New Blood, Old Blood, or No Blood?

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The use of blood transfusions in medicine is so well established that the procedure is an afterthought to many physicians. Scientific advances have rendered blood and blood products extremely safe through the introduction of donor-deferral strategies, infectious-disease testing, pathogen-inactivation methods, and recombinant DNA technologies for particular therapeutic proteins. These advances have dramatically reduced the likelihood of transfusion-transmitted disease so that the risk of transfusion-associated human immunodeficiency virus 1 or hepatitis C infection, for example, is now on the order of 1 in 2 million donated units.[1] Concern persists about the transmission of other infectious agents, for which testing is not routinely available, including variant Creutzfeldt–Jakob disease and leishmaniasis.[2]

But as public concern regarding infectious complications may have softened, other risks have come to the fore, such as transfusion-associated acute lung injury[3] and the potential (if somewhat controversial) adverse effects of immune modulation.[4] So although blood transfusions may be very safe, they are not completely safe, and they probably never will be.

There are other, more subtle issues related to transfusions and possibly adverse outcomes. One of the issues is the time that blood is stored. The Food and Drug Administration allows packed red cells to be refrigerated for up to 42 days. This storage time gives blood centers the flexibility to manage the blood supply through seasonal swings and sudden demands, such as environmental disasters, and to collect and ship blood products from one part of the country to another. Because blood is in short supply in many metropolitan areas, the ability to manage the blood inventory is critical to support health care in certain regions and to avoid critical blood shortages that can and have resulted in canceled elective surgeries.

On the other hand, long storage times may influence the quality of blood that is transfused. During storage, red cells undergo a number of physical and chemical changes, including increased rigidity of the membrane, loss of organic phosphates, and the generation and release of proinflammatory cytokines.[5] Some of the biochemical changes take place slowly and some take place rapidly, factors that call into question the benefits of the use of "newer" blood.[6] Such changes may contribute to the poorer clinical outcomes associated with the transfusion of "older" red-cell units,[7,8] although this association is not universally accepted.[9,10]

In this issue of the *Journal*, Koch and colleagues provide more evidence in support of the concept that the transfusion of older units of red cells is associated with worse outcomes.[11] In a single-center, retrospective analysis of outcomes in approximately 6000 patients who had undergone coronary-artery bypass grafting, valve surgery, or both, patients who had received blood that had been stored for 14 days or less ("newer blood") fared better than did patients who had received blood stored for more than 14 days ("older blood"). Significant differences were seen in virtually all outcomes that were measured, including in-hospital mortality, duration of intubation, and sepsis. There was also a significant difference between the two groups favoring transfusion of newer units of blood in mortality at 1 year (7.4% vs. 11.0%, $P<0.001$). Although some of the baseline characteristics of the patients were unequal in the two groups, including the prevalence of the blood type used (type O was overrepresented among those receiving newer units), multivariable analyses and appropriate statistical adjustment for such imbalances did not change the conclusions or render the differences insignificant.

This is a very important outcome. The results will arm those who believe that the transfusion of older red-cell units carries risks and should be avoided. However, the results of this study will not settle the debate, because the issue is broader than the scope of the study. At least two important questions arise. First, how generalizable are the findings? The median age of the patients in the study was 70 years , and, by definition, the patients had a substantial number of coexisting illnesses. The surgery required cardiopulmonary bypass. Is there some interaction between the bypass machine and circulating red

cells that is particularly deleterious if the red cells have been stored for 3 or 4 weeks, instead of 1 or 2? Would the same result have been seen in other patients who did not share the characteristics of this group and who did not require bypass? Second, in any surgical setting, would the complete avoidance of blood transfusions (or as complete as possible) lead to even better outcomes? This hypothesis brings up the studies that have looked at "liberal" versus "restrictive" transfusion policies in clinical situations that go beyond surgery, such as treating critically ill patients in intensive care units.[12] Thus, the study by Koch et al. simply adds an important piece to the discussion of the risks of transfusion but does not settle the issue of best practices.

With these caveats, what can be done to improve outcomes? To the extent possible, newer blood might be used in clinical situations that seem to call for it — in this case, patients who are undergoing open-heart surgery requiring bypass. But there are practical limitations to that practice: the availability of compatible blood, the ability to recruit in a time-sensitive manner the large numbers of donors that would be needed if the storage time were shortened by even half, and the problems of inventory management, particularly during seasonal blood shortages. It is just not feasible to shorten storage time significantly without restricting the blood supply. Furthermore, if the results of the study by Koch et al. are correct, could there be a continuum of effects, with even better outcomes with even newer blood?

There are other ways to avoid the possible risks of transfusing older blood units or of transfusing blood altogether.[13] Blood-management and blood-conservation programs have been developed to correct anemia before planned surgery. Other methods include the adoption of conservative triggers to avoid transfusion on the basis of hemoglobin or hematocrit values, the use of intraoperative blood salvage or preoperative hemodilution in selected cases, and the administration of erythropoiesis-stimulating agents and iron to promote red-cell recovery after surgery. These methods have had a substantial effect on blood consumption in centers that have embraced management programs. Blood management makes good economic sense and (consistent with the evidence presented here) good medical sense.

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