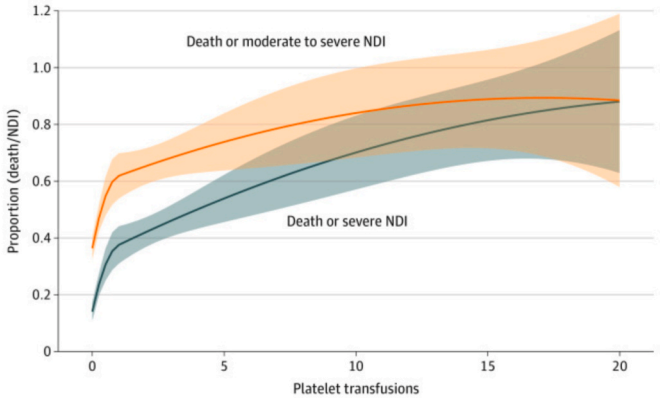

Fig. 1. Probability of death or severe neurodevelopmental impairment (NDI) and death or moderate to severe NDI at 2 years of age in children enrolled in the PENUT study, shown by the number of platelet transfusion exposures. Five infants who received more than 20 transfusions were assigned a value of 20. The shaded areas indicate 95 % confidence intervals. Copied with permission from [19].

The initial studies evaluating the functional characteristics of neonatal platelets were conducted in platelets isolated from full-term cord blood [23]. However, subsequent studies evaluated the activation of platelets obtained from cord blood, preterm and term neonates, infants, children and young adults in response to different agonists [24–26]. These studies revealed that platelets from preterm neonates are more hyporeactive than platelets from term neonates and that platelet function in both groups improves significantly over the first 10 days of life [24]. Surprisingly, however, recent data suggest that some developmental differences persist all the way into adolescence, particularly in regard to the platelet fibrinogen binding ability [26].

While these functional "deficiencies" observed in neonatal platelets would predict a bleeding tendency, tests of whole blood primary hemostasis such as the bleeding time or its *in vitro* equivalent, the Platelet Function Analyzer® Closure Time (PFA-CT), showed that healthy term neonates had *shorter* bleeding times than healthy adults, indicating more than adequate primary hemostasis [27–29]. This paradoxical finding is explained by the presence of factors in the neonatal blood that enhance and accelerate clotting, including the high hematocrit of neonates, their high mean corpuscular volume (MCV), and the high concentrations of von Willebrand factor in neonatal blood [30]. Combined, these factors create a pro-thrombotic milieu that counteracts the hyporeactivity of neonatal platelets, resulting in a neonatal hemostatic system that is very different from that of adults, yet perfectly balanced.

2.3. Non-hemostatic platelet functions

Over the past decade, a growing number of studies revealed that platelets are have multiple non-hemostatic functions, including in angiogenesis, regulation of vascular tone, cancer metastasis, host defense, and particularly immune and inflammatory responses (Fig. 2). The latter functions are so important that platelets are now viewed by many as both hemostatic and immune cells [31,32]. Highlighting this paradigm shift, a study evaluating the mRNA content of neonatal and adult platelets found that the majority of platelet mRNA transcripts were involved in immune functions and regulation of immune responses, more than hemostasis and coagulation [33].

The immune functions of platelets are complex and involve both the innate and adaptive immune systems in highly context-dependent ways. Platelets interact with immune cells, including monocytes and neutrophils directly, through P-selectin-mediated cell-cell interactions, and indirectly through the release of a large number of cytokines, chemokines and immunomodulatory molecules stored in platelet granules or translated in response to specific signals [34–36].

The discovery of these non-hemostatic platelet functions raised the question of whether neonatal platelets also differ from adult platelets in regard to these functions, particularly the regulation of immune and inflammatory responses. Since P-selectin is the main molecule mediating the interaction of platelets with leukocytes, the decreased P-selectin exposure observed in neonatal platelets following activation suggested that neonatal platelets would be less able to form platelet-monocyte or platelet-neutrophil aggregates (PMAs and PNAs, respectively). And since the formation of PMAs and PNAs increases monocyte and neutrophil activation and mobilization, this key developmental difference suggested that neonatal platelets would have a lower ability to activate these cells. Consistent with this hypothesis,

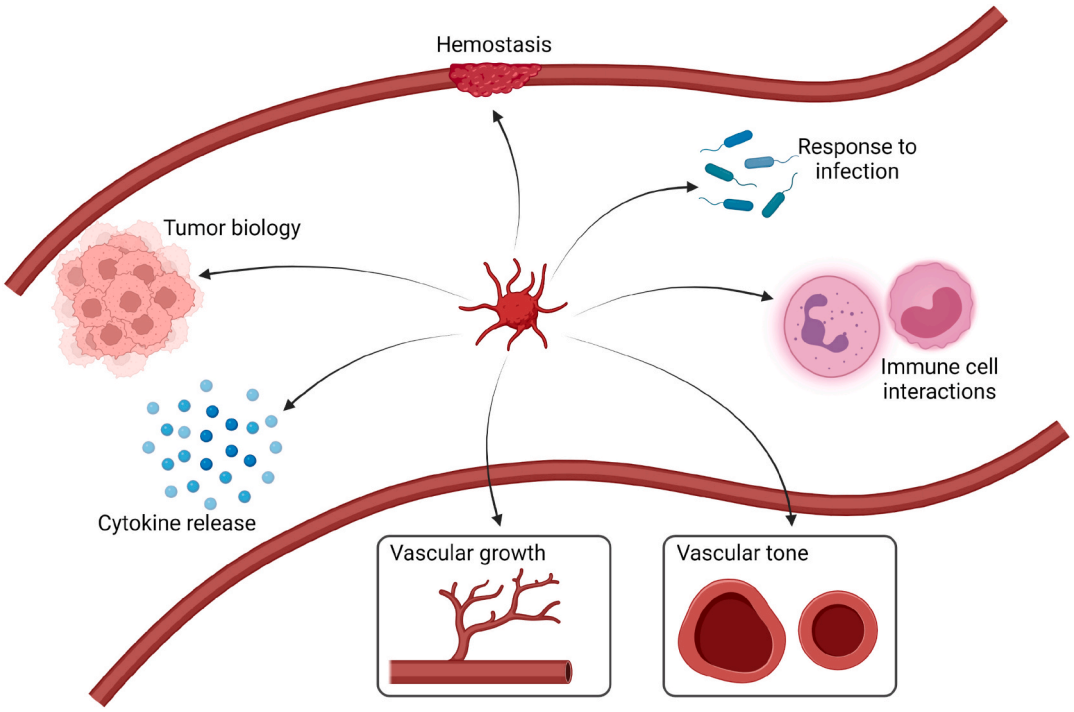

Fig. 2. Multiple functions of platelets including hemostasis, response to infection, immune cell interactions, cytokine/chemokine release, vascular tone, vascular growth, and tumor biology. Copied with permission from [45].

thrombocytopenic newborn mice transfused with adult platelets exhibited more PMAs than newborn mice transfused with neonatal platelets, a difference that was attenuated if P-selectin binding to PSGL-1 was blocked [37].

Two recent studies also identified differences in the protein content of neonatal and adult platelets. Most recently, we used quantitative label-free mass spectrometry to assess the proteome of neonatal (term cord blood)- and adult blood-derived resting platelets. Overall, we identified 4191 platelet proteins across all samples and found 334 proteins with abundance significantly different between neonatal and adult platelets. Analysis of the 172 proteins that were significantly more abundant in adult platelets revealed that these were mostly involved in immune and inflammatory pathways. In contrast, the 162 proteins that were significantly more abundant in neonatal platelets were enriched

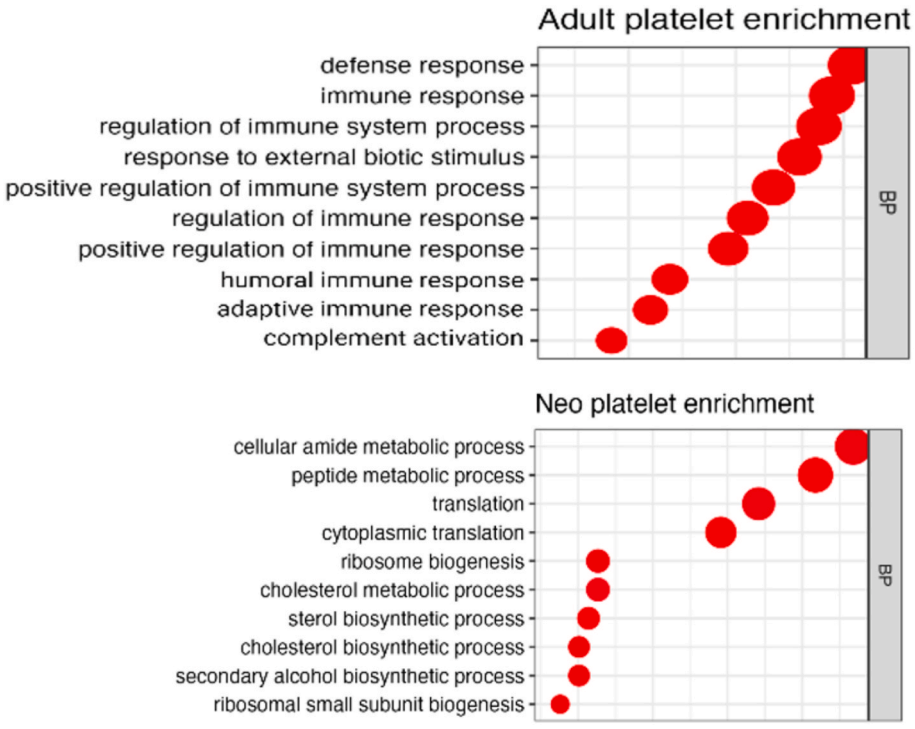

Fig. 3. Gene ontology pathway analysis of the proteins enriched in adult and neonatal platelets. Significantly enriched biological processes are shown. Adapted with permission from [38].

for metabolic pathways (Fig. 3) [38]. These findings were consistent with those of a previously published proteomic study of adult and neonatal platelets, which found 170 differentially abundant proteins, with adult platelets enriched in proteins related to the inflammatory response, complement activation, platelet activation and blood coagulation, and neonatal platelets enriched for proteins involved in mitochondrial energy metabolism, long chain fatty acid metabolism and iron binding [39]. In addition to these human studies, a murine study that compared the mRNA expression profile of neonatal and adult mouse platelets also found adult platelets to be enriched in mRNAs involved in immune pathways [37]. Taken together, these studies suggest that, across species, proteins involved in immune functions are more abundant in adult compared to neonatal platelets, suggesting that these might be more immunologically active compared to neonatal platelets.

2.4. *Effects of platelet transfusions on neonatal hemostasis and immune responses*

The recognition of the substantial differences between neonatal and adult platelet content and functions and between the neonatal and adult hemostatic and immune systems naturally triggered questions about the effects of transfusing adult (more hemostatically and immunologically active) platelets into the very different physiologic environment of a sick neonate. The first study to specifically ask this question removed platelets from full term cord blood samples to generate thrombocytopenic neonatal blood samples, which were then mixed with either adult or neonatal platelet concentrates in order to model *in vitro* neonatal transfusions with adult or neonatal platelets. As hypothesized, this study found that "transfusion" of neonatal blood with adult platelets resulted in significantly shorter *in vitro* bleeding times, compared to "transfusion" with neonatal platelets, to levels that have been associated with an increased risk of cardiovascular event [40]. This *in vitro* study provided the first proof of concept for the potential of adult platelets to alter the delicate neonatal hemostatic balance and tilt it toward a pro-thrombotic phenotype, which could potentially worsen diseases characterized by microvascular thrombosis and tissue ischemia, like necrotizing enterocolitis. This led to the hypothesis that the "developmental mismatch" that occurs when adult platelets are transfused into neonates might be a contributing factor to the worse clinical outcomes associated with platelet transfusions in preterm infants.

While initial studies investigating the consequences of this developmental mismatch naturally focused on the effects of platelet transfusions on the neonatal hemostatic system, recent studies have begun to explore whether adult platelets (with their abundance of proteins involved in immune functions and greater P-selectin exposure upon activation) could similarly dysregulate the neonatal immune system. In an elegant study, Maurya and co-investigators transfused thrombocytopenic newborn mice with either adult or neonatal platelets and explored the effects of these transfusions on the recipient's monocytes. Interestingly, transfusion of adult -but not neonatal-platelets significantly increased the percentages of circulating PMAs and of monocytes expressing CCR2 and CCR5, the receptors for two potent chemokines, MCP-1 (CCL2) and RANTES (CCL5), in the transfused pups [37]. Functionally, this made the monocytes of newborn mice transfused with adult platelets more able to migrate in response to these chemokines, potentially worsening the infiltration of inflammatory cells into tissues. These responses were abrogated if P-selectin interactions with its receptor in immune cells (PSGL-1) were blocked, indicating that the developmental differences in P-selectin exposure were mediating these pro-inflammatory effects [37].

A separate study explored the effects of platelet transfusions in newborn mice with polymicrobial sepsis, and found that transfusion (of adult platelets) into newborn mice with low-mortality sepsis increased the inflammatory response and the mortality. However, the effects were different in newborn mice with high-mortality sepsis, in which platelet transfusions attenuated the inflammatory response and decreased mortality [41]. Whether and how this translates to human neonates is unknown, but these findings highlight the complex and context dependent effects of platelets on immune responses.

Two studies so far have investigated whether clinically ordered platelet transfusions affect plasma cytokines in human neonates admitted to the neonatal intensive care unit. A study by Dr. Moore and collaborators measured a panel of cytokines in dried whole blood samples obtained prior to and 2 h post-transfusion in 17 infants who underwent 26 platelet transfusions [42]. This study found statistically significant increases in the levels of CXCL5, CD40 and TGF-β following platelet transfusion, although it is unclear to what degree these increases reflected the amount of these factors contained in the transfused platelets, given that they were measured in whole blood. In a recent (unpublished) study of 20 thrombocytopenic neonates by our group, we found significant increases in the plasma levels of PDGF-α and PDGF-β 2 and 4 h after transfusion, and significant increases in RANTES (CCL5) levels 4 h after transfusion [43]. Taken together, these murine and human studies support the hypothesis that platelet transfusions increase inflammatory cytokines and growth factors in neonates and induce dysregulated immune responses, which may potentiate existing inflammation in various target organs (lung, intestine, brain) and may contribute to the harmful effects of platelet transfusions observed in preterm babies.

3. Conclusions

In conclusion, observational and randomized studies have shown that platelet transfusions can be associated with worse short- and long-term clinical outcomes in neonates. Thus, better identifying which neonates are likely to benefit from these interventions is critical. Since platelet transfusions remain life-saving interventions in neonates with active bleeding, undergoing surgical procedures, or with levels of thrombocytopenia at which the bleeding risk is likely increased, it is also critical to understand the mechanisms responsible for the undesired effects of transfusions. In addition to the rapid transfusion rate as a potential contributor to bleeding risk, it is now clear that platelets are de facto hemostatic AND immune cells, and that adult platelets are hemostatically and immunologically more active than neonatal platelets, resulting in a potentially harmful "developmental mismatch" associated with platelet transfusions. Emerging evidence suggests that platelet transfusions can dysregulate the neonatal hemostatic balance as well as the immune responses, potentially triggering or potentiating inflammation and tissue injury (Fig. 4). Until these mechanisms are clearly established and potentially attenuated, implementing evidence-based transfusion guidelines in our NICUs to minimize unnecessary platelet transfusions is the best strategy [44].

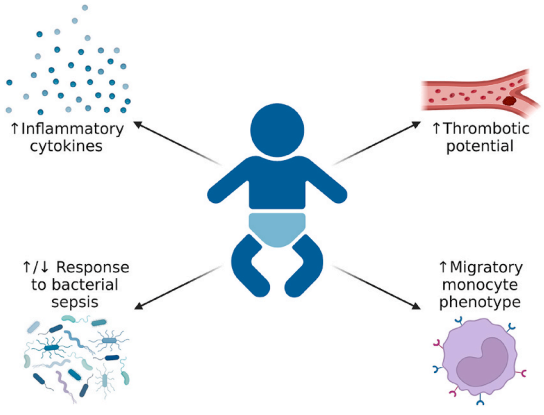

Fig. 4. Schematic representation of potential mechanisms mediating the harm from neonatal platelet transfusions. Copied with permission from [45].

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