Editorial

Age before duty: the effect of storage duration on mortality after red blood cell transfusion

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Provenance: This is an invited Editorial commissioned by the Section Editor Zhiheng Xu (State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, Department of Intensive Care, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China).

Comment on: Heddle NM, Cook RJ, Arnold DM, *et al*. Effect of short-term *vs.* long-term blood storage on mortality after transfusion. N Engl J Med 2016;375:1937-45.

Submitted Dec 25, 2016. Accepted for publication Jan 04, 2017.

doi: 10.21037/jtd.2017.02.60

View this article at: http://dx.doi.org/10.21037/jtd.2017.02.60

The transfusion of blood products is one of the most commonly implemented therapies in modern medicine. Over 20 million blood components are transfused each year in the United States alone, of which approximately 13 million are packed red blood cell (pRBC) units (1). Current US Food and Drug Administration (FDA) regulations allow storage of pRBC units for up to 42 days prior to transfusion (2). Established in 1985, this blood banking policy reflects erythrocyte function as a measure of post-transfusion survival and storage-related hemolysis (3). Since then, many other metrics of red blood cell deterioration have been elucidated. Collectively termed the red blood cell storage lesion, a host of biochemical, metabolic, and structural changes have been shown to occur within the pRBC unit during the storage period (2,4). Elements of this storage lesion cause harm in animal models of transfusion, suggesting that the transfusion of stored pRBC units may lead to worsened outcomes in human patients and highlighting the need for high quality clinical studies (5-7).

Many clinical studies attempting to address this topic have yielded conflicting results. One reason for this is that these studies have been limited by small sample sizes. Another reason is that the definition of fresh blood and aged blood has been inconsistent across studies (*Table 1*) (8-21). Several articles have defined fresh blood as a function of time, ranging anywhere from 5 days (8) to 21 days (17), while others have taken a more practical approach, employing a "freshest available" policy (18,20). The definition of aged blood has also suffered from wide variations. Notably, only one study to date has investigated the effect of pRBC units transfused in their last week of storage, observing adverse outcomes in high-risk patients (17).

Recognizing the need for a definitive, high-powered study, Heddle *et al.* launched a large clinical trial spanning six hospitals across four countries. As published in the *New England Journal of Medicine*, the Informing Fresh versus Old Red Cell Management (INFORM) trial (21) randomized 31,497 transfusion recipients to pRBC units stored for a "short-" or "long-term" duration. The authors employed a "freshest available" approach to short-term storage, and "standard issue" policy to the long-term storage group. Median storage of pRBC units prior to transfusion was 11 days [interquartile ratio (IQR), 8–15] in the short-term group, as compared to 24 days (IQR 18–30) in the long-term group. There were no differences in in-hospital mortality between the two cohorts. Subgroup analysis of high-risk patient populations also revealed no differences in mortality rates with "long-term" storage blood transfusion (e.g., cardiovascular surgery, critically ill, and cancer patients).

The INFORM trial is the largest randomized study to date investigating the effect of blood storage duration on patient mortality. By utilizing a pilot trial (20), any logistical concerns and questions of feasibility were addressed prior to initiation of the study. Unfortunately, several limitations

Table 1 Variability in the definition of fresh blood versus aged blood. Standard issue denotes transfusion of oldest, non-expired pRBC units

Study	Fresh blood	Aged blood
Kor *et al.* (8)	<5 days	Standard issue
Fergusson *et al.* (9)	<7 days	Standard issue
Hébert *et al.* (10)	<8 days	Standard issue
Steiner *et al.* (11)	<10 days	≥10 days
Dhabangi *et al.* (12,13)	<10 days	25–35 days
Weinberg *et al.* (14)	<14 days	≥14 days
Koch *et al.* (15)	<14 days	≥14 days
Zallen *et al.* (16)	<14 days	≥21 days
Goel *et al.* (17)	<21 days	35–42 days
Aubron *et al.* (18)	Freshest available	Standard issue
Lacroix *et al.* (19)	Freshest available	Standard issue
Heddle *et al.* (20,21)	Freshest available	Standard issue

pRBC, packed red blood cell.

prevent the INFORM trial from providing a conclusive statement to the aged blood dilemma. First, the current study is not a true comparison between fresh and aged pRBC units, but rather, a comparison of "standard issue" and "freshest available" policies. While the actual definition of aged blood has been a point of contention, a storage period of 24 days falls near the middle of the accepted storage limit. Second, the authors admit that their electronic medical records do not provide information on coexisting illnesses. A compelling analysis of in-hospital mortality would include medical comorbidities and patient severity of illness as covariates in the statistical models. Third, the indications for blood transfusion are unknown. Ideally, mortality would be best compared in patients receiving pRBC units for similar indications.

Given the power of this large trial, it would be interesting to analyze data concerning the rates of adverse transfusion reactions, such as transfusion-associated acute lung injury. Based on current data, one can conclude that standard practice of transfusing oldest available blood is non-inferior to transfusion of freshest available blood with regard to in-hospital mortality. The question of whether aged blood portends worse clinical outcomes, however, remains to be answered.

Acknowledgements

Funding: This work was supported by NIH grants R01 GM107625 (TAP) and T32 GM008478-24 (YK).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Kim Y, Jung AD, Pritts TA. Age before duty: the effect of storage duration on mortality after red blood cell transfusion. J Thorac Dis 2017;9(3):441-443. doi: 10.21037/jtd.2017.02.60

