Old and New: What Blood Is PROPPR in Trauma Resuscitation?

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In 1825, Dr. James Blundell transfused fresh, whole blood from the husband of a young woman exsanguinating from a postpartum hemorrhage.[1] During the next nearly 2 centuries, the treatment of massive hemorrhage evolved to include blood components (instead of whole blood) and other fluids. Having whole blood available was a logistic challenge; dividing blood into its key components allowed broader deployment across many conditions, enhancing efficient use of a precious resource.

This fractionated blood component approach comes with a potential cost: RBCs that are cold stored incur storage effects.[2] Although the overall effect isn't well defined, several phenomena related to use of stored blood exist. These include neutrophil activation, increases in complement, and release of lipids and proinflammatory proteins.[3] Stored blood has increased cell free hemoglobin, ferrous oxyhemoglobin, and arginase-1, which attenuate nitric oxide and impair nitric oxide synthesis. RBC microparticles, which increase with the duration of RBC storage, also contribute to nitric oxide inactivation and impair nitric oxide bioavailability, all of which may contribute to endovascular dysfunction. Free iron introduces free radical species, which may exacerbate inflammation and cellular damage. In animal studies, the RBC supernatant results in vasoconstriction proportional to the degree of hemolysis observed in the stored product.[4] Aged stored blood further impairs endothelial function through other mechanisms, creating vasodilation.[5]

In the past 25 years and fostered by military experiences, traumatic hemorrhagic therapy has moved from targeting near-normal physiologic endpoints using crystalloid and packed RBCs (PRBCs) into first gaining hemorrhage control, resuscitating with equal ratios of blood products, and tolerating hypotension when necessary.[6,7] The Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial examined the outcomes of resuscitative transfusion for patients with severe traumatic hemorrhage, comparing with 1:1:1 and 1:1:2 ratios of plasma, platelets, and PRBCs.[8] The trial demonstrated no difference in 24-hour or 30-day mortality. This trial focused on the acute resuscitation of a trauma patient with blood and provides the opportunity to examine the performance of resuscitative transfusion.

As we progress toward more blood product use early in resuscitation, what information do we have in regard to blood aging and outcomes? There are greater than 80 observational human studies, most showing associations between "older" blood and mortality or other adverse events (infection, organ dysfunction, lung injury, etc).[9] Several randomized trials failed to find a difference between "fresher" and stored, standard-issue blood. Current evidence-based guidelines conclude "patients should receive RBC units selected at any point within their licensed dating period (standard issue) rather than limiting patients to transfusion of only fresh (storage length: <10 days) RBC units (strong recommendation, moderate quality evidence)."[10] What factors contribute to the discrepancy between the observational and experimental data?

The observed associations between the transfusion of older blood and morbidity or mortality may reflect the confounding effect of total transfusion volume rather than stored RBC age.[11] There is a strong association between transfusion volume and mortality, which may be more relevant in the context of a massive transfusion.[12,13] This concept of dose confounding was not addressed in previous experimental trials because most did not include massively transfused patients (the mean transfusion volume was 4 units). Furthermore, the studies used variable "fresh" blood designations, with some stored up to 19 days. Spinella and Holcomb[3] pointed out that RBC age itself may only be a surrogate for RBC quality. Perhaps blood age should be looked at not as a categoric descriptor but as a continuous mitigatable variable in the assessment of the larger transfusion risk.

In this issue of *Annals*, Jones et al aim to determine the association between PRBC age and mortality among

trauma patients.[14] This secondary analysis of the PROPPR study examined 687 patients receiving 8,830 units of PRBC after trauma injury; enrollees in this cohort had early care (out-of-hospital administration of blood) and a validated objective score noting an increased risk of receiving a massive transfusion. To address potential confounding between the age of the blood and the volume administered, the authors stratified patients according to PRBC age and dichotomized them into groups receiving greater than or less than 10 units. Among patients receiving greater than 10 units of PRBCs, those receiving PRBCs older than 22 days had a higher 24-hour mortality occurrence. The authors accounted for patient characteristics, clustering by site, mechanism, PROPPR treatment group, and age of the blood, demonstrating a signal for harm (odds ratio 1.05; 95% confidence interval 1.01 to 1.08), and concluded that the transfusion of PRBCs aged 22 days or older is associated with an increased risk of death. They also observed that patients have a higher risk of adverse events with transfusion of PRBCs older than 8 days.

Many limits exist in this and any secondary analysis; we are left with strong hypothesis-generation data, but not granular causality. One limitation arises from a seemingly positive feature: the heterogeneity of the population of transfusion donors or recipients. The efforts to adjust for confounders may have led to overfitting of the models and potentially nonsustainable observation if exposed to an experimental research effort. Furthermore, dichotomizing the groups by transfusion volume introduces selection and indication biases. These biases may relate to either the PRBCs or to other components transfused in conjunction. Which component and at what age triggers the biology leading to subsequent adverse events? Is older plasma less effective at reversal of coagulopathy, harming the balanced approach because of one feature? Are older platelets more likely to provoke an inflammatory response? Could other unmeasured procedural differences lead to the observed findings?

Harm associated with blood age is likely a complex interaction including product, donor, and recipient factors. Harm may only come when exposure exceeds a threshold of deleterious factors. A toxic exposure may occur based on a combination of the age and volume of the product or when a percentage of the total product administered reaches a critical level. Donor age and sex influence the quality of transfused product, and those crude phenotypic metrics likely belie other characteristics still undefined.[14] The future might hold an approach in which patient factors (including crude features, underlying need or comorbid conditions, and biologic footprint data) can be combined with blood characteristics to optimize both outcomes and overall resource use.

Susceptibility to blood storage injury may also be the consequence of systems of care. Endothelial injury may vary with crystalloid administration, time to hemorrhage control, and various blood-banking practices. Exposure to older product may be a surrogate for secular trends in trauma care based on system volume, seasonal variation, or geographic location. Blood-transfusion services typically provide the oldest compatible RBCs as an inventory management approach ("first in, first out") to minimize waste of blood components.[2,15] These strategies compound exposure to old blood in some locations in which blood near expiration is returned for use in high-volume trauma centers.

Given these concerns, Jones et al suggest refraining from or minimizing blood products older than 8 days in the trauma population requiring massive transfusion. This recommendation seems unjustified, given the available data and in the context of the authors' own warning that "…caution should be used when interpreting the findings and application to clinical settings is not yet warranted." A rigorous trial comparing fresh blood with standard blood is necessary before blood-banking policy changes are contemplated. Ideally, this effort would include a myriad of donor, recipient, and injury factors to model the risk. Notably, the strategy of providing the freshest blood available in trauma exists in the military and began with the conflicts in Iraq and Afghanistan.[16] Military clinical practice guidelines also have returned to the method used in 1825: focusing on providing product as close as possible to fresh whole blood.[17,18] If better data arrive to further address these knowledge gaps in the transfusion risk-reward calculations during trauma care, the civilian sector will be challenged to alter blood-banking policy without accounting for cost, logistics, or units lost to expiration.

Another opportunity is identifying mitigation strategies to decrease the storage lesion effects. Could a "stored blood index" allow monitoring the dose of aged product and prompt care changes to counter any potential harms? Will precision medicine allow us to identify donors whose blood is tolerant of storage or exclude those whose blood increases recipient risk? Will release strategies account for donor and recipient factors or change according to models of use? The future offers great opportunity, but we do not yet know how and when the next tranche of advances will arrive.

Resuscitation care evolved and will continue to evolve; much of what is new and proper may look as it did 200 years ago, with fresh whole blood used to treat acute hemorrhage.[19,20] Until then, treat with balanced component therapy and, when possible, consider use of

fresh whole blood. For most trauma care, limit large-volume crystalloid resuscitation, control hemorrhage quickly, and deliver balanced component therapy while watching for negative effects of blood products. Universally excluding a blood product because of age is not possible or justified in broad practice, but data on the horizon will hone our approach; we just don't know the specifics today.

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