Commentary: Is there a "storage lesion" in red cells that affects outcomes in transfused cardiac surgical patients? The short answers are "maybe there is" and "maybe it doesn't matter"

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Transfusion of "old" red cells has uncertain consequences but may be safe.

Central Message

Questions remain about the use of aged blood products and the so-called "storage lesion" of transfused red cells.

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The manuscript by Koch and colleagues[1] in this issue of the *Journal* presents the results of a randomized trial investigating the consequences of the so-called "storage lesion" in packed red blood cells (PRBCs).[2] The authors were interested in the effects of storage PRBCs on cardiac surgical outcomes.[2] They randomized cardiac surgical patients who received "older" PRBCs (harvested ≥20 days before transfusion) compared with a group who received "younger" PRBCs (harvested ≤14 days before transfusion). Their measurements included a composite outcome in the study groups that consisted of 10 components, including major morbidities and operative mortality. The trial was discontinued mid-way through the intended enrollment, more than 10 years after protocol inception, because of what the authors describe as "enrollment constraints." The authors suggest that this clinical trial supports neither efficacy nor futility of transfusing either young or old PRBC units. The exact meaning of "enrollment constraints" is vague and requires some explanation and investigation.

There are a few "basics" that need clarification about this trial design. First, this study is not a placebo-controlled trial. The trial compares 2 treatments. In this case, the treatments consist of 2 ranges of days after harvest of PRBCs (either ≤14 days after harvest or ≥20 days after PRBC harvest). As one might expect, there are crossovers and drop-outs within the patient groups. It is important to state that the authors set out to perform a superiority trial, ie, prove that PRBCs harvested ≤10 days before the transfusion produce superior outcomes with reduced morbidity and mortality compared with older PRBCs harvested ≥20 days before transfusion. This superiority comparison is a subset of the noninferiority trial and will require a sample size that is similar to a noninferiority trial unless the difference between the 2 treatments is small, in which case the required

sample size to confirm a difference (or lack thereof) is much larger. As the expected difference between study groups decreases, the required sample size to be sure about the statistical power of a negative result will increase, often dramatically so.[3,4]

After more than 10 years of conducting this study, the authors compiled 2 groups of study patients with more than 680 patients per group (something like 100-120 patients entered into the study per year). This study group was obtained at an institution that does 3000 or more cardiac operations per year, so enrollment in this study was challenging to say the least. The authors acknowledge the difficulties in study accrual, something that they call "enrollment constraints." It is not entirely clear what "enrollment constraints" means, but I infer from the authors' comments that protocol crossovers, relative infrequency of transfusion, and blood bank constraints all combine to make homogeneous study groups a challenge.

One of the comments in the authors' Conclusions section is intriguing. They suggest that it may be better to measure laboratory markers of red blood cell (RBC) degradation as an indicator of viable RBC function and a gauge of adequacy of RBC preservation at the time of transfusion. Although this type of testing is undoubtedly better than simply measuring the time from RBC harvest to transfusion as

an indicator of the quality of transfused product, it may be impractical and possibly unnecessary to add further laboratory measurements to blood products that seem adequate even at the greater end of the storage spectrum. There are opposing opinions about the adequacy and assessment of donor blood products, but solid evidence about need for increased preoperative adequacy testing of donor blood is limited.

The authors' study design is unique. They point out the difficulties when considering a composite endpoint with varying rates of each component of the composite variable. They used a composite outcome measure that will likely be unfamiliar to most readers (me included). As best I can tell, the composite outcome measure was adjusted so that all major complications were given equal weight, as opposed to giving increased weight to more frequent complications of more serious complications. There is no indication that the authors' choice of outcome measure is better or worse than other possible composite outcome measures. It is a bit counterintuitive to consider all complications as having equal weight, but regarding PRBC transfusion category as an independent variable, this is likely an acceptable alternative.

It is a bit simplistic to assume that PRBC transfusions are the only important transfusions received by cardiac surgical patients. The authors are a bit circumspect about the interactions of plasma and platelets with PRBCs. There must be some synergistic relationship between PRBC transfusion and other hemostatic agents, including platelets, plasma, topical hemostatic agents, and intravenous hemostatic drugs. It would be nice to know whether there was a relationship between use of non-PRBC products and reduced PRBC usage. Consideration of these non-PRBC blood components and hemostatic adjuncts adds a level of complexity that both complicates and confounds the analysis. It would be helpful to at least describe both the frequency and usage of non-PRBC products in the study group, but I am not sure that a meaningful analysis would result from this addition.

So, what can we conclude from this study? One thing is clear. This is an incomplete study, even by the authors' admission. It is reasonable to suggest, without definitive evidence to the contrary, that the differences in surgical outcomes related to short and long PRBC pretransfusion storage times are minimal, and possibly unimportant. There is conflicting evidence about the importance of the storage lesion in transfused PRBC. Trauma patients do not seem to be effected by aged PRBC, so there is precedent for a lack of concern about transfusing aged PRBC.[5] Similarly, critically ill patients in the intensive care unit did not benefit from transfusion of fresh PRBCs (average of 6 days storage) compared with older aged blood (average of 22 days).[6] Yet some familiar authors from the Cleveland Clinic published a study suggesting that transfusion of PRBC stored for more than 2 weeks is associated with increased postoperative complications after cardiac operations.[7] Much more elaborate and costly studies are required before a preferred pretransfusion storage time and a proven benefit from transfusion of recently harvested PRBCs can be identified. Further, evaluation of PRBC transfusion in isolation, ignoring other blood products and hemostatic agents, is probably simplistic at best and inaccurate at worst. Available evidence, as limited as it may be, supports use of any PRBCs harvested at any age before use except at the very extremes of PRBC lifetimes (eg, 40-45 days after harvest). The evidence to support this contention is pragmatic and nonrigorous. More studies might fine-tune this concept, but the effort to provide these data may not be helpful, and may not be necessary.

References

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