EDITORIAL

Does the issue of stored blood get old: is all blood equal?

Piotr Przybyłowski[1,2], Bartosz Hudzik[3,4]

1 Silesian Center for Heart Diseases, Zabrze, Poland
2 1st Department of the General Surgery, Jagiellonian University Medical College, Kraków, Poland
3 3rd Department of Cardiology, Silesian Center for Heart Diseases, School of Medicine with a Division of Dentistry in Zabrze, Silesian Center for Heart Diseases, Medical University of Silesia in Katowice, Zabrze, Poland
4 Department of Nutrition-Related Disease Prevention, School of Public Health in Bytom, Medical University of Silesia in Katowice, Bytom, Poland

Transcatheter aortic valve implantation (TAVI) has become a viable therapeutic modality for inoperable or high-surgical-risk patients with severe aortic stenosis, who are not deemed suitable for surgical aortic valve replacement. Bleeding and vascular access site complications range from 26% to 77% and 9.5% to 51.6%, respectively, and have been well documented to be associated with worse outcomes.[1] Aortic stenosis by itself could lead to hemolysis, which in turn may contribute to anemia. Bleeding events often require packed red blood cell (RBC) transfusion. However, the clinical decision regarding the necessity of RBC transfusion is challenging. Studies have shown that baseline anemia is the strongest predictor of the need for RBC transfusion following both TAVI and aortic valve replacement.[2,3] Notwithstanding, everyday clinical practice indicates that RBC transfusions are being administered in the absence of overt major bleeding or hemodynamic instability. More importantly, we must be aware that not every major bleeding results in a significant hemoglobin drop and thus may not require RBC transfusion.

Increased mortality, stroke, and acute kidney injury rates have been reported in patients who received RBC transfusions following TAVI.[4] The adverse effects of bleeding, anemia, and blood transfusion on short- and long-term outcomes are not just specific for TAVI. In addition, blood transfusion has been linked to worse prognosis following acute coronary syndromes,[5] percutaneous coronary intervention,[6] and cardiac surgery.[7] Tchetche et al[4] identified independent predictors of RBC transfusion following TAVI. These included female sex (odds ratio [OR], 2.11; 95% CI, 1.32–3.37; P = 0.002), previous cerebrovascular accident (OR, 1.95; 95% CI, 1.13–3.38; P = 0.016), peripheral vascular disease (OR, 1.94; 95% CI, 1.18–3.20; P = 0.01), major stroke (OR, 9.85; 95% CI, 3.43–28.30; P <0.001), major vascular complication (OR, 12.40; 95% CI, 7.37–20.83; P <0.001), and severe anemia (OR, 3.47; 95% CI, 1.95–6.18; P <0.001). All of these predictors were associated with an increased risk of transfusion of at least 4 RBC units.[4] Unquestionably, there are other factors that predict transfusion, such as lower body mass index, renal dysfunction, and antiplatelet and anticoagulant regimens. Several mechanisms have been proposed to explain the association of blood transfusion with worse outcomes. These include the impairment of oxygen delivery due to an increased oxygen affinity and decrease in deformability of stored RBCs, prothrombotic effects through an increased release of procoagulants, and transfusion-related modulation of the immune system through alterations in cytokine levels.[8] In addition, whether pretreatment of anemia (eg, iron substitution, erythropoietin) prior to TAVI improves the outcome remains to be determined, because anemia may just act as an indicator of frailty in these patients. Still, one could anticipate that the mitigation of anemia could result in a reduction in transfusion rates.[9]

In this issue of the *Polish Archives of Internal Medicine*, Czerwińska-Jelonkiewicz et al[10] focused on different aspects of blood transfusion in patients who underwent TAVI. The authors investigated the association between RBC storage time and the short- and long-term outcomes in this population of patients. In this retrospective, observational study, 101 patients (56.7%) required blood transfusion during or after TAVI. Given that the mean number of transfused RBC units was 2 and the mean hemoglobin concentration prior to transfusion was 9.6 g/dl, patients were managed with a liberal rather than restrictive approach to RBC transfusion. One could only speculate whether the treatment of preexisting anemia prior to TAVI could have resulted in a fewer

Correspondence to:
Prof. Piotr Przybyłowski, MD, PhD, Śląskie Centrum Chorób Serca w Zabrzu, ul. Curie-Sklodowskiej 9, 41-800 Zabrze, Poland,
phone: +48 32 373 36 89,
e-mail: piotr.przybylowski@uj.edu.pl
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blood transfusions. The authors concluded that shorter-stored RBC units and a great discrepancy in RBC age in multi-transfused elderly patients after TAVI might have a deleterious effect on life expectancy. However, the authors did not offer any definition of shorter storage. The mean storage time was 17 days for those who died within 30 days and 19 days for those who survived, while it was 19 days for those who died within 12 months and 25 days for those who survived. Meanwhile, most authors use the 7-day cut-off for shorter-stored RBC units. Therefore, actually the patients who died received RBC units that were stored for a relatively longer time. In a multivariable analysis, only the number of RBC units transfused remained the independent predictor of long-term mortality. The storage time did not reach statistical significance. The minor association or lack thereof is further supported by only a weak *C*-statistic (area under the receiver characteristic operating curve of 0.59 for the number of RBC units and of 0.63 for the storage time of RBC units).

The storage time has recently attracted considerable attention. Current regulations permit the storage of RBC units for up to 42 days. However, over time, several biochemical changes in RBCs may occur, both in RBCs themselves and in the preservative medium.[11] Thus, prolonged storage may render erythrocytes ineffective as oxygen carriers, which leads to the accumulation of substances that exert adverse biologic effects.

There are several methods of producing RBC units. Different production methods may account for the various effects on the degree and magnitude of RBC lesions related to the storage period. The occurrence of RBC storage lesion has raised safety concerns with transfusions, particularly when longer-stored RBC units are used. A systematic review of 18 observational studies and 3 randomized controlled trials (RCTs) involving more than 400 000 patients suggested that the transfusion of longer-stored RBC units was potentially associated with a significantly increased risk of death.[12] However, this effect was reported in observational studies. The results of most RCTs did not detect clinically relevant consequences of longer-stored RBC transfusion.[13-15] Recent studies seem to be more balanced, indicating no relevant relationship between prolonged storage and worse outcomes. Interestingly, some studies have even suggested worse outcomes with fresh RBC transfusion.[14,16]

There is no clear explanation why transfusions of shorter-stored RBC units might be associated with increased mortality. One of the few changes in RBC units that might have a positive clinical effect is the gradual demise of leukocytes. Up to 10^6 of leukocytes are allowed per unit even in the leukodepleted RBC products. Transfusion of fresher RBC units could result in increased microchimerism. Furthermore, microchimerism has also been observed in a substantial fraction of leukodepleted RBC recipients.[17] An excessive amount of donor white blood cells increases the risks of systemic inflammatory response, infectious risk associated with immunomodulation, and of organ failure.[18] These mechanisms could play a central role in everyday clinical practice, as most patients receive only buffy-coat-depleted RBCs, which contain more leukocytes than leukodepleted RBCs. Finally, the oldest erythrocytes in each RBC unit are sensitive to prolonged storage; thus, they may contribute to adverse effects of even fresh RBCs due to microparticle formation, release of hemoglobin and other intracellular components, and iron overload.[19,20] A recent meta-analysis and systematic review has indicated that the current evidence provides moderate certainty that use of fresher RBCs does not influence mortality, and low certainty that it does not influence adverse events but could possibly increase infection rates.[21] In addition, handling of the blood products greatly influences the quality of both the shorter- and the longer-stored RBC units. Once issued by the blood bank, the transfusion of RBC units should be commenced within 30 minutes of removal from the optimal storage conditions.

The transfusion community seems to be losing interest in fierce "new blood – old blood" debates, and instead agrees on the need to welcome the opportunity provided by omics/laboratory studies to further improve blood storage quality. To establish the effect of the storage time of blood products on clinical outcome, a well-controlled clinical trial, particularly with a strictly followed storage, rewarming, and transfusion protocol, is needed.

In conclusion, although literature data present a worrisome picture of potential storage complications, current findings are too inconsistent to drive changes in clinical practice. Perhaps the results of ongoing RCTs will shed new light and contribute to recommendations on RBC storage time in patients undergoing cardiac procedures and in those critically ill.

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